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Oncology Clinical Protocol CINC424C2301 / NCT02913261

# A phase III randomized open-label multi-center study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs. host disease after allogeneic stem cell transplantation

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## List of abbreviations

| | |
|---|---|
| ACS | All Crossover Subjects |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| aGvHD | Acute Graft vs. Host Disease |
| alloSCT | Allogeneic Stem Cell Transplantation |
| ALL | Acute Lymphoblastic Leukemia |
| ALP | Alkaline Phosphatase |
| AML | Acute Myeloid Leukemia |
| ANC | Absolute Neutrophils Count |
| AP | Alkaline phosphatase |
| APC | Antigen-Presenting Cells |
| APTT | Activated partial thromboplastin time |
| ARDS | Acute Respiratory Distress Syndrome |
| ASBMT | American Society for Blood and Marrow Transplantation |
| ATC | Anatomical Therapeutic Chemical |
| ATG | Anti-Thymocyte Globulin |
| BID | bis in diem/twice a day |
| BAT | Best Available Therapy |
| BCC | Basal Cell Carcinoma |
| BCS | Biopharmaceutical Classification System |
| BLQ | Below the Limit of Quantitation |
| BM | Bone Marrow |
| BMI | Body Mass Index |
| BOR | Best Overall Response |
| BP | Blood pressure |
| BSA | Body Surface Area |
| BUN | Blood Urea Nitrogen |
| CAS | Cross over Analysis Set |
| CBC | Complete blood count |
| cGvHD | chronic Graft vs. Host Disease |
| CIBMTR | Center for International Blood and Marrow Transplant Research |
| CLcr | Creatinine clearance |
| CLL | Chronic Lymphocytic Leukemia |
| CMH | Cochran–Mantel–Haenszel |
| CMML | Chronic Myelomonocytic Leukemia |
| CMO & PS | Chief Medical Office and Patient Safety |
| CMV | Cytomegalovirus |
| CNI | Calcineurin Inhibitor |
| CNS | Central Nervous System |
| 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 |
| CTD | Connective Tissue Disease |
| Ctrough | Minimum concentration |
| CYP3A | Cytochrome P450, family 3, subfamily A |
| CYP450 | Cytochrome P450 |
| DILI | Drug-Induced Liver Injury |
| DLI | Donor Lymphocyte Infusion |
| DLT | Dose Limiting Toxicity |
| DMC | Data Monitoring Committee |
| DOR | Duration of Response |
| EBMT | European Bone Marrow Transplant |
| EBV | Epstein-Barr Virus |
| ECP | Extracorporeal Photopheresis |
| eCRF | Electronic Case Report/Record Form |
| EDC | Electronic Data Capture |
| EDTA | Ethylenediaminetetraacetic acid |
| EFS | Event-Free Survival |
| EOS | End of Study |
| EOT | End of treatment |
| ET | Essential Thrombocythemia |
| EU | European Union |
| FACT-BMT | Functional Assessment of Cancer Therapy - Bone Marrow Transplantation |
| FAS | Full Analysis Set |
| FFS | Failure-Free Survival |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GGT | Gamma-Glutamyl Transferase |
| GI | Gastro-Intestinal |
| GM-CSF | Granulocyte Macrophage Colony Stimulating Factor |
| GvHD | Graft vs. Host Disease |
| GvL | Graft vs. Leukemia |
| HBV | Hepatitis B Virus |
| HCV | Hepatitis C Virus |
| HCT | Hematopoietic Cell Transplantation |
| HDL | High Density Lipoprotein |
| [redacted] | [redacted] |
| HHV-6 | Human Herpes Virus |
| HIV | Human Immunodeficiency Virus |
| HLA | Human Leukocyte Antigen |
| HSCT | Hematopoietic stem cell transplantation |
| HSV | Herpes Simplex Virus |
| HU | Hydroxyurea |
| IB | Investigator Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| [redacted] | [redacted] |
| IEC | Independent Ethics Committee |

| | |
|---|---|
| IFN | Interferon |
| IL | Interleukin |
| IN | Investigator Notification |
| 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 Transducers and Activators of Transcription |
| LC-MS/MS | liquid chromatography-tandem mass spectrometry |
| LDL | Low Density Lipoprotein |
| LDH | Lactate dehydrogenase |
| LFS | Leukemia-Free Survival |
| LFT | Liver Function Tests |
| LLN | Lower limit of normal |
| LLOQ | Lower limit of quantification |
| LPLV | Last Patient Last Visit |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |
| MDS | Myelodysplastic Syndromes |
| MEDRA | Medical dictionary for regulatory activities |
| MF | Myelofibrosis |
| MM | Multiple Myeloma |
| MM | Malignant Melanoma |
| MMF | Mycophenolate mofetil |
| MPNs | Myeloproliferative Neoplasms |
| MR | Malignancy Relapse/Progression |
| mPBSC | mobilized Peripheral Blood Stem Cells |
| MSC | Mesenchymal Stromal Cells |
| MTD | Maximum Tolerated Dose |
| mTOR | Mammalian Target of Rapamycin |
| MTX | Methotrexate |
| NCA | Non-compartmental analysis |
| NHL | Non-Hodgkin lymphoma |
| NIH | National Institutes of Health |
| NK | Natural killer |
| NMSC | Non-Melanoma Skin Cancer |
| NOS | Not Otherwise Specified |
| NR | No Response |
| NRM | Non Relapse Mortality |
| NSAID | Nonsteroidal anti-inflammatory drug |
| NYHA | New York Heart Association |
| o.d. | omnia die/once a day |

| | |
|---|---|
| OR | Overall Response |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PAC | Post-Approval Commitment |
| PAS | Pharmacokinetic analysis set |
| PET | Positron emission tomography |
| PD | Pharmacodynamics |
| PHI | Protected Health Information |
| PK | Pharmacokinetics |
| PLL | Prolymphocytic leukemia |
| PLT | Platelets |
| PML | Progressive Multifocal Leuko-Encephalopathy |
| PPS | Per-Protocol Set |
| PR | Partial response |
| PRBC | Packed red blood cells |
| PRO | Patient Reported Outcomes |
| PTT | Partial thromboplastin time |
| PV | Polycythemia Vera |
| QD | quaque die, once a day |
| QOL | Quality of Life |
| RAEB | Refractory anemia with excess blasts |
| RAEB-T | Refractory Anemia with Excess Blasts in Transformation |
| RAP | The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses |
| RARS | Refractory Anaemia with Ring Sideroblasts |
| RBC | Red Blood Cell |
| RDC | Remote Data Capture |
| RDI | Relative Dose Intensity |
| REB | Research Ethics Board |
| RoW | Rest of the World |
| RSV | Respiratory Syncytial Virus |
| [redacted] | [redacted] |
| R Value | ALT/ALP in x ULN |
| SAE | Serious Adverse Event |
| SAP | Statistical analysis plan |
| SC | Steering Committee |
| SCC | Squamous Cell Carcinoma |
| SCT | Stem cell transplantation |
| SD | Stable disease |
| SoC | Standard of Care |
| SOS | Sinusoidal Obstructive Syndrome |
| SR-aGvHD | Steroid Refractory acute Graft vs. Host Disease |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TB | Tuberculosis |
| TBIL | Total Bilirubin |
| TNF | Tumor Necrosis Factor |
| TYK2 | Tyrosine kinase 2 |

| | |
|---|---|
| UCB | Umbilical Cord Blood |
| US | United States of America |
| VOD | Veno-Occlusive Disease |
| VZV | Varicella Zoster |
| WBC | White Blood Cells |

## 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 patient |
| 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 |
| 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 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. |
| Personal Data | Subject information collected by the Investigator is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples |
| 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 as part of the required study procedures, including placebo and active drug run-ins.<br>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 |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints |
| Withdrawal of consent | Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data |

## Amendment 2 (21-Jun-2018)

### Study Status

As of 21-Jun-2018, a total of 384 patients have been screened and 175 patients randomized.

### Amendment rationale:

- The main purpose of the amendment is to allow for more flexibility in the tapering of corticosteroids, calcineurin inhibitors (CNI) and ruxolitinib; and if needed, for this taper to be completed safely beyond Week 24. This change includes clarification that institutional guidelines for the tapering of corticosteroids and CNI may be followed. Additionally, the physician can tailor the tapering strategy to each patient's condition, including stopping ruxolitinib more slowly in case of an acute Graft vs. Host Disease (aGvHD) flare or other safety concerns which may prevent the taper from being completed by Week 24.
- Patients who meet the protocol criteria for treatment discontinuation will not be eligible to continue receiving ruxolitinib within the study. However, as part of Novartis "Post-trial access" commitment, patients who meet all of the following criteria :
  - responded to ruxolitinib at Day 28 (or Cross-Over Day 28),
  - met study discontinuation criteria, other than safety reasons,
  - are assessed by the Investigator to still be deriving clinical benefit from ruxolitinib,

  will be given the possibility to continue ruxolitinib outside the study, if requested; they will then not enter the Long-Term Follow-Up period.
- Similarly, patients who are still receiving ruxolitinib at their end of study (approximately 2 years from randomization), and deriving clinical benefit from ruxolitinib as assessed by the Investigator, will also be given the possibility to continue ruxolitinib outside the study from another source, where permitted by and in accordance to local laws and regulations.
- To align with medical practices in managing adolescent patients, other systemic medications for aGvHD prophylaxis in addition to CNI can now be maintained after randomization for all patients. To be allowed, these additional prophylactic medications start date must precede the diagnosis date of aGvHD. While this change is anticipated to primarily improve adolescent enrolment, its impact on overall patient homogeneity is limited.
- The pharmacokinetic (PK) sampling schedule was simplified following the completion of a preliminary analysis, conducted on a subset of 22 adult and 1 adolescent patients from the present study, with extensive PK sampling after the administration of repeated doses of ruxolitinib at 10 mg twice a day (BID). The results suggested that there was no substantial difference in terms of PK parameters (apparent clearance, apparent volume of distribution) between patients with aGvHD and historical data in healthy volunteers and other indications.
- The secondary endpoint Best Overall Response (BOR) was added to align with aGvHD publications.
- A Data Monitoring Committee (DMC) has been added to address the Study Steering Committee's request to be informed on the balance of safety events between treatment arms. The DMC was added to maintain the Study Steering Committee blinding during

their review of pooled safety data, in order to preserve the integrity of the trial. No efficacy or safety data from the study were considered in the decision to add a DMC.

- Finally, the amendment includes updates to align with the ruxolitinib Investigator Brochure and current Development Safety Update Report. These updates are not expected to impact the design or conduct of the current study.

## 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 key changes were made and applied to the respective sections of the protocol:

**Change #1: Revisions to the tapering guidelines** in Sections 2.2, 4.1, Figure 4-1, Sections 6.1.1.1, 6.1.5, 6.1.5.1, Table 7-1, Table 7-2, Sections 7.1.4 and [redacted]:

- For corticosteroids and CNIs: clarification that taper should follow institutional guidelines.
- For ruxolitinib:
  - Addition that ruxolitinib taper is optional per Investigator's judgment however it must be initiated no later than Week 24 (or Cross-Over Week 24).
  - Addition of the possibility to complete ruxolitinib taper after Week 24 (or Cross-Over-Week 24) in some cases.
  - Revision that several ruxolitinib taper attempts are allowed up to the patient's end of study.

**Change #2: Clarifications to patient management rules** in Sections 4.1, 4.3, 6.1.1.2, 6.1.5, 7.1.4 and 7.1.5:

- Additions and revisions to clarify the patient management rules, depending on their response, treatment arm and/or tapering strategy.
- Clarification that responding patients (i.e. obtaining a Complete Response [CR] or Partial Response [PR]) completing the dosing schedule for ruxolitinib or for their assigned Best Available Therapy (BAT) at any time as per standard of care before Week 24 (or Cross-Over Week 24) must continue to be assessed as per the applicable schedule of assessments until Week 24 (or Cross-Over Week 24).
- Addition that patients who responded to ruxolitinib at Day 28 (or Cross-Over Day 28) and are assessed by the Investigator to still be deriving clinical benefit from ruxolitinib, despite meeting protocol criteria for treatment discontinuation, will be given the possibility to continue ruxolitinib outside the study.
- Addition that patients still receiving ruxolitinib at their end of study (approximately 2 years from randomization), and benefitting from ruxolitinib, may be transitioned to an alternative solution to receive ruxolitinib.

**Change #3: Revision of the "End of study definition"** to include possible prolonged ruxolitinib taper in Section 4.3.

**Change #4: Allow continuation of systemic medications for aGvHD prophylaxis after randomization** in Sections 4.1, 6.1, 6.1.1.2, 6.1.5, 6.4.1 and 7.1.2.

**Change #5: Revisions to the Pharmacokinetic (PK) sampling schedule** in Sections 6.1.1.1, Table 7-1, Table 7-2, Section 7.2.3.1, Tables 7-4 and 7-5

**Change #6: Clarifications on the Safety Follow-Up visit and Long-Term Follow-Up period** in Sections 4.1 and 7.1.7.

**Change #7: Clarifications to the timing for cross-over between Day 28 and Week 24** in Section 4.1, Figure 4-1, and Section 7.1.4.

**Change #8: Clarifications to the timing for further analyses after the primary and key secondary endpoint analysis** in Sections 2.2, 4.3, 10 and 10.7.

**Change #9: Clarifications on the addition of new systemic immunosuppressive therapy in** Sections 2.2, 6.1.1.1, 6.1.5, 6.1.5.1, 6.4.1, 6.4.3 and 7.1.5:

- Clarification that addition of new systemic immunosuppressive therapy is considered a treatment failure, and is a criterion for study treatment discontinuation.
- Removal that patients randomized to ruxolitinib may be treated with new systemic therapy in case of ruxolitinib lack of efficacy. This is to be consistent with the study design as this is a study treatment discontinuation criterion. These patients may use other systemic treatment for aGvHD per Investigator's assessment only outside of the study Treatment Period.
- **Change #10: Addition of a DMC** in Section 8.6.

**Other changes:**

- Sections 1.2.1 and 1.2.1.2: Update to the number of patients who have received ruxolitinib treatment in Novartis- and Incyte-sponsored investigational clinical trials.
- Section 3:
  - Clarification of baseline for aGvHD response assessment in cross-over patients.
  - Removal of timeframe for aGvHD and chronic Graft vs. Host Disease (cGvHD) assessments to align with the assessment schedule in the protocol.
  - Table 3-1: Addition of the secondary efficacy endpoint BOR. Addition of minimum concentration (Ctrough) to the list of PK parameters and "other relevant endpoints" for exposure-response relationship assessments.
- Sections 4.1 and 6.1.5, Table 7-1: Addition of "Day 1 is the day of randomization", and correction of the timing for the Safety Follow-Up visit to "last dose + 30 days", to align with other protocol sections.
- Section 5.3: Exclusion criteria revision with limited impact on patient's homogeneity:
  - Exclusion criterion #15: Revision to allow for heparin or low-molecular-weight-heparin to be used at sub-therapeutic doses with no restrictions on the reason for administration (sinusoidal obstructive syndrome [SOS]/veno-occlusive disease of the liver [VOD] prophylaxis is now only cited as an example). Similar revision was made to section 6.4.3.
  - Exclusion criterion #18: Revision to the required time without any investigational treatment agent amended, from 30 days prior to screening, to 30 days prior to randomization.

  - Exclusion criterion #22: Update to differentiate between contraception requirements in female patients on ruxolitinib (protocol-defined rules) and in female patients on BAT (locally approved BAT label or guidance).
  - Exclusion criterion #23: Replacement to solely refer to locally approved BAT label or guidance for contraception requirements in male patients on BAT.
- Section 6.1.1.1: Addition of instructions in case of missed ruxolitinib doses and vomiting during the course of treatment.
- Sections 6.3.1.1.4 and 6.4.2: Clarification of dosing recommendations for ruxolitinib when combined with cytochrome P450 (CYP450) modulators.
- Section 7, Table 7-1:
  - Reworded "monthly" to every 4 weeks visits ("4-weekly visit") between Week 8 and Week 24 for accuracy. Same change applied to Table 7-2 for Cross-Over patients.
  - Addition of taper follow-up visits when applicable, every 8 weeks from Week 24 to Week 48, and every 12 weeks thereafter. Same change applied to Table 7-2 for Cross-Over patients.
  - Clarification that, at End of Treatment (EOT), height is only to be measured in adolescent patients. Same change applied to Table 7-2 for Cross-Over patients.
  - [redacted]
  - Addition of "Disposition" to align with corresponding Case Report Form (CRF) page. Same change applied to Table 7-2 for Cross-Over patients.
  - Clarification that chimerism testing is required at Cross-Over Week 1 only.
- Section 7.1.4:
  - Addition of the list of assessments required within 7 days of the study treatment last dose, if it occurs before Week 24 (or Cross-Over Week 24) and patients continue to be assessed until Week 24 (or Cross-Over Week 24).
  - Clarification to avoid repeated assessments, if the EOT visit and Cross-Over Day 1 visit are 3 days apart or less.
- Section 7.1.5: Revision to provide a definition for lack of efficacy.
- Section 7.2.1.1: Clarification, to list supportive information for aGvHD organ staging per Harris Criteria.
- Section 7.2.1.3.1: Revision to allow for chimerism results obtained within 28 days prior to Day 1 to be used as baseline.
- Section 7.2.2.1: Correction, to reference time point until which findings should be recorded as Medical History.
- Section 7.2.2.3: Added measurement of height in adolescent patients at Week 48 or Cross-Over Week 48, as applicable.
- Section 7.2.4, Table 7-6:
  - [redacted]
  - Revised EOT (and Cross-Over EOT) time point definitions.

- Sections 8.1.1 and 8.2.2: Revisions to ensure adverse events (AEs)/serious adverse events (SAEs) are monitored up to 30 days after the latest time point in the Treatment Period.
- Section 10.1.3: Correction to "missing or incorrect aGvHD grade at randomization" as aGvHD grade is the stratification factor.
- [redacted]
- Sections 10.2 and 10.4.3: Revision of the baseline definition for efficacy endpoints because some patients may start study treatment as late as 72 hours after randomization.
- Section 10.4.3: Removal of the analysis windows for efficacy endpoints, which are defined in detail in the statistical analysis plan.
- Section 10.5.4: Revisions for clarity and accuracy of planned PK analyses.

**Administrative changes**

- Addition and correction of protocol references, where appropriate.
- Section 7.1.2: Deletion of redundant text at the end of Section 7.1.2.3.
- Section 7.1.6: Revisions to align with the new withdrawal of consent language of the Novartis protocol template.
- Sections 6.6.1 and 8.4: Updated to reflect a change in name in Novartis organization.

## 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 are considered substantial and do require IRB/IEC approval prior to implementation. In addition, the changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

# Amendment 1 (31-May-2017)

## Study Status

As of 30 May 2017, a total of 38 patients have been screened and 8 patients randomized.

## Amendment rationale:

The main purpose of the amendment is to clarify exclusion criterion #5 and other eligibility criteria to follow standard medical practice as detailed below

**Clarification of exclusion criterion #5**

The revision of exclusion criterion #5 is to follow standard medical practice in determining the presence of active viral infection. This determination is based on the treating physician's clinical assessment according to local institutional guidelines at the time of randomization including but not limited to vital signs, physical examination, laboratory and relevant radiologic studies and viral load testing results when available. The investigator will assess at time of randomization if the patient is presenting with a viral infection or not based on his/her medical judgement and without waiting for viral load test results for CMV, EBV, HHV-6, HBV, HCV performed at screening in order not to delay the initiation of aGvHD treatment in this life threatening condition.

Moreover, evidence of an uncontrolled viral infection at time of randomization renders the patient ineligible. However, a patient is eligible for enrollment into this study if she/he has been treated with appropriate anti-viral therapy in the setting of an active viral infection and has responded to treatment such that the viral infection is considered well-controlled by the investigator. Furthermore, as peripheral blood serology for CMV, EBV, HHV-6 are not reliable to detect acute phase antibody response in allogeneic transplant patients rendered B cell aplastic with administered high dose chemo-radiotherapy conditioning and aGvHD immunosuppressive treatment (Tomblyn M 2009), the protocol is amended to no longer require peripheral blood viral serologies for CMV, EBV and HHV-6 as a screening procedure in this protocol. Peripheral blood nucleic acid (viral load) testing can better support medical assessment of the presence of viral replication in patients rendered B cell aplastic with dose intensive conditioning. This testing will be performed routinely during screening and at regular (monthly) intervals during treatment in this trial.

**Clarification of exclusion criterion # 1**

Exclusion criterion # 1 is revised to clarify that there is no restriction on previous prophylaxis received for aGvHD prior to screening or randomization, and that the limitation resides in excluding any patient who has received more than one systemic treatment for steroid resistant aGVHD other than corticosteroids with or without concurrent administration of a calcineurin inhibitor.

**Clarification of exclusion criterion # 15**

Patients with aGvHD often receive heparin or low-molecular-weight heparin at sub-therapeutic low dosing as prophylaxis of sinusoidal obstructive syndrome/veno-occlusive disease (SOS/VOD) of the liver.

This sub-therapeutic dose does not increase the bleeding risk in the patients. Accordingly, exclusion criteria #15 was modified to allow patients to be treated with low-dose heparin as prophylaxis before and during the study treatment period (Section 6.4.3).

**Clarification of inclusion criterion # 8**

The timeframe of 48 hours of SR-aGvHD prior to study treatment start was removed for clarification because all patients who are confirmed steroid refractory aGvHD prior to randomization are eligible in regards to inclusion criteria 8.

Acute GvHD patient progressing after 3 days of high dose systemic corticosteroids are considered SR aGvHD, according to EBMT guidelines. Therefore the time window of inclusion criterion 8-A was changed from "after 5 days" to "after at least 3 days" to ensure such patients are eligible in the trial.

A lower steroid dose threshold is set in this amendment to define steroid taper failure, e.g. methylpredisolone dose <0.5 mg/kg/day reduced from <1 mg/kg/day (for a minimum of 7 days). This lower steroid dose threshold is set based on standard medical practice aiming to provide additional immunosuppression beyond systemic corticosteroids +/- calcineurin inhibitor to avoid more prolonged required systemic steroids with associated risk of infection and malignancy relapse. Therefore, any patient who fails steroid taper at a methylprednisolone dose of 0.5 mg/kg/day or higher (for 7 days duration) would be eligible for enrollment and could start prompt additional immunosuppressive therapy after randomization to either ruxolitinib or investigator choice best available therapy. Similarly, the definition of steroid taper failure is aligned during study treatment and the corticosteroid thresholds dosing are revised in corresponding sections of study protocol.

Finally, the amendment includes updates to align with the ruxolitinib investigator's brochure and current Development Safety Update Report. These updates are not expected to impact the design or conduct of the current study.

The amendment also includes other revisions and administrative changes for clarification purposes.

**Detailed listing of 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 underlined for insertions.

The following sections of the protocol have been changed:

- Section 1.2.1: To update the numbers according to the Development Safety Update report 2017.
- Section 3: Revision of corticosteroid dose thresholds to align with the revised corticosteroid taper failure definition in case of aGvHD flare during corticosteroids taper.
- Section 3, Table 3.1: Removal of Time point Day 56 for ORR assessment to align the secondary endpoint ORR assessment with the study design (i.e. patients not CR/PR from Day 28 will be discontinued or started in cross over if eligible) so ORR assessment at D56 was not accurate.
- Section 3, Table 3.1: Pharmacokinetic parameters updated with omitted information.

- Section 4.1: Revision of corticosteroid dose thresholds for methylprednisolone and prednisolone to align with the new aGvHD steroid refractory definition for patients who failed corticosteroid taper at time of eligibility assessment.
- Section 4.1: Addition aGvHD prophylaxis treatment to be stopped prior to randomization to clarify that all aGvHD treatment including prophylaxis are to be stopped prior to randomization
- Section 4.1: Revision of Study treatment start up to 72 hours from randomization at the latest. To allow more flexibility in the initiation of BAT after randomization as some local institution may require more than 24 hours obtaining the selected BAT and initiating patient's treatment.
- Section 5.2, inclusion criterion # 8:
  - Removal of timeframe confirmed aGvHD within 48 hours from study treatment start. To allow all patients to be enrolled into the trial as long as patient was confirmed SR aGvHD prior to randomization.
  - Revision of steroid treatment duration to align SR aGvHD definition with EBMT guidelines in progressing patients.
  - Revision of corticosteroid dose thresholds for methylprednisolone and prednisolone to align with the new aGvHD steroid refractory definition for patients who failed corticosteroid taper at time of eligibility assessment and ensure timely initiation of treatment.
- Section 5.3, exclusion criterion #1: Addition of "steroid refractory" and removal of the rest of the sentence to clarify that eligible patients may have received no more than one SR aGvHD treatment but that there is no restriction to prior aGvHD prophylaxis therapy or steroids +/-CNI received as aGvHD treatment or prophylaxis.
- Section 5.3, exclusion criterion #5:
  - Addition of "uncontrolled" viral infection and "based on assessment by the treating physician". To clarify that no patient with uncontrolled viral infection is eligible based on treating physician assessment. And to revise that viral load testing is performed as a screening procedure whereas patient may be randomized (treated with ruxolitinib/BAT) in a timely manner if all other eligibility criteria are met.
  - Removal of the 2 last sentences including the confirmation of viral load results prior to randomization. To remove serology testing for CMV, EBV, HHV6 as results are not reliable in aGvHD patients under immunosuppression.
- Section 5.3, exclusion criterion #9: Addition of a note for patients who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse. To clarify those patients who received unscheduled DLI for malignancy relapse are not eligible.
- Section 5.3, exclusion criterion #14: Revision of prednisolone dose 1.5 mg/kg/day replaced by 1.25 mg/kg/day. To correct a typographical error in the equivalent dosing of prednisolone.
- Section 5.3, exclusion criterion #15: Addition of a note that a patient who received a sub-therapeutic dose of heparin or low molecular weight heparin when used as prophylaxis of liver VOD/SOS is eligible.

- Section 6.1.5.1: Revision of corticosteroid dose thresholds for methylprednisolone and prednisolone to align with the revised corticosteroids taper failure definition in case of aGvHD flare during corticosteroids taper.
- Section 6.4.1: Revision of corticosteroid dose thresholds for methylprednisolone and prednisolone to align with the revised corticosteroids taper failure definition in case of aGvHD flare during corticosteroids taper.
- Section 6.4.3:
  - Addition of a note that patients who received a sub-therapeutic dose of heparin or low molecular weight heparin when used as prophylaxis of liver VOD/SOS can be maintained in the trial
  - Addition “Non-scheduled” DLI to clarify that only “non-scheduled” DLI is prohibited during the trial
- Section 6.6.4: Addition of an alternative to study drug supply destruction to reflect the different options for study supply destruction in participating countries according to Novartis standard operational procedures and local regulations.
- Section 7.1, table 7-1: Addition of IRT contact “monthly” and HBV and HCV serology tests to correct omitted information part of initial protocol
- Section 7.1, table 7-2:
  - Addition of IRT contact “monthly” to correct omitted information part of initial protocol.
  - Correction of week number visits for cross-over visits W1- W8 to correct a typographical error.
- Section 7.1.2: Addition of body weight and laboratory examination retests required (CMC Chemistry tests and coagulation) if available results are older than 24 hours from study treatment start. To ensure to have the most accurate values for safety assessment, when patient starts study treatment beyond 24 hours from randomization.
- Section 7.1.2.2: Addition of aGvHD overall grade and organ staging to be recorded in CRF at time of screening. To record aGvHD overall grading and organ staging in CRF at time of screening for all patients including screening failure patients to better understand current aGvHD population characteristics.
- Section 7.1.2.3:
  - Revision of screening period time-frame definition to incorporate assessments made at Day 1 but before start of study treatment.
  - Addition of a window of 48 hours between Screening and Day 1 visits for vital sign examinations and urinalysis tests and 7 days between Screening and Day 1 for viral load assessments. To avoid unnecessarily repeated examinations needed to confirm eligibility criteria, when Screening and Day1 visits occur up to 48 hours apart.
  - Addition of body weight, CBC, Chemistry and coagulation retests to be performed within 24 hours prior to start of study treatment.
- Section 7.1.4:
  - Revision of Day 1 definition to the day of randomization to clarify the definition of Day 1 as the day of randomization and not necessarily the first day of study treatment.

  - Revision of Study treatment start up 24 hours to 72 hours from randomization at the latest**.** To allow more flexibility in the initiation of BAT after randomization as some local institution may require more than 24 hours obtaining the selected BAT and initiating patient's treatment.
- Section 7.2.2.2: Addition of a window of 48 hours between Screening and Day 1 visits for physical examination. To avoid unnecessarily repeated examinations needed to confirm eligibility criteria when Screening and Day1 visits occur up to 48 hours apart.
- Section 7.2.2.3: Addition of a retest for the body weight to ensure the most accurate value is reported before start of study treatment when the patient starts study treatment beyond 24 hours from randomization.
- Section 7.2.2.4, Table 7-3:
  - Addition of "OR" between PPT and aPTT to clarify that one of the two coagulation parameter is required for the study.
  - Update to serology and viral load requirements for HBV and HCV. To clarify that serology assessment and viral load sampling are required for HBV and HCV as screening procedures whereas viral load will also be required during study treatment period.
  - Replacement of footnotes by notes in "Urinalysis", "Hepatitis markers" and "Additional viral testing". To clarify the requirement for respective sections and align with clarification made to exclusion criteria #5
  - Addition of viral load collection not to be repeated at Day 1 if it was performed within 7 days prior to randomization
- Section 7.2.2.4.1: Addition of required laboratory examination retests if available results are older than 24 hours at the time of study treatment start. To ensure that most accurate values are collected when the patient starts study treatment beyond 24 hours from randomization.
- Section 7.2.2.4.2: Addition of required laboratory examination retests if available results are older than 24 hours at the time of study treatment start. To ensure that most accurate values are collected when the patient starts study treatment beyond 24 hours from randomization.
- Section 7.2.2.4.3: Addition of a window of 48 hours between Screening and Day 1 visits to avoid unnecessarily repeated urinalysis examination to confirm eligibility criteria when Screening and Day1 visits occur up to 48 hours apart.
- Section 7.2.2.4.4:
  - Addition of "OR" between PPT and aPTT to clarify that one of the two coagulation parameter is required for the study.
  - Addition of required laboratory examination retests if available results are older than 24 hours at the time of study treatment start. To ensure that most accurate values are collected when the patient starts study treatment beyond 24 hours from randomization.
- Section 7.2.2.4.9: Update of requirements for serology and viral load to clarify for serology and viral load testing requirements at baseline and during the treatment period in alignment with the revised exclusion criteria #5

- Section 7.2.3: Update to subset of patients following the extensive PK sampling. To clarify that extensive sampling apply to all adolescents (randomized and cross over)
- Section 7.2.3: Addition of visit window for PK sampling to align PK sampling window with Visit Evaluation Schedule.

- Section 8.2.2: Removal: "whether the blind was broken or not". To align with study design of an open label study
- Section 8.2.2: Revision of "oncology Novartis drug Safety and Epidemiology (DS&E) to "chief medical office and patient safety (CMO & PS)".To reflect change in Novartis organization
- Section 10.1.3: Update the protocol deviation list defining per protocol set. To exclude from PPS patients who received a treatment different from assigned treatment arm.
- Section 10.4.1: Removal of "discontinuation of randomized treatment prior to or at Day 28" as a criterion for disqualifying the primary response at Day 28. To include in the analysis patients who will receive best available therapies which have a short duration as per standard of care. If a, patient has CR/PR and maintains the response, he/she will continue the on-treatment period assessments schedule after the last dose of BAT and the patient should be assessed for the primary response at Day 28.
- Section 10.4.1: Addition of grade and response calculation by the sponsor. To clarify that grade and response will be calculated by the sponsor for the purpose of data review and sensitivity analysis.
- Section 10.4.3: Revision of analysis window for baseline to align with the baseline definition across the protocol.
- Section 10.4.3: Revision of analysis windows for weeks 12 to 24 to avoid overlap between analysis windows of weeks 12 to 24.
- Section 10.5.1: Removal of "discontinuation from randomized treatment prior to or at Day 56" as a criterion for disqualifying the durable response at Day 56. To include in the analysis patients who will receive best available therapies which have a short duration as per standard of care. If a patient has CR/PR and maintains the response, he/she will continue the on-treatment assessments schedule after the last dose of BAT. The patient should be assessed for the durable response at Day 56.
- Section 10.5.2: Removal of ORR assessment at Day 56 as it is already captured in the key secondary endpoint.
- Section 10.5.2: Removal of censoring based on "discontinuation from randomized treatment" for the duration of response. To include in the analysis patients who will receive best available therapies which have a short duration as per standard of care. If a

patient has CR/PR and maintains the response, he/she will continue the on-treatment assessments schedule after the last dose of BAT. Therefore the duration of response will not be censored based on a short BAT administration per standard of care.

- Section 10.5.3.2: Revision of definitions for on-randomized and on-cross over treatment periods and the post-treatment period. To clarify that the end of treatment period is 30 days after last dose study medication (randomized or crossover) or end of treatment per End of Treatment Disposition eCRFs (randomized or crossover), whichever comes last.
- Section 10.5.4: Addition of Racc and AUC Tau, to add omitted information.
- Section 10.7: Addition of early PK analysis plan to reflect the early PK analysis defined in study analysis plan prior to study start but not described in initial study protocol.

## IRB/IEC

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 are considered substantial and do 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 amended protocol.

# Protocol Summary

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| Title | A phase III randomized open-label multi-center study of ruxolitinib versus best available therapy in patients with corticosteroid-refractory acute graft vs. host disease after allogeneic stem cell transplantation |
| Brief title | Study of efficacy and safety of ruxolitinib vs. best available therapy (BAT) in patients with Grade II-IV steroid-refractory acute graft vs. host disease |
| Sponsor and Clinical Phase | Novartis: 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 Grade II-IV steroid refractory acute graft vs. host disease. Specifically, the study will test if ruxolitinib will result in higher rates of disease response compared with currently used second line treatment modalities, and further that this response will be sustained during steroid taper. The rationale of the study is based on current knowledge of acute graft vs. host disease pathophysiology and published studies that show that ruxolitinib impairs antigen presenting cell function, inhibits donor T cell proliferation, suppresses adverse cytokine production, and improves survival and disease manifestations in GvHD mouse models. Further, published data has shown that ruxolitinib has evidence of clinical efficacy when added to immunosuppressive therapy in patients with steroid refractory acute graft vs. host disease. |
| Primary Objective(s) and Key Secondary Objective | **Primary objective**: to compare the efficacy of ruxolitinib vs. Investigator's choice Best Available Therapy in patients with Grade II-IV steroid refractory-acute Graft vs. Host Disease assessed by Overall Response Rate (ORR) at Day 28. ORR at Day 28 after randomization is defined as the proportion of patients in each arm demonstrating a complete response or partial response without requirement for additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response will be relative to the organ stage at the time of randomization.<br>**Key secondary objective**: to compare the rate of durable ORR at Day 56 between ruxolitinib and Best Available Therapy. ORR at Day 56 is defined as the proportion of all patients in each arm who achieve a complete response (CR) or partial response (PR) at Day 28 and maintain a CR or PR at Day 56. |
| Secondary Objectives | ● To estimate ORR at Day 14<br>● To assess Duration of response<br>● To assess the cumulative steroid dose until Day 56<br>● To assess Overall Survival (OS)<br>● To assess Event-Free Survival (EFS)<br>● To assess Failure-Free survival (FFS)<br>● To assess Non Relapse Mortality (NRM)<br>● To assess incidence of Malignancy Relapse/Progression (MR)<br>● To measure the incidence of cGvHD<br>● To assess Best Overall Response (BOR)<br>● To assess Pharmacokinetics (PK) of ruxolitinib in SR-aGvHD patients<br>● To assess exposure-response relationship of ruxolitinib in SR-aGvHD<br>● To evaluate changes in Patient Reported Outcomes (PROs)<br>● To evaluate the safety of ruxolitinib and Best Available Therapy |
| Study design | This trial is a randomized (1:1) phase III open label study of ruxolitinib compared to Investigator choice Best Available Therapy (BAT) in allogeneic stem cell transplant recipients with Grade II-IV steroid refractory acute graft vs. host disease. Patients randomized to the BAT arm are allowed to cross-over to the ruxolitinib arm if they do not demonstrate complete or partial response at Day 28 or if they lose their response thereafter and meet criteria for progression, mixed response, or no response, necessitating new additional systemic immunosuppressive treatment for aGvHD. |

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| Population | The study will enroll 308 adults and adolescents ≥12 years old who have undergone allogeneic stem cell transplantation and have developed Grade II-IV steroid refractory acute graft vs. host disease. |
| Inclusion Criteria<br>(Please refer to section 5 for full list of inclusion criteria) | 1. Male or female patients aged 12 or older<br>2. Able to swallow tablets<br>3. 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<br>4. Clinically diagnosed Grades II to IV acute GvHD as per standard criteria (Appendix 1) occurring after alloSCT requiring systemic immune suppressive therapy. Biopsy of involved organs with aGvHD is encouraged but not required for study screening.<br>5. Evident myeloid and platelet engraftment (confirmed within 48h prior to study treatment start):<br>● absolute neutrophil count (ANC) > 1000/$mm^3$ AND<br>● platelets ≥ 20,000/ $mm^3$<br>Note: Use of growth factor supplementation and transfusion support is allowed.<br>6. Confirmed diagnosis of steroid refractory aGvHD defined as patients administered high-dose systemic corticosteroids (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]), given alone or combined with calcineurin inhibitors (CNI) and either:<br>A. Progressing based on organ assessment after at least 3 days compared to organ stage at the time of initiation of high-dose systemic steroid +/- CNI for the treatment of Grade II-IV aGvHD,<br>**OR**<br>B. Failure to achieve at a minimum partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of high-dose systemic steroid +/- CNI for the treatment of Grade II-IV aGvHD,<br>**OR**<br>C. Patients who fail corticosteroid taper defined as fulfilling either one of the following criteria:<br>1. Requirement for an increase in the corticosteroid dose to methylprednisolone ≥2 mg/kg/day (or equivalent prednisone dose ≥2.5 mg/kg/day), **OR**<br>2. Failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days |
| Exclusion criteria<br>(Please refer to section 5 for full list of exclusion criteria) | 1. Has received more than one systemic treatment for steroid refractory aGvHD.<br>2. Clinical presentation resembling *de novo* chronic GvHD or GvHD overlap syndrome with both acute and chronic GvHD features (as defined by Jagasia, et al. 2015).<br>3. Failed prior alloHSCT within the past 6 months.<br>4. Presence of an active uncontrolled infection including significant bacterial, fungal, viral or parasitic infection requiring treatment. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.<br>5. Evidence of uncontrolled viral infection including CMV, EBV, HHV-6, HBV, or HCV based on assessment by the treating physician.<br>6. Presence of relapsed primary malignancy, or who have been treated for relapse after the alloHSCT was performed, or who may require rapid immune suppression withdrawal as pre-emergent treatment of early malignancy relapse.<br>7. Previous participation in a study of any investigational treatment agent within 30 days of randomization or within 5 half-lives of the investigational treatment agent, whichever is greater. |

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| Investigational and reference therapy | Ruxolitinib (INC424) 10 mg orally BID |
| Efficacy assessments | The primary and key secondary endpoints of the trial will be based on:<br>• Improvement or resolution of aGvHD manifestations (measures of body surface area aGvHD skin rash, stool volumes or frequency per 24h time period, and serum bilirubin levels)<br>• Reduction or cessation of required systemic corticosteroids<br>• Occurrence of graft failure<br>• Any progression or recurrence of the underlying hematologic disease for which the alloSCT has been performed including malignancy progression or relapse<br>• Incidence of chronic GvHD |
| Safety assessments | Safety assessments include:<br>• Adverse events<br>• Laboratory assessments<br>• Physical examination<br>• Vital signs<br>• Occurrence of any life-threatening infections:<br>• Occurrence of cytopenia<br>• Occurrence of hypertension<br>• Occurrence of bleeding<br>• Occurrence of any second primary malignancies |
| Other assessments | Other assessments include:<br>• Collection of PK data in order to assess exposure data and determine how it compares with data from previous studies, [redacted]<br>• To assess exposure-response relationship of ruxolitinib in SR-aGvHD [redacted]<br>• Patient-reported quality of life (QoL) [redacted] |
| Data analysis | The following statistical hypotheses will be tested to address the primary objective:<br>$H_0: ORR_{rux} \leq ORR_{BAT}$ vs. $H_1: ORR_{rux} > ORR_{BAT}$<br>where $ORR_{rux}$ and $ORR_{BAT}$ are the overall response rates at Day 28 in the ruxolitinib and BAT groups, respectively. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor (i.e., aGvHD Grade II vs III vs. IV), will be used to compare ORR between the two treatment groups, at the one-sided 2.5% level of significance.<br>Analysis of primary and key secondary endpoints will occur when all patients have completed the Day 56 visit or discontinued study treatment. [redacted] No interim analysis or design adaptations are planned. Further analyses on safety and efficacy endpoints will be performed when all patients have completed approximately 6 months treatment after randomization or discontinued earlier. Patients will be followed long-term to assess survival, non-relapse mortality, event free survival, hematologic disease progression or relapse, graft failure, occurrence of cGvHD, and occurrence of any second primary malignancies up to 24 months after randomization. |
| Key words | Acute Graft vs. Host Disease<br>Steroid Refractory<br>Allogeneic Stem Cell Transplantation<br>Stem Cell Transplantation<br>JAK inhibitor |

# 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 (the host) as foreign, thereby initiating an adverse immune reaction leading to an inflammatory cascade with resultant tissue damage, organ failure, or even death. Risk factors for GvHD include donor/recipient Human Leukocyte Antigen (HLA) mismatch, use of peripheral blood stem cells/bone marrow from an HLA matched unrelated or HLA mismatched related donor, multiparous female donor to male recipient, and advanced age of the donor or the recipient. GvHD presents as 2 distinct entities, namely acute GvHD (aGvHD) and chronic GVHD (cGvHD) with distinct clinical manifestations and separation by time of occurrence. Approximately 32,000 alloSCT procedures are performed world-wide annually with approximately 19,000 patients experiencing either aGvHD or cGvHD or both (Niederwieser 2016).

aGvHD is characterized by high levels of pro-inflammatory cytokines (e.g. tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, and interferon [IFN]-γ) which enhance activation and proliferation of donor effector T cells (Ferrara 2009). aGvHD occurs in 30-50% of HLA matched related alloSCT and in 50-70% of HLA matched unrelated alloSCT recipients with signs and symptoms observed generally within 100 days after infusion of allogeneic grafts including donor bone marrow (BM), mobilized peripheral blood stem cells (mPBSC), or umbilical cord blood (UCB). This fairly high incidence of aGvHD is seen despite prophylaxis with two or more immunosuppressive agents such as calcineurin inhibitors (cyclosporine, tacrolimus), short-course methotrexate, mycophenolate mofetil, high-dose cyclophosphamide post-transplant, and anti-thymocyte globulin (ATG).

aGvHD target organs include the skin, liver, upper and lower GI tract, with signs and symptoms including the following: maculopapular skin rash, erythroderma, nausea, vomiting, secretory diarrhea, cholestasis, hyperbilirubinemia, and/or jaundice. aGvHD severity is scored by standard criteria that incorporate severity of individual organ signs and symptoms as well as number of organs affected. Grading systems have evolved over 40 years of alloSCT with the initial widely adopted Glucksberg grading system (Glucksberg 1974) updated by the NIH consensus group adding upper GI involvement to the overall GvHD grading (Przepiorka 1995). In addition, further refinement of the NIH consensus grading has been widely adopted that allows either measurement of the frequency of stools or the stool volume in staging lower GI involvement in aGvHD (Harris 2016). The extent of individual organ staging and overall grade of aGvHD is assessed at presentation as this is an important prognostic indicator. Biopsies of affected organs are often obtained in attempt to rule out non-GvHD etiologies. Histologic evaluations of affected organs are highly specific with however very low sensitivity (<60%), and as such aGvHD remains a clinical diagnosis based on careful integration of all available

clinical information (Ross 2012). Please refer to Appendix 1 for NIH consensus aGvHD organ staging and overall grading criteria.

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

GvHD is a disease of adults and pediatric patients. In fact, a large proportion of pediatric patients undergo alloSCT for treatment of malignancy and a rising number receive alloSCT for non-malignant diseases including bone marrow failure, immunodeficiency, hemoglobinopathies, and inherited metabolic disorders. The incidence of Grade II-IV aGvHD in adolescent patients aged 12-18 years approximates 5% of that observed in adults >18 years (CIBMTR data). As 32,000 alloSCT procedures are performed each year (Niederwieser 2016), approximately 1,600 adolescent patients aged 12-18 years develop Grade II-IV aGvHD with up to 800 of these patients considered at risk for the development of Steroid-Refractory aGvHD (SR-aGvHD) annually. All Grade III-IV aGvHD adult and pediatric patients regardless of frontline corticosteroids have high mortality risk (< 20% EFS at 5 years) (Holtan 2015).

Effective treatment for aGvHD represents a high unmet medical need, particularly in patients with Grade II-IV. While long-term survival following Grade I aGvHD is >90%, it is 80%, 30%, and <10% for Grades II, III, and IV, respectively (Cahn 2005). Systemic corticosteroids are standard of care (SOC) in initial stages of the disease in patients with Grade II-IV aGvHD. Corticosteroids are started with methylprednisolone 2 mg/kg/day (or equivalent prednisone dose 2.5 mg/kg/day) per European Bone Marrow Transplant (EBMT) guidelines (Ruutu 2014), and are tapered as soon as clinical improvement is observed. Calcineurin inhibitor (CNI) prophylaxis, either cyclosporine or tacrolimus, is continued during aGvHD treatment and is tapered off by 6 months after transplantation in responding patients. A flare of aGvHD often occurs after steroid tapering begins. If the flare is determined to be cGvHD with overlap syndrome, standard treatment of cGvHD with immunosuppressive therapy is initiated. If cGvHD is not present, the steroid doses are increased to treat aGvHD and the taper resumed once the aGvHD is controlled. Treatment is continued until all signs of aGvHD have resolved.

As systemic high-dose corticosteroids are immunosuppressive, patients with aGvHD are at a very high risk for life-threatening opportunistic infections that account for one third of deaths after alloSCT (Young 2008). This has prompted development and validation of a grading system based on severity of infection that is predictive of mortality in alloSCT patients (Cordonnier 2006). Administration of high-dose systemic corticosteroids for aGvHD is associated with an increased risk of bacteremia, viral reactivation including cytomegalovirus (CMV), Epstein Barr virus (EBV), human herpes virus 6 (HHV-6), hepatitis B (HBV) and C (HCV), herpes zoster virus, invasive aspergillosis, and mold infection–related death. Treatment of aGvHD therefore includes rapid taper of corticosteroids when response is observed, to minimize the risk of life-threatening infections. Aggressive antimicrobial prophylaxis is also standard of care for patients with aGvHD receiving systemic steroid therapy as signs and

symptoms of infection are often masked. Prophylactic or pre-emptive antiviral therapy or both are used to avoid viral diseases. Patients are closely monitored for any evidence of active viral infection by testing peripheral blood viral copy number (e.g. viral load by DNA titer) rather than just reliance on viral serologies that do not provide information as to whether an active viral infection is present. Peripheral blood DNA titer is therefore used to guide prophylaxis and pre-emptive therapy, including EBV, HBV, HHV-6, HCV, and CMV.

Approximately 50% of Grade II-IV aGvHD patients do not show adequate response to initial treatment with high dose systemic corticosteroids and are termed Steroid Refractory (SR) (Jamil 2015). The European Bone Marrow Transplant (EBMT) group has established clear guidelines for the definition of SR-aGvHD (no response to systemic corticosteroids after 7 days or clear progression after at least 3 days of treatment). SR-aGvHD is nearly always fatal, either from organ damage or from opportunistic infection as a consequence of high dose steroid treatment. Second line treatments that are currently used for Grade II-IV SR-aGVHD are mostly off-label and although they demonstrate initial responses in approximately 50% of patients, they are associated with aGvHD flare during attempted steroid taper. These second line treatments include the following: anti-thymocyte globulin (ATG), extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. Management of aGvHD flare necessitates administration of further high dose systemic corticosteroids over a more prolonged time period and/or additional new systemic immunosuppressive therapy leading to life-threatening infections, and/or malignancy recurrence, with resultant two year survival rates ranging only approximately 20-30% (Martin 2012).

No standard second line treatment has been established for SR-aGvHD and of the systemic therapies that have been investigated in this setting spanning four decades, no specific agent has been shown to exert superior efficacy (Martin 2012). As a result, the selection of a second line treatment is therefore made based on physician preference, taking into account the effects of prior treatments, desired toxicity profile, considerations for drug interactions, convenience and cost. As such, the development of novel treatments that are associated not only with high response rates, but also durable control of aGvHD to allow successful steroid taper, would be highly beneficial for patients with SR-aGvHD.

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

### 1.2.1 Overview of ruxolitinib

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

Dysregulated JAK-STAT signaling, via upregulation of JAK1 and JAK2 or gain of function mutations such as JAK2V617F, has been implicated as a driver of BCR-ABL-negative myeloproliferative neoplasms (MPNs), namely myelofibrosis (MF), polycythemia vera (PV)

and essential thrombocythemia (ET). Ruxolitinib, which is jointly developed in hematology/ oncology and Graft-vs-Host Disease indications by Novartis Pharma AG (Switzerland) and Incyte Corporation (USA), specifically binds to and inhibits JAK1, JAK2 and mutated JAK2V617F, leading to inhibition of growth factor-mediated cell signaling and tumor cell proliferation. Given this mechanism of action of ruxolitinib as a JAK inhibitor and the role played by dysregulation of the JAK pathway in the pathogenesis of MPNs, the primary clinical development plan for ruxolitinib initially focused on studies to support regulatory approval in these disorders. Ruxolitinib has been granted marketing authorization approval for the treatment of patients with myelofibrosis including primary MF, post PV-MF or post ET-MF and for the treatment of patients with PV who are resistant to or intolerant of hydroxyurea.

Of relevance to aGvHD**,** inhibition of JAK1/2 signaling results in reduced proliferation of donor effector T cells, suppression of pro-inflammatory cytokine production in response to alloantigen, as well as impairment of antigen presenting cells *in vitro* and *in vivo* (Betts 2011). *In vivo* JAK1/2 inhibition by ruxolitinib has been shown to improve survival of mice developing aGvHD and to reduce histopathologic GvHD grading, serum levels of pro-inflammatory cytokines, and expansion of allo-reactive luc-transgenic T cells (Spoerl 2014). Furthermore, ruxolitinib impairs differentiation of CD4 T cells into IFN-gamma– and IL17A-producing cells; both T-cell phenotypes are linked to aGvHD pathophysiology (Parampalli 2015). 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).

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

As of 22 Feb 2018, approximately 13,730 patients have received ruxolitinib treatment in Novartis- and Incyte-sponsored investigational clinical trials.

#### 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 (IB).

### 1.2.1.2 Clinical experience

Ruxolitinib has been administered to approximately 430 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 22 Feb 2018, approximately 13,730 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

Fifteen Phase I, nine Phase II and three Phase III registration/pivotal studies clinical studies (two in MF, one in PV) provided clinical pharmacology data on ruxolitinib in healthy volunteers and in patients with MF, ET, PV, as well as in subjects with renal or hepatic impairment, prostate cancer, pancreatic cancer, multiple myeloma (MM), or rheumatoid arthritis (RA). Oral absorption of ruxolitinib is rapid and nearly complete, with ≥95% absorption indicating high *in vivo* permeability in the human gastrointestinal tract, consistent with a Biopharmaceutical Classification System (BCS) Class I compound. Mean peak plasma concentrations (Cmax) is achieved 1-2 h post-dose.

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

Plasma protein binding is approximately 97% *in vitro*. There is moderate distribution to organs and tissues with no long-term retention of drug-related material in preclinical species and limited drug penetration into the central nervous system (CNS) or across the blood-brain barrier. There is >95% [$^{14}$C] drug recovery in a mass balance study with 74% and 22% of the dose excreted in urine and feces of healthy subjects, respectively. Less than 1% of the administered dose is recovered in urine and feces as unchanged parent drug. The mean terminal elimination half-life (T1/2) is ~3 h with no appreciable accumulation of either parent or metabolites with twice daily dosing. Metabolism is predominantly via the cytochrome P450 isozyme CYP3A4

to yield oxygenated and subsequent conjugated metabolites. Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with one half to one fifth of the activity of the parent compound. *Ex vivo* pharmacokinetic/pharmacodynamic analysis indicates that the total of 8 active metabolites contribute to 18% of the overall pharmacodynamic activity of ruxolitinib. When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%. No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers. No dose adjustment is necessary when co-administering ruxolitinib with CYP3A4 substrates. Ruxolitinib did not decrease the exposure of a fixed dose oral contraceptive metabolized via the CYP3A4 pathway, thus demonstrating lack of CYP3A4 induction potential.

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

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

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

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

#### 1.2.1.2.2 Summary of Clinical Efficacy and Safety Data

The results from two phase III registration studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of ruxolitinib in patients with PMF, PPV-MF and PET-MF. The results of these two studies were consistent, demonstrating statistically significant differences in rates of ≥35% spleen volume reduction 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.

Long term outcomes such as OS, Leukemia-Free Survival (LFS), duration of response and safety were reassessed at different time points, most recently in 2015 (5-year follow up report), comparing the patients originally randomized to the ruxolitinib arm to those that were randomized to the control arm. The 5-year follow-up report for COMFORT-I suggested longer survival for patients randomized to ruxolitinib versus control arm patients, with a hazard ratio of 0.693 (95% confidence interval [CI]: 0.503, 0.956, p = 0.0245). In COMFORT-II, long term follow-up also suggested a survival advantage with ruxolitinib treatment compared with BAT. There was a 33% reduction in the risk of death for patients treated with ruxolitinib compared with that for patients treated with BAT (hazard ratio [HR] = 0.67; 95% CI, 0.44-1.02). The estimated survival probability at 5.0 years was 56% (95%CI: 0.40, 0.62) in the ruxolitinib arm and 44% (95%CI: 0.31, 0.56) in the BAT arm. Safety profile in the two studies remained broadly unchanged. There were no new or unexpected safety signals that occurred with the longer treatment exposure and follow-up period.

Consistent with its activity in myelofibrosis, ruxolitinib demonstrated in the RESPONSE pivotal study its efficacy in polycythemia vera patients who are resistant to or intolerant of hydroxyurea. Significantly more patients randomized to ruxolitinib than patients randomized to BAT met the primary endpoint (hematocrit control and at least 35% spleen volume reduction) at Week 32: 23% vs 0.9%, respectively ($p < 0.0001$). More patients randomized to ruxolitinib achieved hematocrit control at Week 32 when compared to patients randomized to BAT: 60.0% (95% CI: 50.2, 69.2) vs 18.75% (95% CI: 12.7, 28.2), respectively. More patients randomized to ruxolitinib achieved at least 35% spleen volume reduction at Week 32 when compared to patients randomized to BAT: 40% (95% CI: 29.1, 47.9) vs 0.9% (95% CI: 0.0, 4.9), respectively. The great majority of these responses in the ruxolitinib arm were also durable at Week 48. Furthermore, significantly more patients randomized to ruxolitinib achieved the key secondary endpoint of complete hematological remission (hematocrit control, platelet count $\leq 400\times10^9$/L, and WBC count $\leq 10\times10^9$/L) at Week 32 when compared to patients randomized to BAT: 23.6% vs 8.0%, respectively ($p=0.0028$, when adjusted for baseline platelet and WBC status). The study is still ongoing and will continue for a total of 5 years.

In GvHD, two recent independent publications have reported encouraging early clinical data with ruxolitinib in SR-aGvHD and SR-cGvHD. The first included data from 6 SR-aGvHD patients who received an initial ruxolitinib dose of 5 mg BID that was advanced to 10 mg BID after 3 days when no side effects were observed (Spoerl 2014). Responses to ruxolitinib treatment in terms of improved GvHD grades and reduction of required corticosteroids were observed in all patients; no patient experienced GvHD flare during steroid taper requiring additional systemic therapy. Further early clinical experience with ruxolitinib in patients with SR-aGvHD was recently reported in a retrospective study that gathered experience in 95 SR-

GvHD patients from 19 stem cell transplant centers (Zeiser 2015). In this study, 54 patients with SR-aGvHD (all severe Grade III/IV) who had received a median of 3 previous GvHD therapies (range 1-7) received a ruxolitinib dose of 5-10 mg BID. Dose reductions were generally not required for worsening cytopenias after initiation of ruxolitinib therapy. The Overall Response Rate (ORR) in SR-aGvHD was 81.5% which included 46.3% of patients demonstrating complete remission (CR). Median time to response was 1.5 weeks (range 1-11). Flare of aGvHD was observed in only 6.8% (3/44) of ruxolitinib-responsive patients during steroid taper. GvL was maintained with only 5 of 54 patients (9.3%) demonstrating relapse of the underlying malignancy. The 6-month survival estimate was 79% (67.3-90.7% CI). Safety profile of ruxolitinib in SR-aGvHD was generally favorable. Although cytopenias were observed in 55.5% of SR-aGvHD patients, cytopenias preceded ruxolitinib administration in 51.8% of these patients. CMV reactivation was observed in 30% of SR-aGvHD patients treated with ruxolitinib. This incidence rate compares favorably with that reported with other second line aGvHD agents including MMF, alemtuzumab, and others where CMV reactivation ranges from 70 to 80% (Rager 2011).

# 2 Rationale

## 2.1 Study rationale and purpose

The scientific rationale for this study of ruxolitinib in adults and adolescents with Grade II-IV SR-aGvHD is based on current knowledge of aGvHD pathophysiology that begins with activation of host antigen-presenting cells (APC) by danger signals expressed by damaged tissues and/or pathogens. Activated host APC then present host antigens to donor immune cells, leading to donor T-cell proliferation and inflammatory cytokine production. These inflammatory cytokines then recruit and induce proliferation of additional immune effector cells, thereby perpetuating an adverse cycle of allo-reactive tissue injury and inflammation (Paczesny 2010). Ruxolitinib has been shown to lower pro-inflammatory cytokines in MF patients. In addition, pre-clinical data support the mechanism of action of ruxolitinib in GvHD to: *i*.) impair APC function, *ii*.) inhibit donor T cell proliferation, *iii*.) suppress adverse cytokine production, and *iv*.) improve survival and disease manifestations in GvHD mouse models (Parampalli 2015, Heine 2013, Spoerl 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 (Zeiser 2015; Spoerl 2014), provides strong rationale to test the hypothesis that ruxolitinib added to immunosuppression therapy for SR-aGvHD 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 steroid 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 Grade II-IV SR-aGvHD.

Very few prospective comparative studies have been carried out to assess the efficacy and safety of currently used second-line therapy for aGvHD. A randomized study is necessary to determine whether administration of ruxolitinib in patients with SR-aGvHD provides better efficacy when compared to BAT and whether control of the underlying hematologic disease for which alloSCT is performed is maintained during steroid taper.

In addition, as SR-aGvHD is associated with a very high mortality rate, including early mortality (i.e. within 30 days) attributable primarily to infection, hematologic disease progression or recurrence during prolonged administration of high dose systemic corticosteroids, and clinically meaningful longer term outcomes such as non-relapse mortality, event free survival, malignancy relapse and overall survival will be followed in each study arm.

Investigator choice BAT is chosen as comparator as currently no treatment for SR-aGvHD is approved in either the United States of America (US) or European Union (EU) 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. Patients will be randomized 1:1 to receive either ruxolitinib or BAT, stratifying on GvHD grade (Grade II vs. III vs. IV). The choice of BAT will be decided by the Investigator before randomization in this study. The open label design of this study is necessary to accommodate the variety of treatments for Grade II-IV SR-aGvHD that may be considered as Investigator's choice BAT, as these vary from administered tablets to cellular therapy and photopheresis, as well as the necessity of using frequent additional new immunosuppressive treatments, modifications, and dose adjustments in these therapies depending on the patient's response. This design is well established in the alloSCT field and in SR-aGvHD, particularly.

Grade II-IV SR-aGvHD adult and adolescent patients age ≥12 years are included in this study as mortality rates are unacceptably high for these patients. Furthermore, data from a phase I study in pediatric patients show that safety of ruxolitinib was generally favorable and their PK data comparable to adults (Loh 2015), hence the same ruxolitinib dosing approach would be used.

Adolescents age ≥12 years comprise approximately 5% of the adult and pediatric aGvHD population (CIBMTR data) and standard treatment does not differ between adolescents and adults. Mortality risks for all adults and adolescents with SR-aGvHD are a continuum, with no age breakpoint, with only approximately 49% of all patients surviving beyond 6 months after alloSCT (Martin 2012). This high mortality risk represents a significant unmet medical need not only for adult patients but also adolescents. Pediatrics patients <12 years of age will be considered for future studies following discussion and agreement with the Paediatric Committee (PDCO) using ruxolitinib liquid formulation currently under development.

The rationale to stratify patients at the time of enrollment and randomization is based on the fact that response rates are variable in patients with different GVHD grades. Grade II vs. Grade III vs. Grade IV disease severity by standard grading criteria also correlates with long-term survival. In a recent randomized Phase II study of aGvHD, the relative risk of non-relapse mortality (NRM) was 1.72 (95% confidence interval 1.13–2.59) for patients with Grade III–IV compared to patients with aGvHD Grade II or lower (Levine 2010).

Multiple measures will be used in this study to reduce bias. First, addition of new systemic immunosuppressive therapy for patients meeting progression, mixed response, or no response

criteria, or aGvHD flare failure in either of the two treatment arms is considered a treatment failure, in order to prevent subjective addition of new therapy in either of the two treatment arms.. Second, the primary and key secondary endpoints of the trial will be based on objective measures of body surface area aGvHD skin rash, stool volumes or frequency per 24h time period, and serum bilirubin levels, and these objective measures are delineated by standard criteria (Harris 2016). Third, in order to minimize the potential for differential steroid tapering of BAT and ruxolitinib, recommendations for dose increases of systemic corticosteroids to manage aGvHD flares as well as steroid dose tapering per standard guidelines in the field are provided.

A Screening period is planned to start at the time of Grade II-IV aGvHD diagnosis to allow sufficient time to obtain results of required tests and ensure that all eligibility criteria are met. Confirmation of eligibility during Screening allows rapid enrollment of patients in the event that steroid refractory status is documented (e.g. no response to standard doses of systemic corticosteroids after 7 days or clear progression after at least 3 days). This approach allows rapid randomization and initiation of study treatment required for these patients, which is critical to management of rapidly progressive SR-aGvHD.

The study's primary endpoint, overall response rate (ORR) without requirement for addition of new systemic immunosuppressive treatment will be assessed after 28 days of therapy, as Day 28 ORR has been shown to correlate best with subsequent long-term survival (Levine 2010). A key secondary endpoint is to compare the ORR at Day 56 after randomization between ruxolitinib vs. BAT, in order to assess the durability of the primary response.

The treatment phase will allow assessment of patient benefit and risk in terms of: *i*.) improvement or resolution of aGvHD manifestations, *ii*.) reduction or cessation of required systemic corticosteroids, *iii*.) any progression or recurrence of the underlying hematologic disease for which the alloSCT has been performed including malignancy progression or relapse (refer to Appendix 4), *iv*.) occurrence of any life-threatening infections, *v*.) occurrence of any graft failure, *vi*.) occurrence of chronic GvHD, *vii*.) occurrence of bleeding, *viii*.) duration of hospitalization and frequency of hospital readmissions for management of aGvHD and/or infections, and *ix*.) patient-reported quality of life (QoL).

Analysis of primary and key secondary endpoints will occur when all patients have completed the Day 56 visit or discontinued study treatment. This analysis will be assessed and considered for regulatory filing. No interim analysis or design adaptations are planned. Further analyses on safety and efficacy endpoints will be performed when all patients have completed approximately 6 months treatment after randomization or discontinued earlier. Patients will be followed long-term to assess survival, NRM, EFS, hematologic disease progression or relapse, graft failure, occurrence of cGvHD, and occurrence of any second primary malignancies up to 24 months after randomization. A final study report will be written when all patients have completed the study or discontinued from the study.

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.

[redacted]

## 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 PO BID. The starting dose is based on the preliminary efficacy and safety data generated with this dose in patients with SR-GvHD (Zeiser 2015). The dose administered in this study is lower than that generally administered in MF patients (15-20 mg BID), as these alloSCT patients with SR-aGvHD will routinely be treated with concurrent calcineurin inhibitors (CNI) and azole prophylaxis which can inhibit the metabolism (via CYP3A4) of ruxolitinib, potentially increasing its exposure.

The 10 mg BID dose will be the same in adolescents as in adult patients. This is supported by published literature showing that adolescents have similar toxicity profiles, maximum tolerated doses, and pharmacokinetic parameters compared to adults, as well as safety and PK data of ruxolitinib from a Phase I study in pediatric patients with various malignancies (Loh 2015). In the latter study, 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.

Ruxolitinib may be taken without regard to food except on days when PK samples are drawn; on those days patients are instructed to fast and refrain from taking ruxolitinib until PK samples are collected.

Patients may have dose reductions or modifications of ruxolitinib during the course of treatment based on adverse events, clinical evaluation, and laboratory assessments. 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 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-aGvHD. 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 patient randomization among the following standard systemic treatments: anti-thymocyte globulin (ATG), extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. No other BAT will be allowed.

## 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 6.1.5.1 and Section 6.3. 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's Brochure.

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

Important identified and potential risks from ruxolitinib 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-aGvHD.

**Myelosuppression:** Myelosuppression is a common occurrence in alloSCT patients with incidence higher at earlier time points when SR-aGvHD occurs, e.g. first 6 weeks after graft infusion. Myelosuppression is observed prior to and during early donor engraftment, and in the setting of CMV reactivation as well as HHV-6 infection. In addition, medications used to treat these viral infections, particularly gancyclovir, are associated with myelosuppression. Case series in acute and chronic GvHD have identified worsening of myelosuppression in approximately 10-20% of GvHD patients treated with ruxolitinib at doses ranging 5-10 mg orally BID spanning several months (Zeiser 2015). This was managed with dose reduction of ruxolitinib to 5 mg orally BID and required holding ruxolitinib in some patients whose ANC dropped below 500/mm$^3$.

Myelosuppression is manageable in SR-aGvHD patients by keeping the starting dose comparatively lower than in MF (10 mg orally BID) and not allowing dose escalation above this starting dose. Dose adjustment or dose holding is based on ANC and platelet count (see Table 6-3). Patients will also be closely monitored for any evidence of secondary graft failure defined as initial whole blood or marrow donor chimerism $\geq$5% declining to <5% on subsequent measurements. In the Phase III clinical protocols in MPN patients, the concurrent use of hematopoietic growth factors was discouraged, but not prohibited. These same guidelines apply to this study as potential benefit of hematopoietic growth factors may exceed any risk. Administration of hematopoietic growth factors will be allowed per Investigator judgement.

**Bleeding:** Hemostatic disturbances are common in patients undergoing alloSCT and have a significant impact on morbidity and mortality. aGvHD correlates strongly with the incidence and severity of bleeding episodes. Ruxolitinib dose adjustment or dose holding will be based on platelet count (see Table 6-3) and platelet transfusions may be given as clinically indicated.

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

**Use in patients with renal impairment:** Renal impairment is a common occurrence in patients with SR-aGvHD due to episodes of mild dehydration attributable to GI involvement in the outpatient setting causing decreased oral intake as well as concurrent administration of CNI.

AlloSCT patients with severely impaired renal function are excluded from enrollment. Diagnostic evaluation and management of renal impairment in SR-aGvHD patients will follow institutional guidelines.

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

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

**Tuberculosis:** Tuberculosis (TB) is very rare in alloSCT patients as all patients are carefully screened prior to the transplant procedure and are not allowed to undergo alloSCT if TB is present. SR-aGvHD 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. Ruxolitinib therapy will not be administered in any patient with an active TB infection.

**Progressive Multifocal Encephalopathy:** Progressive multifocal leukoencephalopathy (PML) is a rare complication in alloSCT recipients. The median time from transplantation to symptom onset has been reported as 11 months, while median time to symptom onset has been notably shorter in other viral encephalitis in this population. These other viral entities, including HHV-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 risk of PML in SR-aGvHD 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.

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

**Safety in pediatric patients:** In a Phase I study, ruxolitinib with BID continuous oral dosing in children aged 2.4–21.4 (median 14.4) years with refractory/recurrent solid tumors (ST) and hematologic malignancies was well tolerated and showed similar pharmacokinetics to those in adults. No maximum tolerated dose was reached and the recommended dose for continuous BID oral administration was 50 mg/m$^2$/dose (Loh 2015).

# 3 Objectives and endpoints

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

**Efficacy assessments**:

aGvHD response assessment will be made with respect to the organ stage at the time of randomization and, in patients entering the Cross-Over Treatment Period, with respect to the last available organ stage prior to or at the time of cross-over**:**

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

Patients requiring additional systemic therapy for aGvHD will be classified as non-responders.

**aGvHD Flare** is defined as any increase in signs or symptoms of aGvHD that is sustained for >24h after an initial response (CR or PR) and requires re-escalation of immunosuppressive therapy (e.g. corticosteroid, CNI, BAT and/or ruxolitinib dosing). While all aGvHD flares will be captured on study whether occurring during steroid, CNI, BAT, or ruxolitinib taper, only flares that fulfil either one the following criteria will be considered a failure of treatment:

1. Addition of new systemic therapy for aGvHD due to inability to taper corticosteroids below methylprednisolone 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone) for a minimum 7 days,

   **OR**

2. Addition of new systemic therapy for aGvHD due to re-escalation of corticosteroids to methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone).

aGvHD assessments will be performed by the treating team according to standard criteria (Harris 2016) as described in Appendix 1. Disease assessments must be performed per the schedule of visits after randomization, unless the patient meets any of the criteria for discontinuation of study treatment (see Section 7.1.5), withdraws consent, dies, or is lost to follow up.

After randomization, signs and symptoms of cGvHD may be observed. cGvHD signs and symptoms may occur in up to 50% of patients based on published literature. Patients will be evaluated for any signs or symptoms of cGvHD and scored using NIH Consensus Criteria (Lee 2015) as described in Appendix 3. Development of cGvHD signs or symptoms is not considered a treatment failure of aGvHD. Treatment of cGvHD will follow institutional standards of procedure and Investigator preference. Ruxolitinib will not be administered for treatment of cGvHD. For patients receiving ruxolitinib at the time of onset of cGvHD, ruxolitinib taper will follow guidelines per Section 6.1.5.1.

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

**Table 3-1 Objectives and related endpoints**

| Objective | Endpoint | Analysis |
|---|---|---|
| Primary | | Refer to Section 10.4 |
| To compare the efficacy of ruxolitinib vs. Investigator's choice Best Available Therapy (BAT) in patients with Grade II-IV SR-aGvHD assessed by Overall Response Rate (ORR) at Day 28 | Overall response rate (ORR) at Day 28 after randomization, defined as the proportion of patients in each arm demonstrating a complete response (CR) or partial response (PR) without requirement for additional systemic therapies for an earlier progression, mixed response or non-response. Scoring of response will be relative to the organ stage at the time of randomization. | CMH analyses, stratified by aGvHD grade |
| Key secondary endpoint | | Refer to Section 10.5.1 |
| To compare the rate of durable ORR at Day 56 between ruxolitinib and BAT | Proportion of all patients in each arm who achieve a complete response (CR) or partial response (PR) at Day 28 and maintain a CR or PR at Day 56. | CMH analyses, stratified by aGvHD grade |
| Other secondary endpoints | | Refer to Section 10.5.2 |
| To estimate ORR at Day 14 | Proportion of patients who achieved OR (CR+PR) at Day 14. | |
| To assess Duration of response | Duration of response (DOR) is assessed for responders only and is defined as the time from first response until aGvHD progression or the date of additional systemic therapies for aGvHD. Onset of chronic GvHD, or death without prior observation of aGvHD progression are considered as competing risks. | |
| To assess the cumulative steroid dose until Day 56 | Weekly cumulative steroid dose for each patient up to Day 56 or end of treatment will be calculated. | |
| 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. | Probability of overall survival at Months 1, 2, 6, 12, 18 & 24 will be estimated from the Kaplan-Meier curves for each arm. |
| To assess Event-Free Survival (EFS) | Event-free survival, defined as the time from the date of randomization to the date of hematologic disease relapse/progression, graft failure, or death due to any cause. | Probability of EFS at Months 1, 2, 6, 12, 18 & 24 will be estimated from the Kaplan-Meier curves for each arm. |

| Objective | Endpoint | Analysis |
|---|---|---|
| To assess Failure-Free Survival (FFS) | Failure-free survival, defined as the time from the date of randomization to date of hematologic disease relapse/progression, non-relapse mortality, or addition of new systemic aGvHD treatment. | Cumulative incidence of FFS at Months 1, 2, 6, 12, 18 & 24 will be estimated, considering each event as a competing risk for the other two. Onset of chronic GvHD is considered as a competing risk. |
| 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 hematologic disease relapse/progression. | Cumulative incidence of NRM at Months 1, 2, 6, 12, 18 & 24 will be estimated, considering hematologic disease relapse/progression as competing events. |
| To assess incidence of Malignancy Relapse/Progression (MR) | Malignancy Relapse/Progression (MR) (refer to Appendix 4), defined as the time from date of randomization to hematologic malignancy relapse/progression. Calculated for patients with underlying hematologic malignant disease. | Cumulative incidence of MR at Months 1, 2, 6, 12, 18 & 24 will be estimated, considering deaths not preceded by hematologic malignancy relapse/progression as competing events. |
| To measure the incidence of cGvHD | cGvHD, defined as the diagnosis of any cGvHD including mild, moderate, severe. | Cumulative incidence of cGvHD at Months 1, 2, 6, 12, 18 & 24 will be estimated, considering hematologic disease relapse/progression and death without prior cGvHD as competing events. |
| To estimate the rate of Best Overall Response (BOR) | Proportion of patients who achieved OR (CR+PR) at any time point up to and including Day 28 and before the start of additional systemic therapy for aGvHD. | |
| To assess Pharmacokinetics (PK) of ruxolitinib in SR-aGvHD patients | Pharmacokinetic parameters of ruxolitinib after a single dose and at steady state. Cmax, AUClast, AUCinf, Ctrough, Racc and AUCtau. Other PK parameters are CL/F, Vz/F, Tmax and T1/2. | |
| To assess exposure-response relationship of ruxolitinib in SR-aGvHD | Pharmacokinetics (exposure) and efficacy (ORR, OS, or other relevant endpoints) relationship.<br>Pharmacokinetics (exposure) and safety (AEs) relationship. | |
| To evaluate changes in Patient Reported Outcomes (PROs) | Change in FACT-BMT from baseline to each visit where measured.<br>Change in EQ-5D-5L from baseline to each visit where measured. | |
| 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 | |

| Objective | Endpoint | Analysis |
|---|---|---|
| | primary malignancies, infections, by performing physical exams, and evaluating changes in vital signs from baseline, routine serum chemistry, hematology results and coagulation profile. | |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |
| [redacted] | [redacted] | |

# 4 Study design

## 4.1 Description of study design

This randomized, Phase III, open-label study will investigate the efficacy and safety of ruxolitinib vs. BAT added to the patient's immunosuppressive regimen in adults and adolescents (≥12 years old) with SR-aGvHD.

The randomization target for this study is 308 patients.

The study is comprised of 4 defined periods, as outlined below:

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

To facilitate rapid randomization and initiation of treatment once patients are diagnosed as steroid refractory, screening activities and assessment of inclusion and exclusion criteria should begin once the patient has been diagnosed with aGvHD and has signed the **Screening Informed Consent.** Any occurrence of Steroid-Refractory aGvHD will be monitored closely.

Steroid-Refractory aGvHD is defined as patients administered high-dose systemic corticosteroids (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]), given alone or combined with calcineurin inhibitors (CNI) either:

A. Progressing based on organ assessment after at least 3 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid +/- CNI for the treatment of Grade II-IV aGvHD,

   **OR**

B. Failure to achieve at a minimum partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid +/- CNI for the treatment of Grade II-IV aGvHD,

   **OR**

C. Patients who fail corticosteroid taper defined as fulfilling either one of the following criteria:
   1. Requirement for an increase in the corticosteroid dose to methylprednisolone ≥2 mg/kg/day (or equivalent prednisone dose ≥2.5 mg/kg/day)

      **OR**

   2. Failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days.

**Note**: Patients will receive systemic corticosteroids +/- continued CNI +/- other systemic treatment for aGvHD per standard of care by the Investigator during the Screening period. Systemic medications for aGvHD other than corticosteroids +/- CNI may be continued after randomization only if used for aGvHD prophylaxis (i.e. started before the diagnosis of aGvHD).

Patients meeting all eligibility criteria including one of the above criteria for Steroid-Refractory aGvHD (SR-aGvHD), may be consented to the Study Informed Consent**.** The Investigator must identify Investigator choice BAT prior to randomization.

Please refer to Section 7 for details on Screening Assessments including assessments to be performed during Screening and those to be performed after obtaining the study written informed consent.

Patients meeting all inclusion and exclusion criteria will be randomized 1:1 to receive either ruxolitinib or BAT stratifying on aGvHD grade at the time of randomization (Grade II vs. III vs. IV).

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

Study treatment will begin on Day 1, following randomization (preferably on the same day but no later than 72 h after randomization). Day 1 is the day of randomization.

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

- Weekly visits from Day 1 up to Day 56;
- 4-weekly visits (every 28 days) beyond Day 56 and until Week 24.
    - The End of Treatment (EOT) visit will occur at Week 24, or earlier in case the patient meets any of the criteria for discontinuation of study treatment (see Section 7.1.5).
        - Responding patients (i.e. obtaining a CR or PR) completing the dosing schedule for ruxolitinib or their assigned BAT at any time as per standard of care before Week 24 must continue to be assessed for all scheduled visits until Week 24.

While these patients will have their EOT visit at Week 24, they must also have assessments performed within 7 days of the last dose, either at a scheduled visit per Table 7-1 (if within 7 days) or as an unscheduled visit. The list of required assessments is detailed in Section 7.1.4.

- Should an aGvHD flare or other safety concerns prevent ruxolitinib taper from being completed by Week 24, the patient must continue to be assessed until the taper of ruxolitinib is complete, i.e. the EOT visit may be delayed until Week 96 at the latest. In this case, taper follow-up visits will occur every 8 weeks from Week 24 to Week 48, and every 12 weeks thereafter, as applicable.

Patients may be treated up to approximately 6 months (see Section 6 for Study Treatment details and permitted/prohibited concomitant therapies), or up to approximately 2 years from randomization, in case the end of ruxolitinib taper is delayed due to an aGvHD flare or other safety concerns.During the Treatment Period, patients randomized to BAT may be eligible to cross-over and receive ruxolitinib between Day 28 and Week 24 if they:

- Fail to meet the primary endpoint response definition (CR or PR) at Day 28

  **OR**

- Lose the response thereafter **AND** meet criteria for progression, mixed response, or no response, necessitating new additional systemic immunosuppressive treatment for aGvHD.

  **AND**

- Do not have signs/symptoms of cGvHD (overlap syndrome, progressive, or *de novo* cGvHD)

Patients who have crossed over from the BAT to the ruxolitinib arm between Day 28 and Week 24 will be followed until completion of treatment with ruxolitinib and will follow the same treatment and taper schedule as patients originally randomized to ruxolitinib treatment. Weekly assessments will be required for 56 days after initiation of ruxolitinib and 4-weekly assessments thereafter until Cross-Over Week 24.

- The Cross-Over EOT visit will occur at Cross-Over Week 24, or earlier in case the patient meets any of the criteria for discontinuation of study treatment (see Section 7.1.5).
    - Responding patients (i.e. obtaining a CR or PR) completing the dosing schedule for ruxolitinib at any time before Cross-Over Week 24 must continue to be assessed for all scheduled visits until Cross-Over Week 24.
        - While these patients will have their Cross-Over EOT visit at Cross-Over Week 24, they must also have assessments performed within 7 days of the last dose, either at a scheduled visit per Table 7-2 (if within 7 days) or as an unscheduled visit. The list of required assessments is detailed in Section 7.1.4.
- Should an aGvHD flare or other safety concerns prevent ruxolitinib taper from being completed by Cross-Over Week 24, the patient must continue to be assessed until the taper of ruxolitinib is complete, i.e. the Cross-Over EOT visit may be delayed until Cross-Over Week 96, or 2 years from randomization, whichever occurs first. In this case, taper follow-up visits will occur every 8 weeks from Cross-Over Week 24 to Cross-Over Week 48, and every 12 weeks thereafter as applicable.

Patients who meet cross-over criteria above and receive ruxolitinib are allowed to continue corticosteroids and CNI for aGvHD treatment as per standard of care, with cessation required of any other systemic immunosuppressive treatment prior to cross-over, unless used for aGvHD prophylaxis (i.e. started before the diagnosis of aGvHD).

Please refer to Section 7 for assessment details.

- **Safety Follow-Up (last dose + 30 days)**

A 30-day Safety Follow-Up visit will be done for all patients after the last dose of ruxolitinib or BAT at the end of the Treatment Period.

Note: for patients randomized to the BAT arm and crossing over to ruxolitinib, the Safety Follow-Up visit will only occur once, i.e. 30 days after the last dose of ruxolitinib in the Cross-Over Treatment Period.

Please refer to Section 7 for assessment details.

- **Long-Term Follow-Up Period (From EOT to Month 24)**

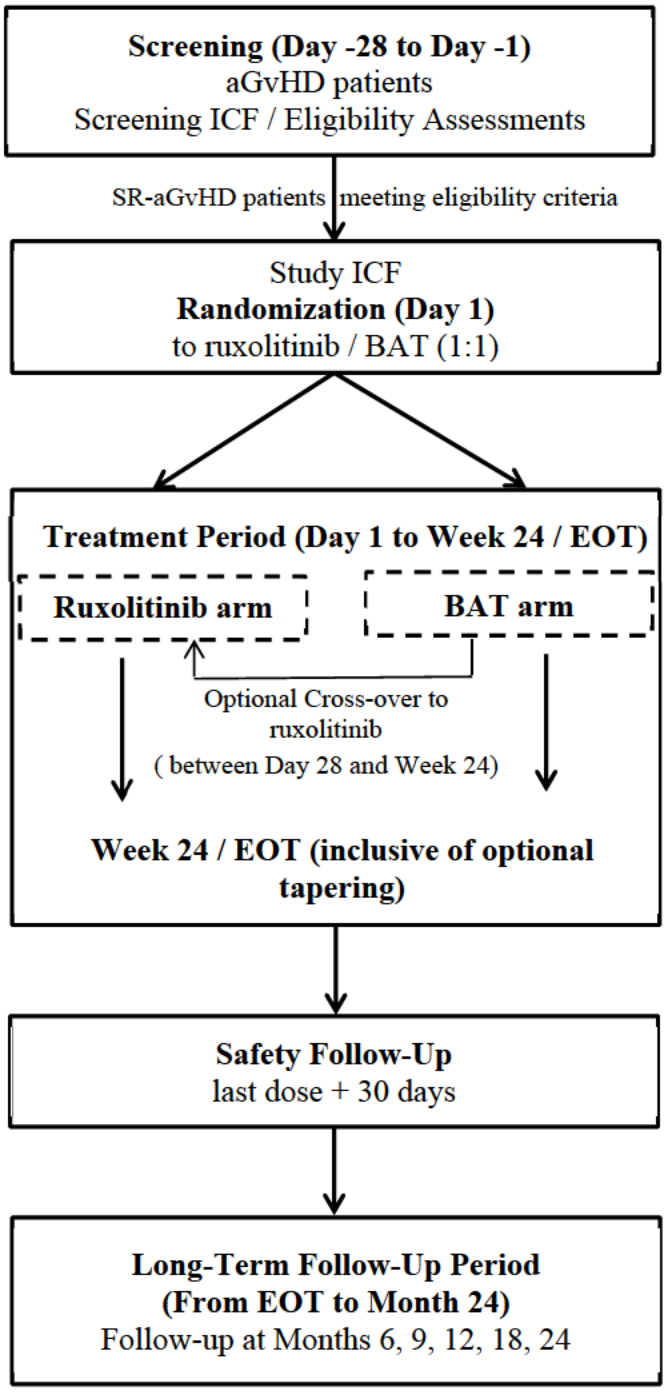
Recognizing that SR-aGvHD is a complication of alloSCT that often leads to death within 2 years after the procedure, and that assessment of long-term safety and durable efficacy is clinically meaningful, **all patients** (responders and non-responders in both arms, regardless of when treatment was discontinued) will be followed to collect long term data including: survival, any relapse/progression of the underlying hematologic disease for which the alloSCT procedure was performed (refer to Appendix 4), NRM, any occurrence of graft failure, EFS, any occurrence of cGvHD, and occurrence of any second primary malignancies.

Visits will be performed after EOT or Cross-Over EOT, at 6, 9, 12, 18, and 24 months from randomization (Day 1), as applicable, once the Treatment Period is completed.

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

Please refer to Section 7 for assessment details.

**Figure 4-1 Schematic Study Design**




## 4.2 Timing of interim analyses and design adaptations

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

## 4.3 Definition of end of study

End of Study (EoS) will occur when all patients have reached Month 24 (2 years from randomization), unless the patient withdraws consent.

The primary analysis including the analysis on primary and key secondary endpoints will be performed after all patients have completed Day 56 or discontinued from study participation earlier. The primary analysis data will be summarized in the primary clinical study report (CSR).

Further analyses on secondary endpoints will be performed when all patients have completed approximately 6 months treatment or discontinued from study participation earlier.

The final analysis will occur once all patients have completed the study (up to 24 months from randomization). All available data from all patients up to EoS, inclusive of OS, will be reported in a final CSR.

Patients who are still receiving ruxolitinib at their end of study (approximately 2 years from randomization), and deriving clinical benefit from ruxolitinib as assessed by the Investigator, will be given the possibility to continue ruxolitinib outside the study from another source, where permitted by and in accordance to local laws and regulations.

## 4.4 Early study termination

The study can be terminated at any time for any reason by Novartis or by a regulatory authority based on the occurrence of any of the following:

- New side effects unknown in respect to their nature, severity, and duration or unexpected incidence of known side effects.
- Medical or ethical reasons that affect the continued performance of the study.
- Further development of the study drug has been permanently discontinued due to safety reasons.
- Other reasons that are not known at this time.

Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.5 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 will include male or female patients aged 12 or older, who have undergone alloSCT, have evidence of myeloid and platelet engraftment (ANC >1,000/$mm^3$ AND platelet count >20,000/$mm^3$), and have been diagnosed with aGvHD requiring systemic treatment (Grade II-IV) which is determined to be steroid-refractory (Appendix 1).

This trial will have a two-step enrollment process as defined in Section 4:

1. Enrollment into the Screening segment will occur after a diagnosis of aGvHD requiring systemic treatment (Grade II-IV) and after the Screening informed consent form is signed
2. Randomization will occur when any one criterion for steroid-refractory disease is met, and the patient has signed the Study informed consent form.

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

## 5.2 Inclusion criteria

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

1. Written **Screening informed** consent and/or assent from the patient, parent, or guardian at the time of Screening, i.e. at the time of aGvHD Grade II-IV diagnosis.
2. Written **Study informed consent** and/or assent from the patient, parent, or guardian once SR-aGvHD is confirmed.
3. Male or female patients aged 12 or older at the time of Screening informed consent
4. Able to swallow tablets.
5. 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.
6. Clinically diagnosed Grades II to IV acute GvHD as per standard criteria (Appendix 1) occurring after alloSCT requiring systemic immune suppressive therapy. Biopsy of involved organs with aGvHD is encouraged but not required for study screening.
7. Evident myeloid and platelet engraftment (confirmed within 48h prior to study treatment start):
   - Absolute neutrophil count (ANC) > 1000/$mm^3$

     **AND**
   - Platelets ≥ 20,000/ $mm^3$

   **Note**: Use of growth factor supplementation and transfusion support is allowed.
8. Confirmed diagnosis of steroid-refractory aGvHD defined as patients administered high-dose systemic corticosteroids (methylprednisolone 2 mg/kg/day [or equivalent prednisone dose 2.5 mg/kg/day]), given alone or combined with calcineurin inhibitors (CNI) and either:
   A. Progressing based on organ assessment after at least 3 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid +/- CNI for the treatment of Grade II-IV aGvHD,

      **OR**
   B. Failure to achieve at a minimum partial response based on organ assessment after 7 days compared to organ stage at the time of initiation of high-dose systemic corticosteroid +/- CNI for the treatment of Grade II-IV aGvHD,

      **OR**
   C. Patients who fail corticosteroid taper defined as fulfilling either one of the following criteria:

1. Requirement for an increase in the corticosteroid dose to methylprednisolone ≥2 mg/kg/day (or equivalent prednisone dose ≥2.5 mg/kg/day)

**OR**

2. Failure to taper the methylprednisolone dose to <0.5 mg/kg/day (or equivalent prednisone dose <0.6 mg/kg/day) for a minimum 7 days.

## 5.3 Exclusion criteria

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

1. Has received more than one systemic treatment for steroid-refractory aGvHD,
2. Clinical presentation resembling de novo chronic GvHD or GvHD overlap syndrome with both acute and chronic GvHD features (as defined by Jagasia, et al. 2015)
3. Failed prior alloHSCT within the past 6 months.
4. Presence of an active uncontrolled infection including significant bacterial, fungal, viral or parasitic infection requiring treatment. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
5. Evidence of uncontrolled viral infection including CMV, EBV, HHV-6, HBV, or HCV based on assessment by the treating physician.
6. Evidence of active tuberculosis (clinical diagnosis per local practice; skin testing is not required as not informative due to anergy).
7. Known human immunodeficiency virus infection (HIV).
8. Presence of relapsed primary malignancy, or who have been treated for relapse after the alloHSCT was performed, or who may require rapid immune suppression withdrawal as pre-emergent treatment of early malignancy relapse.
9. SR-aGvHD occurring after non-scheduled DLI administered for pre-emptive treatment of malignancy recurrence. **Note**: Patients who have received a scheduled DLI as part of their transplant procedure and not for management of malignancy relapse are eligible.
10. Significant respiratory disease including patients who are on mechanical ventilation or who have resting O2 saturation <90% by pulse-oximetry.
11. 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 48h prior to study treatment start**).
12. Clinically significant or uncontrolled cardiac disease including any of the following:
    - Acute myocardial infarction within 6 months from Day 1 of study treatment administration
    - Uncontrolled hypertension
    - New York Heart Association Class III or IV congestive heart failure
    - Unstable angina within last 6 months from screening

- Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia requiring therapy).

13. Cholestatic disorders, or unresolved sinusoidal obstructive syndrome/veno-occlusive disease of the liver (defined as persistent bilirubin abnormalities not attributable to aGvHD and ongoing organ dysfunction).
14. Any corticosteroid therapy for indications other than aGvHD at doses > 1 mg/kg/day methylprednisolone (or equivalent prednisone dose 1.25 mg/kg/day) within 7 days of Screening. Routine corticosteroids administered during conditioning or cell infusion is allowed.
15. Current therapy with medications that interfere with coagulation or platelet function including but not limited to aspirin and related drugs, heparin, and warfarin (to minimize risk of bleeding). **Note:** Heparin or Low Molecular Weight Heparin (LMWH) is allowed if used at sub-therapeutic dose (e.g. for prophylaxis of sinusoidal obstructive syndrome/veno-occlusive disease of the liver).
16. History of progressive multifocal leuko-encephalopathy (PML).
17. Patients who received JAK inhibitor therapy for any indication after initiation of current alloSCT conditioning.
18. Previous participation in a study of any investigational treatment agent within 30 days of randomization or within 5 half-lives of the investigational treatment agent, whichever is greater.
19. Any condition that would, in the Investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the patient; or interfere with interpretation of study data.
20. Known allergies, hypersensitivity, or intolerance to systemic immunosuppressive therapy.
21. Pregnant or nursing (lactating) women
22. 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,

    **OR**

    Female patients randomized to ruxolitinib, ≥ 18 years of age and of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception as defined below, throughout the study and for up to 90 days after stopping treatment.

    Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). 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 patient.
- Use of oral, injected or implanted hormonal methods of contraception. 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 oral contraception, patients should have been using the same pill on a stable dose for a minimum of 3 months before Screening).

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 (e.g. 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.

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

# 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 assigned study treatment (either ruxolitinib or BAT) stratifying on aGvHD grade (Grade II vs. III vs. IV) until Day 28. Further study treatment duration and management up to Week 24 / EOT are described for ruxolitinib and BAT, respectively, in Section 6.1.1.1 and Section 6.1.1.2, as well as in Section 6.1.5.1.

In addition to assigned ruxolitinib or BAT, patients may receive standard alloSCT supportive care including anti-infective medications and transfusion support. Continued use of systemic corticosteroids, calcineurin inhibitors (CNI) (cyclosporine or tacrolimus), and topical corticosteroid therapy per institutional guidelines is permitted. Other systemic medications for aGvHD may be continued after randomization only if used for aGvHD prophylaxis (i.e. started before the diagnosis of aGvHD). Permitted concomitant therapies are described in Section 6.4.1.

### 6.1.1 Dosing regimen

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

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

**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<br>(2 tablets orally BID) | Daily |
| 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, approximately 12 hours apart (morning and night) without regards to food. Ruxolitinib will be administered by hospital personnel in an inpatient setting, or self-administered by the patient in an outpatient setting.

Patients should be instructed not to make up for 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.

Within the first 28 days, patients meeting criteria of aGvHD disease progression, mixed response, no response, can move to new systemic treatment per Investigator choice. Requirement for initiation of this new systemic treatment will be considered a treatment failure. In this case, the patient must discontinue study treatment (see Section 7.1.5).

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

Patients should be instructed not to take study treatment at home on Day 1 and Day 7 (PK sampling [redacted]) and at Weeks 2, 4, 8 and 24 on the day of the scheduled pre-dose blood collection (Section 7). Dosing will be administered post-blood collection at these visits.

Patients responding to treatment may be tapered off ruxolitinib as needed, starting no earlier than Day 56. The dose tapering strategy should be based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the Investigator.

- If a taper of ruxolitinib is considered appropriate, the taper should be completed by no later than Week 24 (or Cross-Over Week 24) unless prolonged tapering is indicated due to an aGvHD flare or other safety concerns. In such case, the taper of ruxolitinib must be initiated no later than Week 24 (or Cross-Over Week 24) and completed by no later than the patient's end of study (up to approximately 2 years from randomization). Guidelines for the tapering of ruxolitinib and of immunosuppression (corticosteroids and CNI) are provided in Section 6.1.5.1.

- Should a tapering strategy not be in the best interest of the patient, or should the taper be completed prior to Week 24 (or Cross-Over Week 24, as applicable), the patient must still follow the assigned Visit Evaluation Schedule in Table 7-1 Randomized Treatment (or Table 7-2 Cross-Over Treatment), including all safety and efficacy assessments, until Week 24 (or Cross-Over Week 24, as applicable), as detailed in Section 4.1 and Section 7.1.4.

#### 6.1.1.2 Best Available Therapy

Patients will receive Best Available Therapy based on Investigator's best judgment, taking into account the manufacturer's instructions, labeling, patient's medical condition, and institutional guidelines for any dose adjustment. The BAT in this study will be identified by the Investigator prior to patient randomization among the following treatments currently used in this setting: anti-thymocyte globulin (ATG), extracorporeal photopheresis (ECP), mesenchymal stromal cells (MSC), low-dose methotrexate (MTX), mycophenolate mofetil (MMF), mTOR inhibitors (everolimus or sirolimus), etanercept, or infliximab. No other types or combinations of BATs are permitted in this study.

Note: Medications used for aGvHD prophylaxis (i.e. started before the diagnosis of aGvHD) which have failed to prevent aGvHD in a patient prior to randomization must not be chosen as BAT in this same patient.

Within the first 28 days, patients meeting criteria of disease progression, mixed response, no response, can move to treatment with another BAT within the Treatment Period of the study. Requirement for initiation of this new systemic treatment will be considered a failure of initial BAT.The dose and administration schedule may be changed at any time based on the judgment of the Investigator and in accordance with accepted medical practices.

The EOT visit will occur at Week 24, or earlier in case the patient meets any of the criteria for discontinuation of study treatment (see Section 4.1, Section 7.1.4 and Section 7.1.5).

Guidelines for the tapering of immunosuppression (corticosteroids and CNI) in the BAT arm are provided in Section 6.1.5.1.

### 6.1.2 Ancillary treatments

Not Applicable

### 6.1.3 Rescue medication

Not applicable

### 6.1.4 Guidelines for continuation of treatment

Refer to Section 6.3 on dose modifications and follow-up for toxicities for guidelines for continuation of treatment.

### 6.1.5 Treatment duration

The planned duration of aGvHD treatment is approximately 6 months.

The Treatment Period will begin for each patient on the day of randomization (Day 1) and continue on assigned treatment arm (ruxolitinib or BAT) until the patient reaches the Week 24 visit from randomization, unless the patient meets any of the criteria for discontinuation of study treatment (see Section 7.1.5).

During the Treatment Period, and beyond Day 28, patient's treatment will be managed according to their response as described in Table 6-2:

**Table 6-2 Treatment management based on patient response at Day 28**

| | |
|---|---|
| **Patients meeting the primary endpoint at Day 28** | **Patients responding to ruxolitinib** will continue ruxolitinib until Day 56. These patients may be tapered off ruxolitinib as needed, starting no earlier than Day 56. The dose tapering strategy should be based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the Investigator.<br>• **If a taper of ruxolitinib is considered appropriate**, the taper should be completed by no later than Week 24 unless prolonged tapering is indicated due to an aGvHD flare or other safety concerns. In such case, the taper of ruxolitinib must be initiated no later than Week 24 and completed by no later than Week 96. Guidelines for the tapering of ruxolitinib are provided in Section 6.1.5.1.<br>• **Should a tapering strategy not be in the best interest of the patient, or should the taper be completed prior to Week 24**, the patient must still follow the assigned Visit Evaluation Schedule (Table 7-1), including all safety and efficacy assessments, until Week 24. |
| | **Patients responding to BAT** will be managed as per institutional practices. These patients may further cross-over to the ruxolitinib treatment arm between Day 28 and Week 24 if they meet cross-over criteria after an initial response.<br>• Responding patients (i.e. obtaining a CR or PR) completing the dosing schedule for their assigned BAT at any time as per standard of care before Week 24 must continue to be assessed for all scheduled visits until Week 24. |
| **Patients not meeting the primary endpoint at Day 28** | **Patients who are randomized to ruxolitinib**, will discontinue study treatment, and be treated per Investigator's judgement. These patients will then enter the Long-Term Follow-Up period. |
| | **Patients who are randomized to BAT and who do not meet cross-over criteria at Day 28** will have their EOT visit, Safety Follow-Up visit and enter the Long-Term Follow-Up period. |
| | **Patients who are randomized to BAT, and who meet cross-over criteria at or after Day 28**, may cross-over to the ruxolitinib treatment arm.<br>Patients who cross-over at Day 28 or thereafter will follow the same treatment duration and taper schedule as patients originally randomized to ruxolitinib treatment. Corticosteroids and CNI for aGvHD treatment is allowed to be continued, with cessation required of any other systemic immunosuppressive treatment prior to cross-over, unless used for aGvHD prophylaxis (i.e. started before the diagnosis of aGvHD).<br>• Patients not achieving a CR or PR at Cross-Over Day 28 will discontinue treatment with ruxolitinib and will be treated per Investigator's judgement. These patients will then enter the Long-Term Follow-Up period.<br>• **If a taper of ruxolitinib is considered appropriate**, the taper should be started no earlier than Cross-Over Day 56 and completed by no later than Cross-Over Week 24 unless prolonged tapering is indicated due to an aGvHD flare or other safety concerns. In such case, the taper of ruxolitinib must be initiated no later than Cross-Over Week 24 and completed by no later than Cross-Over Week 96, or 2 years from randomization, whichever occurs first. Guidelines for the tapering of ruxolitinib are provided in Section 6.1.5.1. |

| | |
|---|---|
| | • **Should a tapering strategy not be in the best interest of the patient, or should the taper be completed prior to Cross-Over Week 24**, the patient must still follow the assigned Visit Evaluation Schedule (Table 7-2), including all safety and efficacy assessments, until Cross-Over Week 24. |

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

Addition of any **new** systemic immunosuppressive therapy after randomization may be decided by the Investigator for patients meeting aGvHD criteria for progression, mixed response, or no response criteria, or aGvHD flare failure as defined in Section 3. Requirement for initiation of such treatment will be considered a treatment failure. In this case, the patient must discontinue study treatment (see Section 7.1.5).

All patients, responders and non-responders, will be followed up for long-term observation up to 24 months from randomization.

#### 6.1.5.1 Tapering guidelines

Tapering of immunosuppression will follow 2 steps: first taper of corticosteroids, followed with taper of CNI and/or ruxolitinib in responding patients. During the Treatment Period in both the ruxolitinib and BAT arms, immunosuppression taper guidelines are as follows:

- **Corticosteroids:** the taper of corticosteroids in patients demonstrating a PR or CR as observed by the Investigator must not be initiated earlier than Day 7, and should then be performed per institutional guidelines (e.g. 10% dose reduction every 5 days, beginning no earlier than Day 7 and continuing to approximately Day 56 to allow 7-8 week taper).
- **CNI (cyclosporine or tacrolimus):** CNI taper is allowed in patients demonstrating a PR or CR, once off corticosteroids, and should then be performed per institutional guidelines (e.g. 25% dose reduction per month).
- **Ruxolitinib:** ruxolitinib taper is allowed in patients demonstrating a PR or CR, once off corticosteroids, and must not start earlier than Day 56. The following guidance may be followed based on evaluation of the condition of the patient, current dosing regimen and the clinical judgement of the Investigator: a 50% dose reduction every 2 months (56 days) i.e. initial dose reduction to 5 mg orally BID and, if sustained aGvHD stable disease is observed, patient is further tapered by a second 50% dosage reduction to 5 mg orally QD for an additional 56 days, prior to cessation (see Section 6.3.1.1.3)

It is expected that the taper of corticosteroids, CNI, and ruxolitinib will be completed by Week 24. Should an aGvHD flare or other safety concerns prevent taper from being completed by then, the dose of ruxolitinib may be maintained until Week 24. In such case, ruxolitinib taper must be initiated no later than Week 24 and must be completed by no later than Week 96. Similarly, patients receiving ruxolitinib after cross-over may have their taper initiated no later than Cross-Over Week 24 and completed by no later than Cross-Over Week 96, or 2 years from randomization, whichever occurs first.

If aGvHD flare occurs during the taper of immunosuppressive medications prior to Day 56, the dose of corticosteroids may be re-escalated at the Investigator's discretion and will not be considered treatment failure, as long as criteria defined below and in Section 3 are not met. The

taper of corticosteroids should be attempted again once the patient demonstrates a PR or CR. In these circumstances the taper of corticosteroids may be extended beyond Day 56, delaying the initiation of CNI and/or ruxolitinib taper. If aGvHD flare requires addition of a new systemic therapy due to inability to taper corticosteroids below methylprednisolone 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone) for a minimum 7 days, OR due to re-escalation of corticosteroids to methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone), the patient will be considered to have experienced an aGvHD flare failure per protocol, and new systemic treatment is indicated per Investigator's judgement. Patients requiring new systemic treatment for aGvHD must discontinue study treatment (see Section 7.1.5).

If aGvHD flare occurs during ruxolitinib taper after Day 56, patients may have their ruxolitinib dose increased to the prior dose level (maximum 10 mg BID), their response monitored, and ruxolitinib taper attempted again as needed until the patient's end of study (up to approximately 2 years from randomization). The patient will be considered to have experienced an aGvHD flare failure when further treatment is indicated per Investigator's judgment including: starting a new systemic treatment. Patients requiring new systemic treatment for aGvHD must discontinue study treatment (see Section 7.1.5).

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

## 6.2 Dose escalation guidelines

Not applicable.

## 6.3 Dose modifications

### 6.3.1 Dose modification and dose delay

A standardized dosing paradigm will be used to determine dose adjustments for safety and efficacy so that each patient is titrated to their most appropriate dose.

These changes must be recorded on the Dosage Administration Record eCRF.

#### 6.3.1.1 Dose adjustments for ruxolitinib safety

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

#### 6.3.1.1.1 Dose adjustments of ruxolitinib for hematologic safety

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

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

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

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

#### 6.3.1.1.2 Dose adjustments of ruxolitinib for non-hematologic safety

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

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

Ruxolitinib must be permanently discontinued upon any one of the following AE 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:

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

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

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

In the event that any patients permanently discontinues the study treatment, regardless of reason, reasonable efforts should be made to have the patient return for an early termination visit and have the End of Treatment evaluations completed as described in Section 7. All patients completing/discontinuing study treatment at any time point after randomization will be followed in the Long-term follow-up period until they reach 2 years from randomization.

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

The instructions provided in this table and the criteria for dose reduction / interruption are used to determine a protocol deviation

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

| **Dose modifications for ruxolitinib for adverse events suspected to be drug-related** | |
|---|---|
| **Worst toxicity** | |
| **Investigations (Hematologic)** | |
| **Neutropenia (ANC)** | |
| Grade 1 (ANC < LLN - 1500/mm3) | **Recommendation**: Maintain dose level |
| Grade 2 (ANC < 1500 - 1000/mm3) | **Recommendation**: Maintain dose level |
| Grade 3 (ANC < 1000 - 750/mm3) | **Recommendation**: Maintain dose level |
| Grade 3 (ANC < 750 - 500/mm3) | **Mandatory**: ↓ 1 dose level (see Table 6-4), monitor ANC daily until resolved to ≤ Grade 2, then resume initial dose level |
| Grade 4 (ANC < 500/mm3) | **Mandatory:** Hold dose, monitor ANC daily until resolved to ≤ Grade 3, then resume ↓ 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** | |
| 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<br>If resolved in ≤ 7 days, then resume initial dose level<br>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. |

| **Dose modifications for ruxolitinib for adverse events suspected to be drug-related** | |
|---|---|
| **Worst toxicity** | |
| **Investigations (Renal)** | |
| **Serum creatinine** | |
| Grade 1 (> ULN - 1.5 x ULN)<br>Grade 2 (> 1.5 - 3.0 x ULN)<br>Grade 3 (> 3.0 - 6.0 x ULN) | **Recommendation**: Maintain dose level<br>**Mandatory:** ↓ 1 dose level until resolved to ≤ Grade 1 or baseline, then resume initial dose level<br>**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<br>> 1.5 - 3.0 x ULN<br>> 3.0 - 5.0 x ULN*<br><br><br><br>> 5.0 - 10.0 x ULN*<br><br><br><br>> 10.0 x ULN* | **Recommendation**: Maintain dose level<br>**Recommendation**: Maintain dose level<br>**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:<br>If resolved in ≤ 14 days, then increase by one dose level<br>If resolved in > 14 days, then maintain the decreased dose level<br>**Mandatory**: Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN:<br>If resolved in ≤ 14 days, then resume same dose level<br>If resolved in > 14 days, then resume at ↓ 1 dose level<br>**Mandatory**: Hold dose. Monitor LFTs[b] weekly, or more frequently if clinically indicated, until resolved to ≤ 3.0 x ULN:<br>If resolved in ≤ 14 days, then resume at ↓ 1 dose level<br>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<br>> 3.0 - 5.0 x ULN<br>For patients with baseline value ≤ 3.0 x ULN | **Recommendation**: Maintain dose level<br><br>**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:<br>If resolved in ≤ 14 days, then then increase by one dose level |

| **Dose modifications for ruxolitinib for adverse events suspected to be drug-related** | |
|---|---|
| **Worst toxicity** | |
| For patients with baseline value > 3.0 -5.0 x ULN | If resolved in > 14 days, then continue at the ↓ 1 dose level<br><br>**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:<br>If resolved in ≤ 14 days, then resume same dose level<br>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<br>**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<br>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. |

| **Dose modifications for ruxolitinib for adverse events suspected to be drug-related** | |
|---|---|
| **Worst toxicity** | |
| **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:<br>If resolved in ≤ 7 days, then resume same dose level<br>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. |
| **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:<br>If resolved in ≤ 7 days, then increase by one dose level<br>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 |

| **Dose modifications for ruxolitinib for adverse events suspected to be drug-related** | |
|---|---|
| **Worst toxicity** | |
| Grade 3 | **Recommendation**: ↓ 1 dose level until resolved to ≤ Grade 2<br>**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 |
| All dose modifications should be based on the worst preceding toxicity.<br>For dose level refer to Table 6-4 and Table 6-5<br>[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 4.03)<br>[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.)<br>* 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.<br>** 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.<br>*** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea | |

**Table 6-4 Dose reduction steps for ruxolitinib**

| Current Dose | First Dose Reduction | Second Dose Reduction |
|---|---|---|
| 10 mg BID | 5 mg BID | 5 mg QD |
| 5 mg BID | 5 mg QD | Discontinue |

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).

Dose re-escalation levels of ruxolitinib are described in Table 6-5. Dose increases may not exceed 10 mg BID, with increments of 5 mg BID and not more often than every 2 weeks.

**Table 6-5 Dose re-escalation levels for ruxolitinib**

| Current Dose | First Dose Escalation | Second Dose Escalation |
|---|---|---|
| 5 mg QD | 5 mg BID | 10 mg BID |
| 5 mg BID | 10 mg BID | - |

#### 6.3.1.1.3 Optional dose tapering strategy in the event of study treatment discontinuation

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

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

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

#### 6.3.1.1.4 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 6.3.1.1.1 and Section 6.3.1.1.2).

See Appendix 7 for a list of cytochrome P450 3A4 (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). The concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily is prohibited.

**CYP3A4 inducers**

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

### 6.3.2 Anticipated risks and safety concerns of the study treatment

Please refer to Section 2.6. Risks and Benefits

## 6.4 Concomitant medications

### 6.4.1 Permitted concomitant therapy

Supportive treatments per institutional guidelines for management of alloSCT patients with SR-aGvHD 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.

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

Corticosteroids may be taken or administered without regard to food except on days when 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 patient are converted to mg/kg/day. For patients that weigh over 100 kg, maximal starting dose of prednisone will be 200 mg (or 2 mg/kg/day based on a modified starting weight of 100 kg). For calculation of subsequent prednisone doses/kg on subsequent measures, the modified starting weight of 100 kg will be used.

It is recommended that any patient 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 (Tomlyn 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.

All medications (other than ruxolitinib and BAT) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications, Surgeries and Procedures CRFs. Relevant prior medication received up to 30 days prior to the first dose of ruxolitinib/BAT will also be recorded in the appropriate CRF. 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.

### 6.4.2 Permitted concomitant therapy requiring caution and/or action

SR-aGvHD 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/plt transfusions, narcotics, and sedatives, warrant close monitoring of potential drug-drug interactions effects of these concurrent drugs.

Ruxolitinib dose adjustments may be required, particularly in patients treated with CYP450 modulators (See Section 6.3.1.1.4).

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 6-3) and Investigator judgment, with appropriate corticosteroid immunosuppression provided to avoid aGvHD flare.

### 6.4.3 Prohibited concomitant therapy

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

- Due to the high risk of bleeding in alloSCT patients with SR-aGvHD, aspirin, NSAIDs, and related medications that would expectedly reduce platelet function and/or heparin, warfarin or related medication that would adversely affect blood coagulation are prohibited. Note: Heparin or LMWH is allowed if used at sub-therapeutic dose (e.g. for prophylaxis of sinusoidal obstructive syndrome/veno-occlusive disease of the liver).
- Concomitant use of another JAK inhibitor.
- Any investigational medication (other than ruxolitinib or BAT) that is not approved for any indication. Use of such medications within 30 days or 5 half-lives, whichever is

longer, prior to the first dose of study treatment and until treatment discontinuation is prohibited.

- Use of chemotherapeutic agents and/or non-scheduled DLI for malignancy progression/relapse prophylaxis after alloSCT is not permitted. If required for patient management, the patient is discontinued from study treatment.
- Any pre-emergent intervention related to graft failure or hematologic disease relapse/progression 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 patient management, the patient is discontinued from study treatment.
- Administration of fluconazole at daily doses higher than 200 mg is prohibited (Section 6.3.1.1.4).
- Addition of any new systemic immunosuppressive therapy after randomization may be decided by the Investigator for patients meeting aGvHD criteria for progression, mixed response, or no response criteria, or in case of aGvHD flare, due to inability to taper corticosteroids below methylprednisolone 0.5 mg/kg/day (or equivalent <0.6 mg/kg/day of prednisone) for a minimum 7 days, or due to re-escalation of corticosteroids to methylprednisolone >2 mg/kg/day (or equivalent >2.5 mg/kg/day of prednisone). Requirement for initiation of such treatment will be considered a treatment failure per protocol. In this case, the patient must discontinue study treatment (see Section 7.1.5).

## 6.5 Patient numbering, treatment 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 patient 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.

At Screening, the investigator or designated staff will contact the Interactive Response Technology (IRT) system 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 patient 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 and indicated in the IRT system.

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

### 6.5.2 Treatment randomization

Patients will be randomized 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 aGvHD grade (Grade II vs. III vs. IV).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A patient randomization list will be produced by the 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.

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 on the ruxolitinib arm. The randomization number will not be communicated to the caller.

### 6.5.3 Treatment blinding

Not applicable

## 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 CRF.

### 6.6.1 Study treatment packaging and labeling

Study treatment, ruxolitinib, will be provided as global clinical open supply and will be packed and labeled under the responsibility of Novartis, Global Clinical Supply.

The study medication packaging has a 2-part label (base plus tear-off label). A unique medication number is printed on each part of this label.

Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique patient number.

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 | 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, ruxolitinib should be stored according to the instructions specified on the drug label and in the Investigator's Brochure.

**Table 6-7 Supply and storage of study treatments**

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

### 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 ruxolitinib 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 unused ruxolitinib and packaging on a regular basis, at the end of the study or at the time of ruxolitinib discontinuation.

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

#### 6.6.3.3 Handling of other study treatment

In the context of this aGvHD protocol, the following non-investigational treatment will be taken by the patient as per standards of care but will be monitored specifically because dose adjustment 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 Dosage Administration Record CRF Details will be described in the monitoring plan.

### 6.6.4 Disposal and destruction

The study drug supply (ruxolitinib) can be destroyed at the local Novartis facility, Drug Supply group, third party, or at the site only if permitted by local regulations and authorized by Novartis in a prior agreement as appropriate.

# 7 Visit schedule and assessments

## 7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 Visit evaluation schedule for Cross-Over patients list all of the assessments and indicate with an "X", the visits when they are performed.
All data obtained from these assessments must be supported in the patient's source documentation.
No CRF will be used as a source document.
(S) is defined as 'source' and (D) as 'data based'.

Assessments noted as (D) in the category column will remain in the clinical database.

**Table 7-1 Visit evaluation schedule**

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1-Week 8 (weekly)** | **Week 12-Week 20 (4-weekly)** | **Taper follow-up (as applicable)** Week 24 Taper - Week 48 Taper (8-weekly) | **Taper follow-up (as applicable)** Week 60 Taper - Week 84 Taper (12-weekly) | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| **Weeks of treatment** | | | | | 1-8 | 12-20 | 24-48 (max.) | 60-84 (max.) | Week 24 or last dose (Week 96 max.) | | | | | | |
| **Day** | | | -28 to -1 | 1 | 7-56 | 84-140 | 168-336 (max.) | 420-588 (max.) | 168 or last dose (672 max.) | Last Dose + 30d | 182 | 273 | 365 | 546 | 730 |
| **Visit window** | | | | | +/- 3d | +/- 7d | +/- 14d | +/- 28d | +/- 7d (Week 24) | +7d | +/- 28d | +/- 28d | +/- 28d | +/- 28d | +/- 28d |
| **Screening Informed Consent** | D | | X | | | | | | | | | | | | |
| **Study Informed Consent** | D | | X | | | | | | | | | | | | |
| **Inclusion / Exclusion criteria** | D | | X | | | | | | | | | | | | |
| **Disease history** (alloSCT and aGvHD history, CIBMTR risk assessment) | D | | X | | | | | | | | | | | | |

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1-Week 8 (weekly)** | **Week 12-Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| | | | | | | | **Week 24 Taper - Week 48 Taper (8-weekly)** | **Week 60 Taper - Week 84 Taper (12-weekly)** | | | | | | | |
| **Weeks of treatment** | | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **Week 24 or last dose (Week 96 max.)** | | | | | | |
| **Day** | | | **-28 to -1** | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | **182** | **273** | **365** | **546** | **730** |
| HCT-Specific Co-Morbidity Index Score | D | | X | | | | | | | | | | | | |
| **Intended BAT** treatment in case of SR-aGvHD | D | | X | | | | | | | | | | | | |
| Demography | D | | X | | | | | | | | | | | | |
| Other relevant Medical History | D | | X | | | | | | | | | | | | |
| Prior/concomitant medications | D | | X | X | X | X | X | X | X | X | | | | | |
| Blood Component Transfusions (pRBC PLT and Cryoprecipitate, Fresh frozen plasma) | D | | | X | X | X | X | X | X | X | | | | | |

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1-Week 8 (weekly)** | **Week 12-Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| | | | | | | | **Week 24 Taper - Week 48 Taper (8-weekly)** | **Week 60 Taper - Week 84 Taper (12-weekly)** | | | | | | | |
| **Weeks of treatment** | | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **Week 24 or last dose (Week 96 max.)** | | | | | | |
| **Day** | | | **-28 to -1** | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | **182** | **273** | **365** | **546** | **730** |
| IRT (Registration Randomization, Cross-over, EOT) | D | | X | X | X (4-weekly) | X | X | X | X | | | | | | |
| **Physical examination** | S | 7.2.2.1 | X | X | X | X | X | X | X | X | | | | | |
| Height | D | 7.2.2.3 | X | | | | X (Week 48: adolescents) | | X (adolescents) | | | | | | |
| Weight | D | 7.2.2.3 | X | X | X | X | X | X | X | X | | | | | |
| Vital signs | D | 7.2.2.2 | X | X | X | X | X | X | X | X | | | | | |
| **Laboratory assessments** | | 7.2.2.4 | | | | | | | | | | | | | |
| Hematology | D | 7.2.2.4.1 | X | X | X | X | X | X | X | X | | | | | |
| Chemistry | D | 7.2.2.4.2 | X | X | X | X | X | X | X | X | | | | | |
| Coagulation | D | 7.2.2.4.4 | X | X | X | X | X | X | X | X | | | | | |

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1-Week 8 (weekly)** | **Week 12-Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| | | | | | | | **Week 24 Taper - Week 48 Taper (8-weekly)** | **Week 60 Taper - Week 84 Taper (12-weekly)** | | | | | | | |
| **Weeks of treatment** | | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **Week 24 or last dose (Week 96 max.)** | | | | | | |
| **Day** | | | **-28 to -1** | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | **182** | **273** | **365** | **546** | **730** |
| Hepatitis viral serology testing (HBV, HCV) | D | 7.2.2.8 | X | | | | | | | | | | | | |
| Hepatitis viral load testing (HBV, HCV) | D | 7.2.2.8 | X | X | X (4-weekly) | X | X | X | X | X | | | | | |
| Testing for CMV, EBV, HHV-6 viral load | D | 7.2.2.8 | X | X | X (4-weekly) | X | X | X | X | X | | | | | |
| Urinalysis | D | 7.2.2.4.3 | X | X | X | X | X | X | X | X | | | | | |
| Pregnancy test (serum) | D | 7.2.2.4.5 | X | | | | | | X | | | | | | |
| Pregnancy test (urine) | D | 7.2.2.4.5 | | X | X (4-weekly) | | X | X | | | | | | | |
| **acute GvHD** assessment | D | 7.2.1.1 | X | X | X | X | X | X | X | | | | | | |

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1-Week 8 (weekly)** | **Week 12-Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| | | | | | | | **Week 24 Taper - Week 48 Taper (8-weekly)** | **Week 60 Taper - Week 84 Taper (12-weekly)** | | | | | | | |
| **Weeks of treatment** | | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **Week 24 or last dose (Week 96 max.)** | | | | | | |
| **Day** | | | **-28 to -1** | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | **182** | **273** | **365** | **546** | **730** |
| **aGvHD Response** assessment | D | 7.2.1.1 | | | X | X | X | X | X | | | | | | |
| **Chronic GvHD** assessment | D | 7.2.1.2 | | | X (4-weekly) | X | X | X | X | X | X | X | X | X | X |
| **Graft failure assessment** | D | 7.2.1.3 | | X | X | X | X | X | X | X | X | X | X | X | X |
| **Hematologic disease relapse/progression assessment** | D | 7.2.1.4 | | X | X | X | X | X | X | X | X | X | X | X | X |
| **Second primary malignancy assessment** | | 7.2.2.9 | | X | X | X | X | X | X | X | X | X | X | X | X |
| **Chimerism** | D | 7.2.1.3.1 | X | | X (4-weekly) | | | | | | | | | | |

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1-Week 8 (weekly)** | **Week 12-Week 20 (4-weekly)** | **Taper follow-up (as applicable)** Week 24 Taper - Week 48 Taper (8-weekly) | **Taper follow-up (as applicable)** Week 60 Taper - Week 84 Taper (12-weekly) | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| **Weeks of treatment** | | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **Week 24 or last dose (Week 96 max.)** | | | | | | |
| **Day** | | | **-28 to -1** | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | **182** | **273** | **365** | **546** | **730** |
| **Pulmonary Function Test** | S | 7.2.2.5 | | | X (as clinically indicated) | | | | | | | | | | |
| **Safety** | D | 8. | | | | | | | | | | | | | |
| Adverse events | D | 8.1 | X | X | X | X | X | X | X | X | | | | | |
| Infection, Bleeding monitoring | D | 7.2.2.6, 7.2.2.7 | | X | X | X | X | X | X | X | | | | | |
| [redacted] | | | | | | | | | | | | | | | |

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1-Week 8 (weekly)** | **Week 12-Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| | | | | | | | **Week 24 Taper - Week 48 Taper (8-weekly)** | **Week 60 Taper - Week 84 Taper (12-weekly)** | | | | | | | |
| **Weeks of treatment** | | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **Week 24 or last dose (Week 96 max.)** | | | | | | |
| **Day** | | | **-28 to -1** | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | **182** | **273** | **365** | **546** | **730** |
| [redacted] | | | | | | | | | | | | | | | |
| **Patient Reported Outcomes** | D | 7.2.6 | | | | | | | | | | | | | |
| FACT-BMT (patients ≥ 18 only) | D | 7.2.6 | | X | X | X | X | X | X | X | | | | | |
| EQ-5D-5L | D | 7.2.6 | | X | X | X | X | X | X | X | | | | | |
| [redacted] | | | | | | | | | | | | | | | |

| | Category | Protocol Section 7.2 | Screening | Treatment Period From Day 1 (randomization) to Week 24 / End of Study Treatment (EOT), whichever occurs first Taper follow-up visits from Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12, 18, 24 from randomization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **Screening** | **Day 1** | **Week 1- Week 8 (weekly)** | **Week 12- Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **EOT (premature treatment discontinuation, or Week 24, or end of ruxolitinib taper if delayed [Week 96 max.])** | **Safety Follow-up Visit** | **Month 6** | **Month 9** | **Month 12** | **Month 18** | **Month 24** |
| | | | | | | | **Week 24 Taper - Week 48 Taper (8-weekly)** | **Week 60 Taper - Week 84 Taper (12-weekly)** | | | | | | | |
| **Weeks of treatment** | | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **Week 24 or last dose (Week 96 max.)** | | | | | | |
| **Day** | | | **-28 to -1** | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | **182** | **273** | **365** | **546** | **730** |
| **Study Drug Treatment administration (ruxolitinib or BAT)** | **D** | | | X | X | X | X | X | | | | | | | |
| **PK sampling** | D | 7.2.3 | | X | X (Weeks 1, 2, 4, 8) | | X (Week 24) | | X (Week 24) | | | | | | |
| **Survival Follow-up** | D | | | | | | | | | | X | X | X | X | X |
| **Disposition** | D | | X | | | | | | X | | | | | | |

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

| | Category | Protocol Section 7.2 | Cross-Over (CO) Treatment Period From CO Day 1 to CO Week 24 / CO EOT, whichever occurs firstTaper follow-up visits from Cross-Over Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12 18, 24 from randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **CO Day 1** | **CO Week 1 – CO Week 8 (weekly)** | **CO Week 12 – CO Week 20 (4-weekly)** | **Taper follow-up (as applicable)** **CO Week 24 Taper - CO Week 48 Taper (8-weekly)** | **CO Week 60 Taper - CO Week 84 Taper (12-weekly)** | **CO EOT (premature treatment discontinuation, or CO Week 24, or end of ruxolitinib taper if delayed [CO Week 96 max.])** | **Safety Follow-Up Visit** | |
| **Weeks of treatment** | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **CO Week 24 or last dose (CO Week 96 max.)** | | |
| **Day from Cross-Over** | | | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | |
| Time window | | | | +/- 3d | +/- 7d | **+/- 14d** | **+/- 28d** | +/- 7d | +7d | |
| Eligibility for Cross-Over | D | | X | | | | | | | |
| Contact IRT system | D | | X | X (4-weekly) | X | X | X | X | | |
| Concomitant medications | D | | X | X | X | X | X | X | X | |
| Blood Component Transfusions (pRBC, PLT ,Cryoprecipitate, Fresh frozen plasma) | D | | X | X | X | X | X | X | X | |
| **Physical examination** | S | 7.2.2.1 | X | X | X | X | X | X | X | |

Please refer to Table 7-1

| | Category | Protocol Section 7.2 | Cross-Over (CO) Treatment Period From CO Day 1 to CO Week 24 / CO EOT, whichever occurs firstTaper follow-up visits from Cross-Over Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12 18, 24 from randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **CO Day 1** | **CO Week 1 – CO Week 8 (weekly)** | **CO Week 12 – CO Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **CO EOT (premature treatment discontinuation, or CO Week 24, or end of ruxolitinib taper if delayed [CO Week 96 max.])** | **Safety Follow-Up Visit** | |
| | | | | | | **CO Week 24 Taper - CO Week 48 Taper (8-weekly)** | **CO Week 60 Taper - CO Week 84 Taper (12-weekly)** | | | |
| **Weeks of treatment** | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **CO Week 24 or last dose (CO Week 96 max.)** | | |
| **Day from Cross-Over** | | | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | |
| Height | D | 7.2.2.3 | X | | | X (CO Week 48: adolescents) | | X (adolescents) | | |
| Weight | D | 7.2.2.3 | X | X | X | X | X | X | X | |
| Vital signs | D | 7.2.2.2 | X | X | X | X | X | X | X | |
| **Laboratory assessments** | | 7.2.2.4 | | | | | | | | |
| Hematology | D | 7.2.2.4.1 | X | X | X | X | X | X | X | |
| Chemistry | D | 7.2.2.4.2 | X | X | X | X | X | X | X | |
| Coagulation | D | 7.2.2.4.4 | X | X | X | X | X | X | X | |
| Hepatitis testing (HBV, HCV) viral load | D | 7.2.2.8 | X | X (4-weekly) | X | X | X | X | X | |

| | Category | Protocol Section 7.2 | Cross-Over (CO) Treatment Period From CO Day 1 to CO Week 24 / CO EOT, whichever occurs firstTaper follow-up visits from Cross-Over Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12 18, 24 from randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **CO Day 1** | **CO Week 1 – CO Week 8 (weekly)** | **CO Week 12 – CO Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **CO EOT (premature treatment discontinuation, or CO Week 24, or end of ruxolitinib taper if delayed [CO Week 96 max.])** | **Safety Follow-Up Visit** | |
| | | | | | | **CO Week 24 Taper - CO Week 48 Taper (8-weekly)** | **CO Week 60 Taper - CO Week 84 Taper (12-weekly)** | | | |
| **Weeks of treatment** | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **CO Week 24 or last dose (CO Week 96 max.)** | | |
| **Day from Cross-Over** | | | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | |
| Testing for CMV, EBV, HHV-6 viral load | D | 7.2.2.8 | X | X (4-weekly) | X | X | X | X | X | |
| Urinalysis | D | 7.2.2.4.3 | X | X | X | X | X | X | X | |
| Pregnancy test (serum) | D | 7.2.2.4.5 | X | | | | | X | | |
| Pregnancy test (urine) | D | 7.2.2.4.5 | | X (4-weekly) | | X | X | | | |
| **Acute GvHD** assessment | D | 7.2.1.1 | X | X | X | X | X | X | | |
| **aGvHD Response** assessment | D | 7.2.1.1 | X | X | X | X | X | X | | |
| **Chronic GvHD** assessment | D | 7.2.1.2 | X | X | X | X | X | X | X | |

| | Category | Protocol Section 7.2 | Cross-Over (CO) Treatment Period From CO Day 1 to CO Week 24 / CO EOT, whichever occurs firstTaper follow-up visits from Cross-Over Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12 18, 24 from randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **CO Day 1** | **CO Week 1 – CO Week 8 (weekly)** | **CO Week 12 – CO Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **CO EOT (premature treatment discontinuation, or CO Week 24, or end of ruxolitinib taper if delayed [CO Week 96 max.])** | **Safety Follow-Up Visit** | |
| | | | | | | **CO Week 24 Taper - CO Week 48 Taper (8-weekly)** | **CO Week 60 Taper - CO Week 84 Taper (12-weekly)** | | | |
| **Weeks of treatment** | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **CO Week 24 or last dose (CO Week 96 max.)** | | |
| **Day from Cross-Over** | | | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | |
| **Graft failure assessment** | D | 7.2.1.3 | X | X | X | X | X | X | X | |
| **Hematologic disease relapse/progression assessment** | D | 7.2.1.4 | X | X | X | X | X | X | X | |
| **Second Primary Malignancy assessment** | D | 7.2.2.9 | X | X | X | X | X | X | X | |
| Chimerism | D | 7.2.1.3.1 | | X (CO Week 1 only) | | | | | | |
| Pulmonary Function Test | S | 7.2.2.5 | | X (as clinically indicated) | | | | | | |
| **Safety** | | 8 | | | | | | | | |

| | Category | Protocol Section 7.2 | Cross-Over (CO) Treatment Period From CO Day 1 to CO Week 24 / CO EOT, whichever occurs firstTaper follow-up visits from Cross-Over Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12 18, 24 from randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **CO Day 1** | **CO Week 1 – CO Week 8 (weekly)** | **CO Week 12 – CO Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **CO EOT (premature treatment discontinuation, or CO Week 24, or end of ruxolitinib taper if delayed [CO Week 96 max.])** | **Safety Follow-Up Visit** | |
| | | | | | | **CO Week 24 Taper - CO Week 48 Taper (8-weekly)** | **CO Week 60 Taper - CO Week 84 Taper (12-weekly)** | | | |
| **Weeks of treatment** | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **CO Week 24 or last dose (CO Week 96 max.)** | | |
| **Day from Cross-Over** | | | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | |
| Adverse events | D | 8.1 | X | X | X | X | X | X | X | |
| Infection, Bleeding monitoring | D | 7.2.2.6, 7.2.2.7 | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | |

| | Category | Protocol Section 7.2 | Cross-Over (CO) Treatment Period From CO Day 1 to CO Week 24 / CO EOT, whichever occurs firstTaper follow-up visits from Cross-Over Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12 18, 24 from randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **CO Day 1** | **CO Week 1 – CO Week 8 (weekly)** | **CO Week 12 – CO Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **CO EOT (premature treatment discontinuation, or CO Week 24, or end of ruxolitinib taper if delayed [CO Week 96 max.])** | **Safety Follow-Up Visit** | |
| | | | | | | **CO Week 24 Taper - CO Week 48 Taper (8-weekly)** | **CO Week 60 Taper - CO Week 84 Taper (12-weekly)** | | | |
| **Weeks of treatment** | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **CO Week 24 or last dose (CO Week 96 max.)** | | |
| **Day from Cross-Over** | | | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | |
| [redacted] | | | | | | | | | | |
| **Patient Reported Outcomes** | | 7.2.6 | | | | | | | | |
| FACT-BMT (patients ≥ 18) | D | 7.2.6 | X | X | X | X | X | X | X | |
| EQ-5D-5L | D | 7.2.6 | X | X | X | X | X | X | X | |
| [redacted] | | | | | | | | | | |

| | Category | Protocol Section 7.2 | Cross-Over (CO) Treatment Period From CO Day 1 to CO Week 24 / CO EOT, whichever occurs firstTaper follow-up visits from Cross-Over Week 24 (as applicable) | | | | | | Safety Follow-up Visit | Long-Term Follow-up Visits at Month 6, 9, 12 18, 24 from randomization |
|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | | | **CO Day 1** | **CO Week 1 – CO Week 8 (weekly)** | **CO Week 12 – CO Week 20 (4-weekly)** | **Taper follow-up (as applicable)** | | **CO EOT (premature treatment discontinuation, or CO Week 24, or end of ruxolitinib taper if delayed [CO Week 96 max.])** | **Safety Follow-Up Visit** | |
| | | | | | | **CO Week 24 Taper - CO Week 48 Taper (8-weekly)** | **CO Week 60 Taper - CO Week 84 Taper (12-weekly)** | | | |
| **Weeks of treatment** | | | | **1-8** | **12-20** | **24-48 (max.)** | **60-84 (max.)** | **CO Week 24 or last dose (CO Week 96 max.)** | | |
| **Day from Cross-Over** | | | **1** | **7-56** | **84-140** | **168-336 (max.)** | **420-588 (max.)** | **168 or last dose (672 max.)** | **Last Dose + 30d** | |
| **Study Drug administration (ruxolitinib)** | D | | X | X | X | X | X | | | |
| PK sampling | D | 7.2.3 | X | X (CO Weeks 1, 2, 4, 8) | | X (CO Week 24) | | X (CO Week 24) | | |
| Disposition | D | | | | | | | X | | |

### 7.1.1 Molecular pre-screening

Not Applicable

### 7.1.2 Screening

Patients will be proposed to enroll in the Screening period of the study once diagnosed with aGvHD (grades II-IV) after alloSCT.

The Screening period will begin once the patient has signed the Screening Informed Consent and will be a maximum of 28 days (Day -28 to Day -1).

Screening procedures are outlined in the visit evaluation schedule (Table 7-1) including blood sample tested as needed, and assessment of inclusion and exclusion criteria.

These Screening assessments performed during the Screening period will be reported in source notes, however the corresponding data will only be fully reported in the eCRF for patients diagnosed with SR-aGvHD during the Screening period and who signed the Study Informed Consent. Limited information on screening failures will be reported in the clinical database, as described in Section 7.1.2.2.

Patients will be treated for aGvHD with systemic corticosteroids +/- continued CNI +/- another systemic aGvHD treatment per standard of care by the Investigator during the Screening period. Any occurrence of Steroid Refractory aGvHD as defined in Section 4.1 will be also closely monitored by the Investigator to identify if the patient is eligible for this study as follows:

**Patients who develop SR-aGvHD, will be proposed to continue in the Study.**

Patients meeting all eligibility criteria including SR-aGvHD criteria, may be consented to the Study Informed Consent. The Investigator must ensure availability of laboratory assessments including CBC, chemistry, and coagulation studies not older than 48 hours prior to start of study treatment with remainder of laboratory assessments performed within 28 days before randomization. The Investigator must identify Investigator choice BAT prior to randomization.

Note: Medications used for aGvHD prophylaxis (i.e. started before the diagnosis of aGvHD) which have failed to prevent aGvHD in a patient prior to randomization must not be chosen as BAT in this same patient.

Continued use of systemic corticosteroids +/- CNI and topical corticosteroid therapy per institutional guidelines is permitted. Other systemic medications for aGvHD other than corticosteroids +/- CNI may be continued after randomization only if used for aGvHD prophylaxis (i.e. started before the diagnosis of aGvHD).

A patient who has a laboratory test result(s) that does not satisfy the entrance criteria may have the test(s) repeated. These tests may be repeated as soon as the investigator believes the retest result is likely to be within the acceptable range to satisfy the entrance criteria, and can be completed within 48 hours prior to study treatment start. 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.

If study treatment does not start within 24 hours after randomization, body weight, CBC, Chemistry and coagulation tests should be repeated to have laboratory assessments not older than 24 hours prior to study treatment start.

A patient is considered a screen failure in the event that the laboratory test(s) cannot be available within 48 hours from treatment start, or the retest(s) do not meet the entrance criteria or the patient's medical condition has changed significantly during the screening period so that the inclusion/exclusion criteria are no longer met, more details outlined on Section 7.1.2.1

**Patients who do not develop SR- aGvHD within the 28 days of the screening period will be considered a screen failure**.

If a patient fails corticosteroid taper after the 28 days from initial screening as per SR-aGvHD criteria outlined in Section 4.1, they may be considered for re-screening.

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

**Patients meeting all inclusion and exclusion criteria** will be randomized 1:1 to receive either ruxolitinib or BAT stratifying on aGvHD grade at the time of randomization (Grade II vs. III vs. IV).

#### 7.1.2.1 Eligibility screening

Patients must meet all inclusion and exclusion criteria in order to be eligible to proceed to the Treatment Period of the study.

Investigative staff will capture patient's eligibility within source documents maintained at the site. Additionally the sites will enter patient information into the eCRF.

Eligibility information in source documents will be made available during planned interim monitoring visits and compared against the clinical database for accuracy.

The site will also be asked to confirm eligibility with the IRT system.

Following registering in IRT for Screening, patient eligibility data will be verified by the investigator once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer to and comply with detailed guidelines in the IRT manual. Only when eligibility data has been confirmed with the IRT system will the IRT allow patient's randomization and assign study treatment arm.

#### 7.1.2.2 Information to be collected on screening failures

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

The reason for not being started on treatment will be entered on the applicable Screening Disposition CRF pages.

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

No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Period (see Section 8 for SAE reporting details). For Patients who signed a Screening ICF only and no Study informed consent, only SAEs possibly related to a study procedure will be reported.

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 will have the following assessments performed before the start of study treatment:

- Review of medical history including alloSCT and CIMBTR risk assessment at the time of the alloSCT (Appendix 6), aGvHD history and disease diagnosis
- HCT Specific Comorbidity index score (Appendix 5)
- Prior aGvHD therapy (drug and non-drug) and aGvHD prophylaxis
- Intended BAT strategy in case of SR-aGvHD prior to randomization
- Prior/Concomitant medications and Blood transfusions, adverse events including infections/second primary malignancy (Section 7.2)
- Physical examination including height, weight, vital signs, (Section 7.2.2.1)
- Laboratory assessments – Hematology, Chemistry, Coagulation, Urinalysis
- Hepatitis serology (HBV and HCV) if applicable (Section 7.2.2.8)
- CMV, EBV, HHV-6, HBV and HCV viral load tests. (Section 7.2.2.8)
- Pregnancy test (if applicable) (Section 7.2.2.4.5)
- aGvHD assessment as per standard criteria (Appendix 1)
- Chimerism if applicable (Section 7.2.1.3.1)
- Hematologic underlying disease relapse/progression baseline assessment (Section 7.2.1.4)
- Graft failure baseline assessment (Section 7.2.1.3)
- Patient reported outcomes: FACT-BMT, EQ-5D-5L as applicable (Section 7.2.6)
- [redacted]
- The investigator must confirm all the inclusion and exclusion criteria **prior to contacting IRT for randomization**.

  **Notes**:
  - Vital signs and urinalysis assessments as detailed in Table 7-1 performed within 48 hours prior to randomization do not need to be repeated at Day 1.
  - Viral load tests performed within 7 days from Day 1 do not need to be repeated at Day 1.

- If study treatment does not start within 24 hours after randomization, body weight, CBC, Chemistry and coagulation tests should be repeated to have laboratory assessments not older than 24 hours prior to study treatment start.

### 7.1.3 Run-in period

Not Applicable

### 7.1.4 Treatment period

- Study treatment will be initiated on Day 1 after randomization and treatment assignment by IRT system (or within 72 hours from randomization at the latest).
- Day 1 is defined as the day of randomization.
- Study treatment will be administered until the patient meets any of the criteria for discontinuation of study treatment (see Section 7.1.5) or, in responders (i.e. patients achieving PR or CR) until the dosing schedule for ruxolitinib or BAT is complete. Patients in the BAT arm may be eligible to cross-over between Day 28 and Week 24.
- Patients in the randomized Treatment Period should follow the schedule of assessments in Table 7-1 and patients who cross-over to ruxolitinib should follow the schedule of assessments in Table 7-2. In addition, the frequency of visits and possible time-points for the EOT are detailed in Section 4.1.
- All cross-over patients should complete the EOT CRF at the time of discontinuation of randomized treatment (BAT) and again at the time of discontinuation of cross-over treatment (ruxolitinib). Should the EOT visit and Cross-Over Day 1 visit be 3 days apart or less, assessments due at both visits do not need to be repeated.
- Unscheduled visits may be performed as necessary. Additional assessments may be done as per institutional guidelines at investigator's discretion at any time during the trial. aGvHD assessments performed at unscheduled visit and leading to a change in patient's management or, during treatment period to a change in patient's response should be recorded in the CRF, as well as any relevant safety assessment performed.

**Assessments required at the time of last dose if before Week 24, in responding patients:**

As noted in Section 4.1, responding patients (i.e. obtaining a CR or PR) completing the dosing schedule for ruxolitinib or their assigned BAT before Week 24, will have their EOT visit at Week 24 **AND** must also have assessments performed within 7 days of the last dose. These assessments will be performed:

- At a scheduled visit (if planned within 7 days of last dose),

**OR**

- At an unscheduled visit.
  - In this case, assessments identified below, which are not part of the assessments for the scheduled visit, must be performed and recorded as unscheduled assessments, in addition to planned assessments.

The same rules apply in the Cross-Over Treatment Period.

The following assessments are required:

- Contact IRT system
- Physical examination: height (adolescent patients only), weight, vital signs
- Laboratory assessments: hematology, chemistry, coagulation, viral load testing, urinalysis, pregnancy test (serum), if applicable
- aGvHD assessment and aGvHD response assessment
- Chronic GvHD assessment, Graft failure assessment, Hematologic disease relapse/progression assessment, Second primary malignancy assessment
- Adverse events, including Infection, Bleeding Monitoring
- Prior/concomitant medications and Blood Component Transfusions
- [redacted]
- PROs: FACT-BMT (patients ≥ 18 only), EQ-5D-5L
- [redacted]
- PK sampling (unscheduled), if applicable

### 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 CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

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

In addition to mandatory Study treatment discontinuation for toxicity listed in Table 6-3, study treatment must also be discontinued under the following circumstances:

- Lack of efficacy of aGvHD treatment, i.e. patients:
  - Not achieving PR or CR at Day 28 or Cross-Over Day 28 (see Section 3), **and/or**
  - Requiring additional systemic therapy for aGvHD, at any time

  Note: change of BAT within the list of authorized BATs (see Section 6.1.1.2) is allowed until Day 28 in the BAT arm.
- Development of signs or symptoms of cGvHD including *de novo*, overlap, or progressive onset.
- Underlying hematological disease progression or relapse (Refer to Section 7.2.1.4).
- Evidence of graft failure necessitating rapid taper of immunosuppression, administration of non-scheduled DLI, stem cell boost, chemotherapy, or other treatment that would expectedly affect aGvHD.
- Adverse events leading to study treatment discontinuation (Section 6.3).
- Pregnancy (Section 7.2.2.4.5).

- Protocol deviation that results in a significant risk to the patient's safety including use of prohibited treatment (refer to Section 6.4.3)

The Investigator may opt for a dose tapering strategy in the event of ruxolitinib treatment discontinuation, e.g. in patients who develop cGvHD (see Section 6.3.1.1.3 and Section 6.1.5.1). Patients with hematologic disease progression, graft failure, AE, patient safety, or pregnancy may require abrupt cessation of ruxolitinib study treatment per Investigator discretion. Patients should return for assessments as specified at the end of treatment (EOT) visit in Table 7-1 (or Table 7-2 for cross-over patients).

Patients who discontinue ruxolitinib study treatment should NOT be considered withdrawn from the study. After the EOT visit, they will still undergo the Safety Follow-Up visit and then enter the Long-Term Follow-Up period (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.

Patients who meet the protocol criteria for treatment discontinuation will not be eligible to continue receiving ruxolitinib within the study. However, as part of Novartis "Post-trial access" commitment, patients who meet all of the following criteria:

- responded to ruxolitinib at Day 28 (or Cross-Over Day 28),
- met study discontinuation criteria (Section 7.1.5), other than safety reasons,
- are assessed by the Investigator to still be deriving clinical benefit from ruxolitinib,

will be given the possibility to continue ruxolitinib outside the study, if requested; they will then not enter the Long-Term Follow-Up period.

The Investigator must also contact the IRT to register the patient's discontinuation from study treatment. All patients who discontinue treatment for any reasons, must continue in the Long-Term Follow-Up period with visits every 12 weeks in the 1st year from randomization (Day 1) and thereafter, every 6 months in the 2nd year from randomization and follow assessments as described in Section 7.1.7 unless discontinued from the study earlier.

#### 7.1.5.1 Replacement policy

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

### 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 from the study occurs only when a patient does not want to participate in the study any longer, does not allow further collection of personal data.

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

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

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

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

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

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

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

### 7.1.7 Follow-up for Safety Evaluations

- **Safety Follow-Up visit**

All patients must have a follow-up visit for safety evaluations 30 days following the last dose of study treatment at the end of the Treatment Period.

Note: for patients randomized to the BAT arm and crossing over to ruxolitinib, the Safety Follow-Up visit will only occur once, i.e. 30 days after the last dose of ruxolitinib in the Cross-Over Treatment Period.

At the Safety Follow-Up visit, adverse events and therapies after treatment discontinuation will be reviewed, physical examinations, laboratory assessment, patient reported outcomes [redacted] will be collected. Refer to Table 7-1 or Table 7-2 for a complete list of assessments at the 30-day Safety Follow-Up visit.

- **Long-Term Follow-Up**

All patients who discontinue study treatment (responders, non-responders, completing or prematurely discontinued from the Treatment Period for any reasons as outlined above) will enter in the Long-Term Follow-Up period which lasts up to 24 months from randomization.

Visits are scheduled after EOT or Cross-Over EOT, at Month 6 (in case of premature discontinuation), Month 9, Month 12, Month 18 and Month 24 from randomization (Day 1).

If visits on site are not possible during the Long-Term Follow-Up period, patients may be contacted by the site to collect similar information.

Information to be collected is detailed (Table 7-1). Data collected should be entered in the appropriate CRF. Unscheduled visits may be performed as necessary. Additional assessments may be done as per institutional guidelines at investigator's discretion at any time during the trial.

### 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 CRF.

## 7.2 Assessment types

### 7.2.1 Efficacy assessments

#### 7.2.1.1 aGvHD assessment

aGvHD grading will be performed by the Investigator at every visit during the treatment period and at EOT visit as outlined in Table 7-1 and Table 7-2.

aGvHD will be performed using standard criteria (Harris 2016): measures of body surface area aGvHD skin rash, stool volumes or frequency per 24h time period, and serum bilirubin levels, staging by organ (skin; liver; upper GI; Lower GI) and overall grading at the time of the evaluation should be reported according to Appendix 1.

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

Once randomized, response to study treatment will be assessed by the Investigator at every visit during the Treatment Period according to definitions outlined in this protocol (Section 3). Response assessment by the Investigator at Day 28 and at Day 56 will support respectively, the primary and key secondary endpoints assessments for this trial.

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

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

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

Note: Additional assessments may be done as per institutional guidelines at investigator's discretion. aGvHD assessments performed at unscheduled visit and leading to a change in patient's management including within 7 days from last dose of study treatment, or a change in patient's response should be recorded in the CRF.

#### 7.2.1.2 Chronic GVHD Assessment

Occurrence of definitive and possible manifestations of cGvHD will be assessed monthly from Day 1 to Day 56 and at every visits thereafter during the treatment period, at the time of last dose if before Week 24, in responding patients (see Section 7.1.4), and at EOT (or Cross-Over EOT).

After EOT (or Cross-Over EOT), patients will be assessed for occurrence of cGvHD at the Safety Follow-Up visit, and at Month 6, at Month 9, at Month 12, at Month 18 and at Month 24 during the Long-Term Follow-Up period (see Table 7-1 and Table 7-2). Occurrence of cGvHD will be reported on appropriate specific CRF and, not as an adverse event (Section 8.1.1). Ruxolitinib taper may be initiated or continued as outlined in Section 6.1.5.1 Tapering guidelines.

Investigator will assess cGvHD as per NIH consensus guidelines for cGVHD (Appendix 3): overall grading (mild, moderate, severe) at the time of cGvHD diagnosis which will be reported in corresponding CRF.

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

#### 7.2.1.3 Graft failure monitoring

Patients will also be monitored for any evidence of secondary graft failure at each visit from Day 1 during the Treatment, at the time of last dose if before Week 24, in responding patients (see Section 7.1.4), at EOT (or Cross-Over EOT), Safety Follow-Up if applicable, and Long-Term Follow-Up periods.

In addition, considering that graft failure is defined as initial whole blood or marrow donor chimerism $\geq$5% declining to <5% on subsequent measurements, donor chimerism will be also closely monitored (Section 7.2.1.3.1)

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 appropriate specific CRF and also as an adverse event (Section 8.1.1).

##### 7.2.1.3.1 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 or bone marrow (or peripheral blood selected CD3+ T cells) will be performed during screening (prior to study treatment start), at Day 28 and at Day 56 as outlined in Table 7-1. If prior chimerism was performed as part of standard of care within 28 days from Day 1, results may be used for purposes of baseline and do not need to be repeated during the Screening Period.

In addition, for patients who cross-over from BAT to ruxolitinib, chimerism will be also performed at Cross-Over Week 1 only as described in Table 7-2.

Note: chimerism may be performed at any time during study (Treatment and Long-Term Follow-Up period) at the treating investigator's discretion according to local institutional practice as indicated.

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)).

#### 7.2.1.4 Hematologic disease relapse/progression assessment

Patients will be closely monitored for any evidence of underlying hematologic disease relapse or progression at each visit from Day 1 during the Treatment period, including during cross-over period if applicable, at the time of last dose if before Week 24, in responding patients (see Section 7.1.4), at EOT (or Cross-Over EOT), Safety Follow-Up if applicable, and the Long-Term Follow-Up period as outlined in Table 7-1 and Table 7-2.

Investigator will assess relapse and progression of the underlying hematologic disease according definitions outlined in Appendix 4, and indicate if any therapy was instituted to treat persistent, progressive or relapsed hematologic disease, including the withdrawal of immunosuppressive therapy, chemotherapy administration, and/or donor lymphocyte infusion.

Evaluation and/or evidence of malignancy relapse/progression will be conducted according to local institutional practices. Available information on the malignant hematologic disease progression/relapse will be documented in the appropriate CRF and, not as an adverse event (Section 8.1.1).

### 7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, laboratory assessments, PROs, Adverse event data will be collected at every visit. For details on AE collection and reporting, refer to Section 8.

#### 7.2.2.1 Physical examination

A physical exam as per local standard of care will be performed during screening, all scheduled, study visits up to EOT during Treatment period (Table 7-1) including at the time of last dose if before Week 24, in responding patients (see Section 7.1.4).

It will include the examination of general appearance and vital signs (Section 7.2.2.2).

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

#### 7.2.2.2 Vital signs

Vital signs include blood pressure (supine or seated position), pulse measurement, and body temperature. Vital signs will be performed during screening, all scheduled study visits up to EOT during the Treatment Period (Table 7-1) including at the time of last dose if before Week 24, in responding patients (see Section 7.1.4).

Vital signs of screening visit performed within 48 hours prior randomization do not need to be repeated at Day 1.

#### 7.2.2.3 Height and weight

Height will be measured at screening for all patients, at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and at EOT (and Cross-Over EOT as applicable) in adolescents patients (<18 years old at screening) as specified in Table 7-1 and Table 7-2. Adolescent patients requiring prolonged ruxolitinib taper will also have their height measured at Week 48 or Cross-Over Week 48, as applicable.

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.

If study treatment does not start at Day 1, body weight assessment may need to be repeated within 24 hours prior to start of study treatment.

#### 7.2.2.4 Laboratory evaluations

**Table 7-3 Local Clinical laboratory parameters collection plan**

| Test Category | Test Name |
|---|---|
| Hematology | Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Platelets, Red blood cells (RBC), White blood cells. RBC Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Absolute Neutrophil Count (ANC), Absolute Reticulocytes, Bands |
| Chemistry | Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Gamma glutamyl transferase (GGT), Lactate Dehydrogenase (LDH), Bicarbonate, Calcium, Creatinine, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Total Bilirubin, Direct Bilirubin, (Indirect Bilirubin only if Total Bilirubin out of range), Blood Urea Nitrogen (BUN) or Urea, Creatine kinase, Total Cholesterol, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Total Protein, Triglycerides, Uric Acid, Amylase, Lipase, Glucose (fasting) |
| Urinalysis | Macroscopic Panel (Dipstick)* (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)<br>Note: Any findings on dipstick will be followed up with a microscopic evaluation (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) |
| Coagulation | Prothrombin time (PT), International normalized ratio (INR), Partial thromboplastin time (PTT) or Activated partial thromboplastin time (APTT), D-Dimer, Fibrinogen |
| Hepatitis markers | Hepatitis B surface antigen, Hepatitis B surface antigen antibody, Hepatitis B core antibody (baseline) and HBV DNA-PCR (baseline and during treatment period)<br>Hepatitis C virus antibody (baseline) and HCV RNA-PCR (baseline and during treatment period)<br>Note :<br>Prior HBV and HCV serology test results obtained as part of standard of care prior to alloSCT that confirm a patient is immune and not at risk for reactivation (i.e., hepatitis B or C surface antigen negative, surface antibody positive) within 28 days from Day 1 may be used |

| Test Category | Test Name |
|---|---|
| | for purposes of eligibility and baseline serology tests do not need to be repeated during the Screening period |
| Additional viral testing | Cytomegalovirus(CMV), Epstein Barr Virus (EBV), and Human herpes Virus 6 (HHV-6) : viral load by PCR (screening, Day1 and during treatment period)<br>**Notes** :<br>● Patient must have baseline viral load assessments performed within 28 days prior to randomization.<br>● Viral load collected during screening period (within 7 days from Day 1) does not need to be repeated at Day1 |
| Pregnancy Test | Serum at Screening and End of Treatment (EOT)<br>Urine at all other time points |

#### 7.2.2.4.1 Hematology

Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, RBC, White blood cells with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils), ANC[with bands] (ANC), Absolute Reticulocytes will be measured at screening, all scheduled visits during the treatment period up to EOT (or Cross-Over EOT as applicable), at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and at the Safety Follow-Up visit as noted in Table 7-1 and Table 7-2.

If study treatment does not start at Day 1, CBC test may need to be repeated for safety assessment within 24 hours prior to start of study treatment.

#### 7.2.2.4.2 Clinical chemistry

Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, LDH, Calcium, Creatinine, Magnesium, Phosphorus, Sodium, Potassium, Total Bilirubin, Direct Bilirubin, BUN or Urea, Creatine kinase, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Uric Acid Amylase, Lipase, Glucose will be measured at screening, all scheduled visits during treatment period up to EOT (or Cross-Over EOT as applicable), at the time of last dose if before Week 24, in responding patients (see Section 7.1.4), and at Safety Follow-Up visit as stated in Table 7-1 and Table 7-2.

Indirect Bilirubin will be measured only if Total Bilirubin is out of range.

If study treatment does not start at Day 1, chemistry test may need to be repeated for safety assessment within 24 hours prior to start of study treatment.

#### 7.2.2.4.3 Urinalysis

Urinalysis will be performed using macroscopic evaluation of color, bilirubin, blood, glucose, pH, protein, specific gravity will be measured at screening, scheduled visits during treatment period up to EOT (or Cross Over EOT as applicable), at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and at Safety Follow-Up visit as outlined in Table 7-1 and Table 7-2.

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

Urinalysis assessment performed within 48 hours prior randomization does not need to be repeated at Day 1.

#### 7.2.2.4.4 Coagulation

Prothrombin time (PT), International normalized ratio (INR), Partial thromboplastin time (PTT) or Activated partial thromboplastin time (APTT), D-Dimer, Fibrinogen will be measured at screening, scheduled visits during treatment period up to EOT (or Cross-Over EOT as applicable), at the time of last dose if before Week 24, in responding patients (see Section 7.1.4), and at Safety Follow-Up visit as outlined in Table 7-1 and Table 7-2.

If study treatment does not start at Day 1, coagulation assessment may need to be repeated within 24 hours prior to start of study treatment.

#### 7.2.2.4.5 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 to confirm eligibility in the trial, at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and at end of treatment as noted in Table 7-1 and at Cross-Over Day 1 and Cross-Over EOT as applicable as noted in Table 7-2. These female patients will have urine pregnancy tests performed at the other scheduled visits (monthly) as outlined in Table 7-1 and Table 7-2.

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 treatment period.

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 safety follow up period.

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 Pulmonary function test

Pulmonary function test may be performed as clinically indicated during the treatment period at investigator's discretion according to local institutional practice.

### 7.2.2.6 Bleeding

Bleeding complications are important identified and potential risks in the setting of alloSCT due to profound thrombocytopenia and/or coagulopathy and therefore will be monitored closely throughout the treatment period from Day 1 and, at every visit until EOT (Cross-Over EOT as applicable), at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and at the Safety Follow-Up visit as outlined in Table 7-1and Table 7-2.

Bleeding will be reported as an adverse event and the AE severity grade will be assessed according to CTCAE grading as defined in Section 8.1.

During the Long Term Follow-Up period, monitoring of bleeding and management will be performed according to local institutional practice.

#### 7.2.2.7 Infection monitoring

Infections (including opportunistic infections) are important risks identified with ruxolitinib and BAT aGvHD therapy and therefore will be monitored closely throughout the treatment period from Day 1 and, at every visit until EOT (Cross Over EOT as applicable), at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and at the Safety Follow-Up visit as outlined in Table 7-1 and Table 7-2.

Infections will be reported as adverse event and the AE severity grade will be assessed according to CTCAE grading as defined in Section 8.1.

In addition, Investigator will detail type of infection as well as method of diagnosis and assess the event according to the Infection severity grading (Appendix 2).

During the Long-Term Follow-Up period, monitoring of infections including any serology testing will be performed according to local institutional practice at the treating investigator's discretion in order to monitor any potential viral reactivation.

#### 7.2.2.8 Viral reactivation monitoring

Investigator must confirm patient is immune and not at risk for reactivation at screening based on medical assessment as defined in Exclusion criteria 5 and the rationale for amendment 1.

The following viral serology testing should be performed during screening and peripheral blood nucleic acid (viral load) testing should be performed at Screening and Day 1 visits as baseline assessment:

- Hepatitis B surface antigen, Hepatitis B AB (IgG) Hepatitis B Core Antibody (IgM) and, HBV viral DNA-PCR
- Hepatitis C virus antibody and HCV RNA-PCR
- EBV viral load
- HHV-6 viral load
- CMV DNA quantification

Testing can be done once the patient has signed the Screening informed consent.

However, serology Hepatitis test results for HBV and HVC obtained as part of standard of care prior to alloSCT that confirm a patient is immune and not at risk for reactivation (i.e., hepatitis B surface antigen negative, surface antibody positive, or HCV antibody) within 28 days from Day 1 may be used for purposes of eligibility and baseline serology tests do not need to be repeated during the Screening period.

If viral load tests were collected during the screening period (within 7 days from Day 1), viral load tests do not need to be repeated at Day 1.

The results of the baseline viral load tests to assess CMV, EBV, HHV6, HCV and HBV performed during screening, may become available by the time of randomization or a later date as these specialized laboratory viral load tests may take up to several days.

In the absence of international guidelines on validated nucleic acid testing methods to assess CMV, EBV, HHV6 viral copies/mL in the peripheral blood, no threshold is set in this study protocol. Definition of active infection is based on institutional guidelines and treating physician's assessment. Once eligible patients are randomized, their viral load will be monitored for potential viral reactivation throughout the treatment period at Day 1(if applicable) and then on a monthly basis up to EOT (Cross-Over EOT as applicable), at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and at the Safety Follow-Up visit as outlined in Table 7-1 and Table 7-2.

#### 7.2.2.9 Second primary malignancy monitoring

Occurrence of any new malignancies other than the underlying hematologic disease, including non-melanoma skin cancer, will be monitored closely up to 24 months after randomization (from Day 1 throughout the treatment period including at the time of last dose if before Week 24, in responding patients (see Section 7.1.4) and Long-Term Follow-Up period outlined in Table 7-1and Table 7-2.

Second primary malignancy will be reported as adverse event as defined in Section 8.1.

### 7.2.3 Pharmacokinetics

#### 7.2.3.1 Blood sampling schedules

Blood sampling for PK of ruxolitinib will be performed in all patients enrolled in the study to explore PK characteristics of aGvHD patients (Refer to Table 7-4 as described in Table 7-1).

**Extensive PK sampling schedule**

Early enrolling patients randomized to ruxolitinib arm (or who crossed over from BAT to ruxolitinib) will follow an "extensive PK" sampling schedule as outlined in Table 7-4. Approximately the first twenty-five (25) adult patients and all 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.

The 'Extensive PK' sampling scheme includes a pre-dose and seven (7) post-dose samples on Day 1 and Day 7 thereafter, two (2) samples (1 pre-dose and 1 post-dose) per scheduled visit will be collected as outlined in Table 7-4. PK samples should be taken on the day of study visit as indicated on Table 7-4, or within the following visit windows indicated on Table 7-1 (i.e. ±3 days up to Week 8, and ±7 days after Week 8). Every effort should be made to take the PK sample as scheduled.

**Sparse PK sampling schedule**

Once the requirement for "extensive PK sampling" is fulfilled for Day 1 and Day 7, all sites will be notified by the Sponsor. Subsequent adult patients randomized to ruxolitinib, and any patients crossing over from BAT to ruxolitinib after Day 28, will follow the "Sparse PK"

sampling schedule and will have a total of two (2) samples (1 pre-dose and 1 post-dose) per scheduled visit as outlined in Table 7-5.

**Table 7-4 Ruxolitinib Pharmacokinetic blood collection log for extensive PK (First 25 adult patients and all adolescents)**

| Treatment Period | Week | Day | Scheduled timepoint | PK collection number / Dose reference ID | | PK Sample No | Sample volume [mL] |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | Pre-dose | 1 | -- | 1 | 2 |
| | | | Post-dose 0.5 hour (± 15 min) | 1 | -- | 2 | 2 |
| | | | Post-dose 1 hour (± 15 min) | 1 | -- | 3 | 2 |
| | | | Post-dose 1.5 hours (± 15 min) | 1 | -- | 4 | 2 |
| | | | Post-dose 2 hours (± 15 min) | 1 | -- | 5 | 2 |
| | | | Post-dose 4 hours (± 1 hr) | 1 | -- | 6 | 2 |
| | | | Post-dose 6 hours (± 1 hr) | 1 | -- | 7 | 2 |
| | | | Post-dose 9 hours (± 1 hr) | 1 | -- | 8 | 2 |
| 1 | 1 | 7 | Pre-dose | 2 | 201[a] | 9 | 2 |
| | | | Post-dose 0.5 hour (± 15 min) | 2 | | 10 | 2 |
| | | | Post-dose 1 hour (± 15 min) | 2 | | 11 | 2 |
| | | | Post-dose 1.5 hours (± 15 min) | 2 | | 12 | 2 |
| | | | Post-dose 2 hours (± 15 min) | 2 | | 13 | 2 |
| | | | Post-dose 4 hours (± 1 hr) | 2 | | 14 | 2 |
| | | | Post-dose 6 hours (± 1 hr) | 2 | | 15 | 2 |
| | | | Post-dose 9 hours (± 1 hr) | 2 | | 16 | 2 |
| 1 | 2 | 14 | Pre-dose | 3 | 301[a] | 17 | 2 |
| | | | Post-dose 2 hour (± 15 min) | 3 | | 18 | 2 |
| 1 | 4 | 28 | Pre-dose | 5 | 501[a] | 21 | 2 |
| | | | Post-dose 2 hour (± 15 min) | 5 | | 22 | 2 |
| 1 | 8 | 56 | Pre-dose | 7 | 701[a] | 25 | 2 |
| | | | Post-dose 2 hour (± 15 min) | 7 | | 26 | 2 |
| 1 | 24 | 168 | Pre-dose | 9 | 901[a] | 29 | 2 |
| | | | Post-dose 2 hour (± 15 min) | 9 | | 30 | 2 |
| | Unscheduled Sample[b] | | --- | --- | | 1001+ | 2 |

| Treatment Period | Week | Day | Scheduled timepoint | PK collection number / Dose reference ID | PK Sample No | Sample volume [mL] |
|---|---|---|---|---|---|---|

[a] Dose reference IDs to collect previous dose information for PK trough samples. For the PK trough (pre-dose) samples, the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table
[b] Unscheduled PK sampling is required at the time of last dose in responding patients (i.e. obtaining a CR or PR) completing the dosing schedule for ruxolitinib at any time before Week 24, and continuing to be assessed until Week 24. Such patients will have a PK trough sample taken ("pre-dose" tube) if they still took a ruxolitinib dose approximately 12 hours prior to the visit. If the last dose of ruxolitinib is administered on the day of the visit, a second sample will be taken at post dose 2 hour (± 15 min).

**Table 7-5 Ruxolitinib Pharmacokinetic blood collection log for sparse PK sampling (all other adult patients)**

| Treatment Period | Week | Day | Scheduled timepoint | PK collection number / Dose reference ID | | PK Sample No | Sample volume [mL] |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | Pre-dose<br>Post-dose 2 hours (± 15 min) | 10<br>10 | --<br>-- | 101<br>102 | 2<br>2 |
| 1 | 1 | 7 | Pre-dose<br>Post-dose 2 hours (± 15 min) | 20<br>20 | 2001[a] | 103<br>104 | 2<br>2 |
| 1 | 2 | 14 | Pre-dose<br>Post-dose 2 hour (± 15 min) | 30<br>30 | 3001[a] | 105<br>106 | 2<br>2 |
| 1 | 4 | 28 | Pre-dose<br>Post-dose 2 hour (± 15 min) | 50<br>50 | 5001[a] | 109<br>110 | 2<br>2 |
| 1 | 8 | 56 | Pre-dose<br>Post-dose 2 hour (± 15 min) | 70<br>70 | 7001[a] | 113<br>114 | 2<br>2 |
| 1 | 24 | 168 | Pre-dose<br>Post-dose 2 hour (± 15 min) | 90<br>90 | 9001[a] | 117<br>118 | 2<br>2 |
| | Unscheduled Sample[b] | | --- | --- | | 1001+ | 2 |

[a] Dose reference IDs to collect previous dose information for PK trough samples. For the PK trough (pre-dose) samples , the actual date and time of administration of the previous dose of study medication should also be recorded with appropriate Dose reference IDs as indicated in the above table
[b] Unscheduled PK sampling is required at the time of last dose in responding patients (i.e. obtaining a CR or PR) completing the dosing schedule for ruxolitinib at any time before Week 24 (or Cross-Over Week 24, as applicable), and continuing to be assessed until Week 24 (or Cross-Over Week 24, as applicable). Such patients will have a PK trough sample taken ("pre-dose" tube) if they still took a ruxolitinib dose approximately 12 hours prior to the visit. If the last dose of ruxolitinib is administered on the day of the visit, a second sample will be taken at post dose 2 hour (± 15 min).

#### 7.2.3.2 Pharmacokinetic blood collection and handling

Whole blood (2 mL) per sampling time as outlined in Table 7-4 and Table 7-5 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

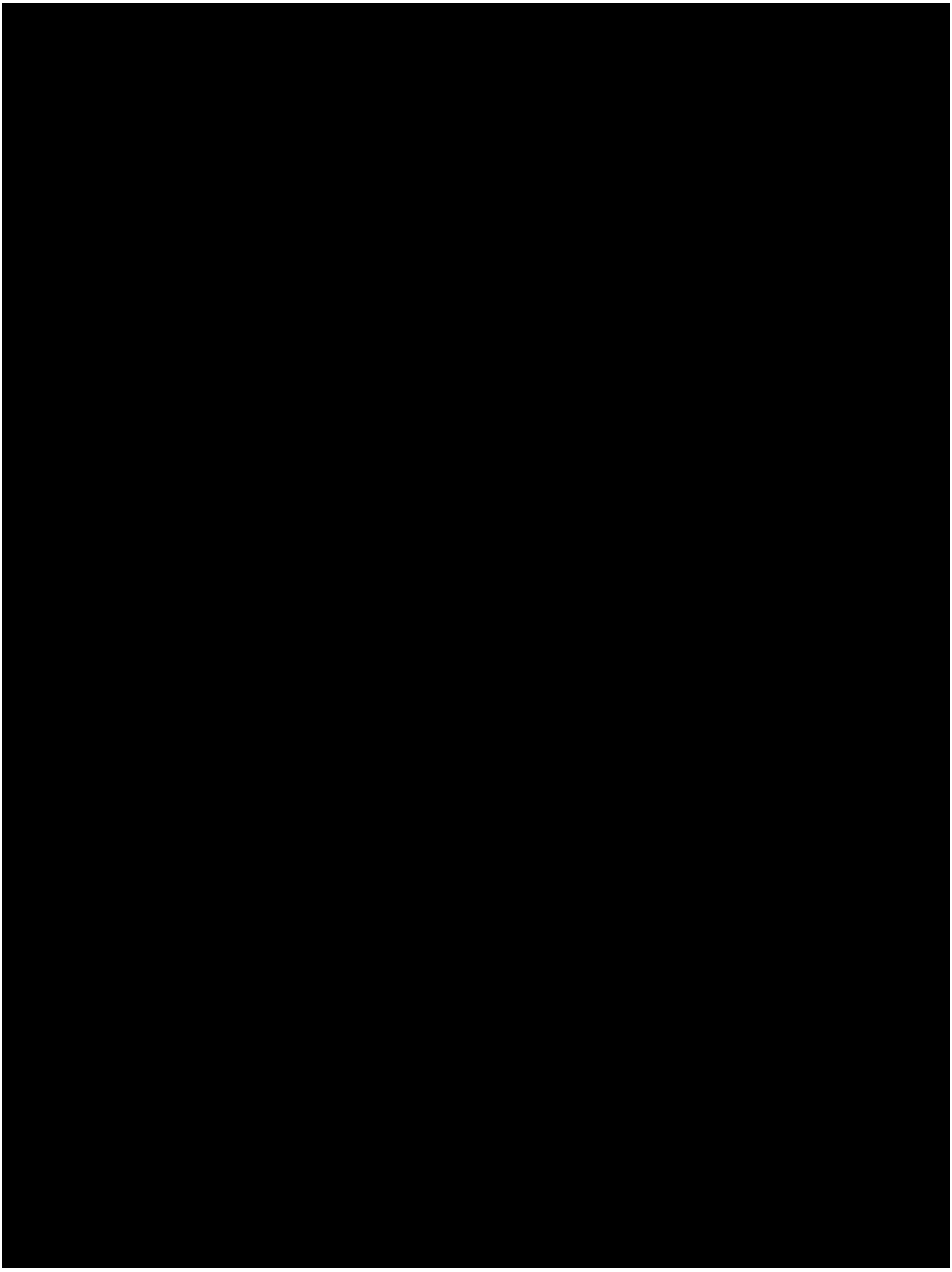
collection at approximately 2000 x g at 4°C for 15 minutes to yield plasma. The plasma will be decanted and transferred into a 2-mL polypropylene screw- cap tube, the tube capped, and then immediately placed in a freezer at ≤ -60°C until shipment to sponsor and/or designated central laboratory. Refer to the [CINC424C2301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

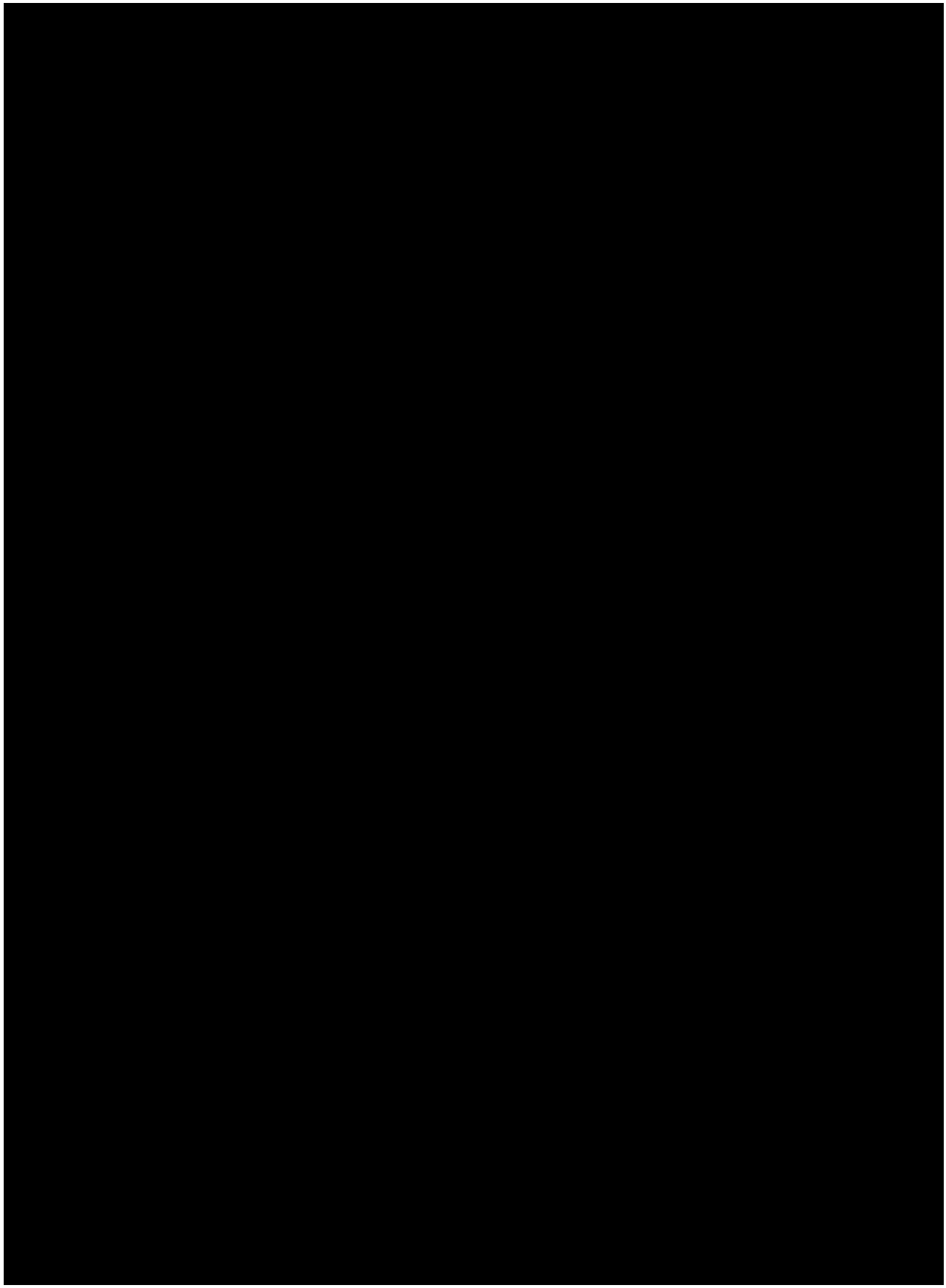
#### 7.2.3.3 Analytical method

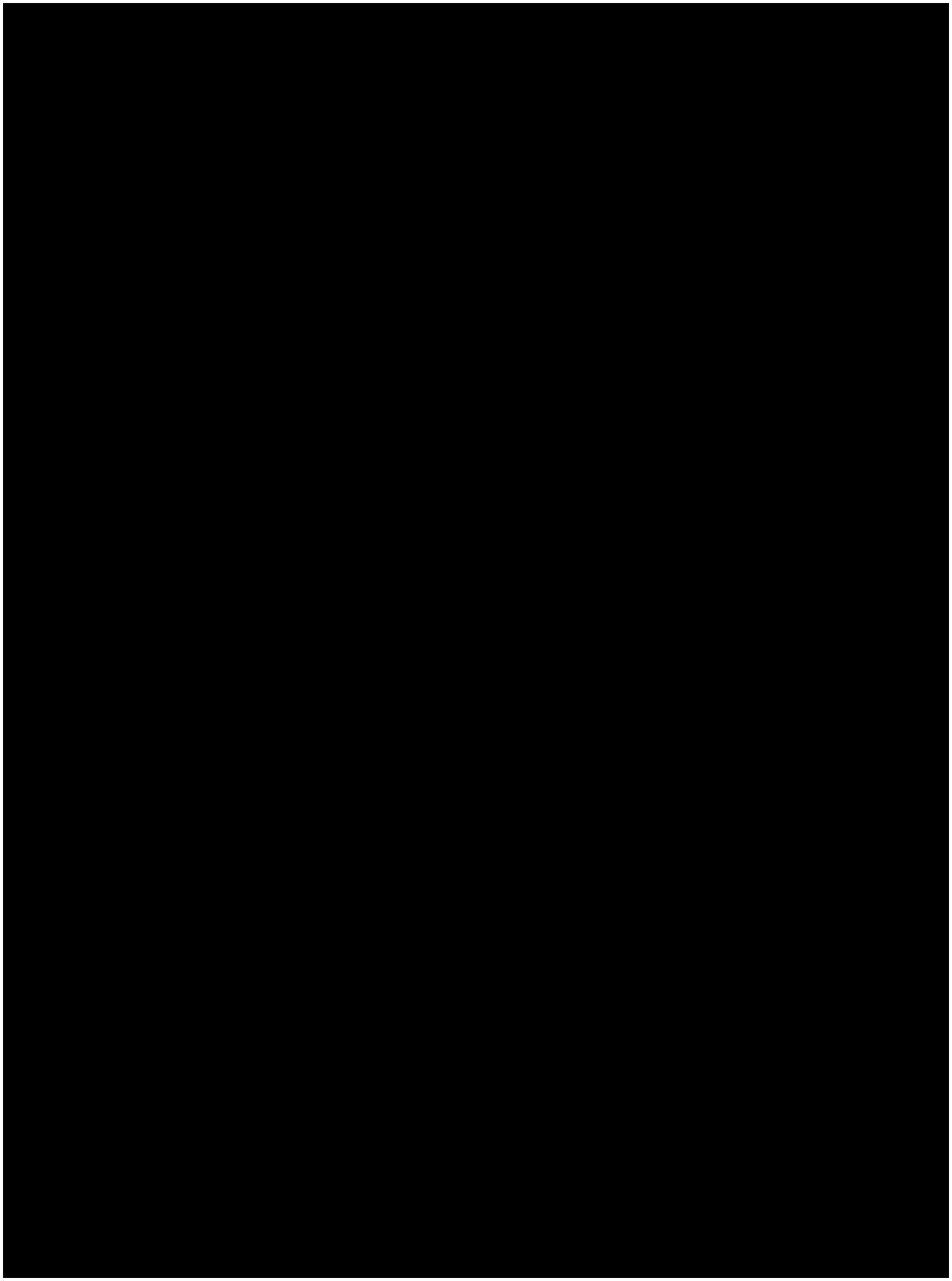
The plasma samples from all patients will be assayed for ruxolitinib concentrations using validated liquid chromatography-tandem mass spectrometry method (LC-MS/MS).

Values below the lower limit of quantification (LLOQ) of ruxolitinib at approximately 0.500 ng/mL will be reported at 0.0 ng/mL. Missing values will be labeled accordingly.

[redacted]







[redacted]

### 7.2.6 Patient reported outcomes

In order to measure Quality-of-Life for patients affected by aGVHD, and potential changes overtime, two PRO instruments are administered, FACT-BMT (Appendix 8) and EQ-5D-5L (Appendix 9) PRO instruments are to be administered as outlined in Table 7-1and Table 7-2.

- 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 EQ-5D-5L descriptive classification consists of five dimensions of health: mobility, self-care, usual activities, anxiety/depression, and pain/discomfort (Brooks 1996). In the older and most commonly used version, each dimension of health has three levels of severity; however, a new five-level version has recently been published (Herdman 2011).

There are currently no validated PROs in aGvHD but several studies provide some insight into how aGvHD does or does not affect patient-reported measures (Lee 2010). The group at the Dana-Farber Cancer Institute studied 96 patients transplanted from 1999 to 2004 who provided a baseline Short Form 12 (SF-12) and FACT-BMT with at least 1 follow-up at 6 or 12 months. Grade II-IV aGvHD was associated with worse quality of life at 6 months (Lee and Williams, BBMT 2010; Lee et al. BMT 2006). Some ongoing aGvHD prevention and treatment trials include PROs that will further help define the role of these endpoints in GVHD trials. For example, the recently completed, randomized, placebo-controlled trial of mesenchymal stem cells for steroid-refractory aGvHD treatment collected the FACT-BMT at treatment days 0, 30, 100, and 180 (N5280) (Lee 2010).

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-5L 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. London: NICE; 2008).

# 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.

For patients who sign the Screening ICF only (and not Study ICF), AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.2 and are possibly related to study procedures (e.g. an invasive procedure such as biopsy). Once the study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

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 CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment or at least 30 days after the End of Treatment visit, whichever occurs last. 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.

AEs will not be collected beyond 30 days after the End of Treatment visit, with the exception of any occurrence of second primary malignancy including non-melanoma skin cancer which will be captured under the AE form throughout the study, including the Long Term Follow-up period, as outlined in Section 8.1.3.

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

Grade 1 to 5 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening and death due 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 through 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).
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.
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF 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 CRF 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 CRF.

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

The following events, which are components of study endpoints: worsening of study indication (aGvHD) including occurrence of aGvHD flare as defined in Section 3, occurrence of chronic GvHD, or progression/relapse of underlying hematologic disease (including fatal outcomes) as defined in Appendix 4, should not be reported as a serious adverse event and will be reported on specific CRFs other than AE CRF.

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 study 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 CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

### 8.1.3 Adverse events of special interest

Adverse Events of Special Interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Risks and Benefits (Section 2.6) and the most recent Investigator Brochure.

AESI will include but may be not limited to:

- Cytopenias
- Infections
- Bleeding
- Hypertension
- Second primary Malignancies including non-melanoma skin cancer .

## 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 study indication
  - Occurrence of chronic GvHD
  - Progression/relapse of underlying hematologic disease (including fatal outcomes), as defined in Appendix 4
  - 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

### 8.2.2 Reporting

For patients who sign the Screening ICF, SAE collection will start upon signing the Screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the Study ICF is not signed (screen failure), SAE collection ends 30 days after the last study related procedure.

For patients who sign the Study ICF, SAE collection starts at time of Study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided Study informed consent and until at least 30 days after the patient has stopped study treatment or at least 30 days after the End of Treatment visit, whichever occurs last, must be reported to Novartis within 24 hours of learning of its occurrence. Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30-day safety evaluation follow-up, or later than 30 days after the End of Treatment visit, whichever occurs last, should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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

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

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the Novartis study treatment, a Chief Medical Office and Patient Safety (CMO & PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees 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 Novartis within 24 hours of learning of its occurrence. Occurrence of Pregnancy should be monitored for 90 days after stopping treatment (i.e. End of treatment or Cross-Over End of treatment whichever comes last). 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. The follow-up to three months after delivery is mandatory for all reported pregnancy cases and in cases of live birth, the follow-up on any development issues or abnormality that would not be seen at birth.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO & PS). 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 should be collected for the female partners of any males who took study treatment including best available therapy (BAT) in this study. 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 review safety data as outlined in a separate DMC charter that is established between the sponsor and the DMC.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and conclusion will also be described in the DMC charter. 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 dedicated analysis plan.

## 8.7 Steering Committee

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

# 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.

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 patients 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 CRFs 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 CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs 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 CRF 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 CRFs are performed according to the study-specific monitoring plan.

## 9.3 Data collection

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

## 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.

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

Randomization codes and data about 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, who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

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

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

# 10 Statistical methods and data analysis

The primary efficacy and safety analysis will be conducted when all patients have completed the Day 56 visit or discontinued earlier. Prior to this analysis time, no summary reports by actual

treatment groups will be produced. Further analyses on secondary endpoints will be performed when all patients have completed approximately 6 months treatment or discontinued earlier. The final study report will be written once all patients have completed the study. An analysis cut-off date will be defined corresponding to these time points and all data captured in the study up to that cut-off will be reported.

## 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.

### 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 the requirements of the clinical study protocol.

The protocol deviations leading to exclusion from the PPS include:

- Not steroid refractory aGvHD.
- More than one prior systemic therapy for the treatment of aGvHD other than corticosteroids +/- CNI (prophylaxis or treatment).
- Missing or incorrect aGvHD grade at randomization.
- Taking any prohibited medication as specified in this protocol after start of study treatment and before end of study treatment.
- Study treatment received is different from treatment arm 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 patients who provide at least one evaluable PK concentration. For a concentration to be evaluable, patients are required to:

- Take a dose of ruxolitinib prior to sampling.

For pre-dose samples, do not vomit within 2 hours after the dosing of ruxolitinib prior to sampling; for post-dose samples, do not vomit within 2 hours after the dosing of ruxolitinib. The PAS will be used for NCA analysis for patients where extensive PK sampling is obtained.

This analysis set will also be used for any exposure-response analysis and/or exploratory exposure-biomarker analysis.

### 10.1.6 Other analysis sets

The Crossover Analysis Set (CAS) comprises all patients randomized to and received BAT who then crossed over and received at least one dose of ruxolitinib. This analysis set will be used for all analyses for crossover patients.

## 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.

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 crossover treatment.

Baseline for efficacy endpoints is defined as the last assessment or procedure conducted prior to or on the date of randomization + 3 days, but no later than the treatment start 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 (computed as the ratio of actual cumulative dose received and actual duration of exposure) for the ruxolitinib arm will be summarized.

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.

The number of patients with dose adjustments and the reasons will be summarized for 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 to BAT as assessed by overall response rate at Day 28.

### 10.4.1 Variable

The primary variable is the overall response rate (ORR) at Day 28, defined as the proportion of patients with complete response (CR) or partial response (PR), according to standard criteria (Harris 2016). Note that response is relative to the assessment of aGvHD at randomization.

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

A flare in aGvHD is defined as any increase in signs or symptoms of aGvHD after an initial response (CR or PR).

Only flares in GvHD that require new additional systemic therapy, will be considered aGvHD flare failure. Patients with missing baseline or Day 28 aGvHD response assessment will be considered as treatment non-responders.

Acute GvHD will be assessed according to standard criteria (Harris 2016), as described in Appendix 1. Grade will be calculated based on the staging of the organs and recorded on the eCRF by the Investigator. The Investigator reported grade will be used for randomization and all analyses. Grade and response will be calculated by the sponsor for the purposes of data review and sensitivity analysis.

### 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 Day 28 in the ruxolitinib and BAT groups, respectively. The Cochrane-Mantel-Haenszel chi-square test, stratified by the

randomization stratification factor (i.e., aGvHD Grade II vs III vs. IV), 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 Day 28, will be analyzed at the time when all patients have completed their Day 56 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 be also 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 aGvHD response assessments at baseline and Days 28, 56. Patients who discontinue the randomized treatment prior to the completion of the Day 28 visit will be considered non-responders on that treatment arm.

The analysis windows will be further defined in the analysis plan.

Baseline assessment is the last aGvHD assessment prior to or on the date of randomization (Day 1). A tolerance of up to 3 days from randomization will be considered in the analysis, but the baseline assessment will not be later than the date of treatment start.

### 10.4.4 Supportive and Sensitivity analyses

As supportive analyses, the primary endpoint will also be evaluated with the same analysis conventions as for the primary efficacy analysis using all patients in PPS.

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 on the FAS. The subgroups include but may not be limited to:

- Age group (12- <18 vs. 18-65 vs. >65)
- Gender
- Race
- aGvHD grade (Grade II vs. III vs. IV)
- Source of grafts
- Criteria for SR-aGvHD (progression after at least 3 days, failure to achieve a response after 7 days, flare failure during taper)
- Prior aGvHD therapy (steroid +/- CNI vs. steroid +/- CNI +/- BAT)

## 10.5 Secondary objectives

The secondary objectives in this study are durable overall response rate at Day 56, duration of response, overall survival (OS), non-relapse mortality (NRM), incidence of malignancy relapse and onset of chronic GvHD, pharmacokinetics (PK), patient reported outcomes (PROs), and safety.

Durable ORR at Day 56 is identified as the key secondary endpoint. A hierarchical testing strategy will be used to control the overall type I error rate, where durable ORR at Day 56 will

only be formally tested and interpreted if the primary analysis of ORR at Day 28 is statistically significant.

The other secondary estimates will be estimated for both treatment arms, ruxolitinib and BAT but no comparison or testing between arms will be performed.

### 10.5.1 Key secondary objective(s)

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

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

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

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

where $DORR_{rux}$ and $DORR_{BAT}$ are the durable overall response rates at Day 56 in the ruxolitinib and BAT groups, respectively. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factor (i.e., aGvHD Grade II vs III vs. IV), will be used to compare the durable ORR between the two treatment groups, at the one-sided 2.5% level of significance, if the primary endpoint is significant.

The key secondary efficacy variable, durable ORR at Day 56, will be analyzed at the time when all patients have completed their Day 56 visit or discontinued earlier. The analysis will be based on FAS according to ITT principle. Durable 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 be also presented.

As supportive analyses, the key secondary endpoint will also be evaluated with the same analysis conventions using the PPS.

### 10.5.2 Other secondary efficacy objectives

All other secondary efficacy endpoint analyses are non-comparative in nature and will be analyzed using the full analysis set (FAS).

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

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

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

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

DOR will be listed and summarized by treatment group for all patients in the FAS with overall response of CR or PR at Day 28.

- Overall survival (OS)

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

OS will be analyzed according to the randomized treatment group and strata assigned at randomization (aGvHD grade: Grade II vs. III vs. IV). The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, 1, 2, 6, 12, 18 and 24 month survival estimates and 95% confidence intervals will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

- Event Free Survival (EFS)

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

- Failure Free Survival (FFS)

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

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

- Non-relapse mortality (NRM)

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

NRM will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization (aGvHD grade: Grade II vs. III vs. IV). The cumulative

incidence curve for NRM as well as estimates at 1, 2, 6, 12, 18 and 24 months with 95% confidence intervals will be presented for each treatment group.

- Incidence of Malignancy Relapse/Progression (MR)

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

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

- Best Overall Response (BOR)

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

- Cumulative steroid dosing until Day 56

Overall and weekly cumulative steroid dose for each patient up to Day 56 or discontinuation of randomized treatment will be tabulated. In addition the relative dose intensity (RDI), by week, will be calculated relative to the starting dose of corticosteroids and categorized as (1) Complete reduction where patients are tapered off corticosteroids by D56, (2) $\leq$ 50% RDI and (3) > 50% RDI. The proportion of patients in each category and corresponding 95% confidence intervals will be presented by treatment group.

- Proportion of patients who developed cGvHD

The cumulative incidence of cGvHD will be estimated, accounting for deaths without prior onset of cGvHD and hematologic disease relapse/progression as the competing risks. If a patient is not known to have event or competing risks, then the incidence of cGvHD will be censored at the latest date the patient was known to be alive (on or before the cut-off date).

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

#### 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 (randomized or crossover), the treatment-emergent AEs.

For reporting of AEs, the overall observation period will be divided into mutually exclusive categories, including the on-treatment period as defined below.

1. pre-treatment period: from day of patient's informed consent to the day before first dose of randomized study medication
2. on-randomized treatment period: from day of first dose of randomized study medication to 30 days after last dose of randomized study medication 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, or end of randomized treatment per End of Randomized Treatment Disposition eCRF, whichever is later (ii) the day before first dose of crossover treatment
3. on-crossover treatment period: from day of first dose of crossover study medication to 30 days after last dose of crossover study medication or end of crossover treatment per End of Crossover Treatment Disposition eCRF, whichever is later.
4. post-treatment period: starting at Day 31 after last dose of study medication or the day after end of study treatment per end of treatment disposition eCRFs, whichever is later

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) such as worsening cytopenias, infections, etc. 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.

The proportion of patients developing Grade 2 to 3 infections using infection severity (Appendix 2) during the aGvHD treatment period Day 1 to Day 56 will be summarized in addition to standard CTC grading. In addition, proportion of patients developing second primary malignancies will be summarized based on the entire study period.

#### 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.

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 v4.03 grades to compare baseline to the worst on-treatment value

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.

[redacted]

#### 10.5.3.4 Other safety data

**Vital signs**

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

#### 10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

#### 10.5.3.6 Tolerability

The number and percentage of patients who have a dose adjustment, interruption, or permanent discontinuation due to a treatment related Adverse Event will be summarized by preferred term and treatment group. The number and percentage of patients who have a dose increase, reduction, or interruption will be summarized.

### 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.

**Pharmacokinetic variables:**

Pharmacokinetic 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 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, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1) |
| Ctrough | The observed plasma concentration obtained prior to administration of the next dose (pre-dose concentration) (mass x volume-1) |
| Tmax | The time to reach maximum (peak) plasma, blood, serum, or other body fluid 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). |
| 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) |
| Racc | Accumulation ratio (AUC at steady state/AUC Day 1) |

**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), SD, 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, standard deviation (SD), coefficient of variation (CV)% for mean, geometric mean, geometric CV%, median, minimum and maximum) will be provided for all PK parameters by 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.

[redacted]

**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 exposure and efficacy response, with efficacy response defined as: overall response rate at Day 28 and durable response at Day 56; overall survival at 6 months; any other relevant endpoints, and exposure defined plasma concentration, PK parameter or dose, as appropriate.
- Characterize the exposure-safety relationship of ruxolitinib in terms of exposure and safety response, where safety response is defined as various categorizations of AEs (frequency of AEs, severity of AEs, AEs of interest) or laboratory parameters.
- Average steady-state exposures and/or other PK parameters for the population will be computed by the POP PK model accounting for dose modifications or dose interruptions up to the day prior to the day of assessments. Population PK derived parameters will be used for exposure-response analysis by appropriate methods.

#### 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]

### 10.5.7 Patient-reported outcomes

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

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) will be used to summarize the scored scales at each scheduled assessment time point for the FACT-BMT and EQ-5D-5L. 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.

FACT-BMT will not be used in patients under age 18 years.

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]

## 10.7 Interim analysis

No formal interim analysis is planned for this trial. The primary efficacy and safety analysis will be performed after all patients have completed Day 56 visit or discontinued earlier. Further analyses on secondary endpoints will be performed when all patients have completed approximately 6 months of treatment or discontinued earlier. The final study report will be written once all patients have completed the study. Formal testing of the primary and key secondary endpoints with full alpha will be performed for the primary analysis only.

**Early PK analysis**

The early extensive PK data on ruxolitinib from 25 adult patients 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-aGvHD population to the known exposure in MPN patients 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 study with a total of 308 patients and 1:1 randomization (ruxolitinib vs. BAT) stratified on aGvHD grade (Grade II vs. Grade III vs. Grade IV) has 90% power to test for the primary endpoint (ORR at Day 28) and approximately 90% power to test for the key secondary endpoint (durable ORR at Day 56). The family wise α-level will be controlled at 0.025 overall for the two comparisons. Specifically, this study will claim to have achieved the efficacy objective when the primary endpoint ORR at Day 28 shows a significant treatment effect at one-sided $\alpha = 0.025$. Conditional on significance of the primary endpoint, the key secondary endpoint durable ORR at Day 56 will be tested at one-sided $\alpha = 0.025$.

The sample size calculation is based on the primary variable ORR at Day 28. The hypotheses to be tested and details of the testing strategy are described in Section 10.4.2 and Section 10.8.

Based on Martin P. et al BBMT 2013, the ORR at Day 28 in the BAT arm is expected to be 58%. The stratum specific rates (Grade II 69%, Grade III 59%, Grade IV 50%) are obtained assuming that the ratio of aGvHD Grade II: III: IV is 0.2:0.4:0.4. It is expected that treatment with ruxolitinib will result in an 18% increase in the ORR, i.e., an expected odds ratio of 2.25 (which corresponds to an increase in ORR to 75%). Power for the CMH test, stratifying on aGvHD grade, was calculated using software package East V6. In order to ensure 90% power a total sample size of 308 patients are needed.

With a sample size of 154 patients in each treatment arm, an observed odds ratio greater than or equal to 1.63 would achieve statistical significance for the primary endpoint. Assuming that the observed response rates in Grades II/III/IV in BAT arm are 69%/59%/50% (overall 57%), observed response rates ≥ 78%/70%/62% (overall 68%) in the ruxolitinib arm would achieve statistical significance.

## 10.9 Power for analysis of key secondary variables

Durable ORR at Day 56, as the key secondary variable, will be formally statistically tested, provided that the primary endpoint ORR at Day 28 is statistically significant. The hypotheses to be tested and details of the testing strategy are provided in Section 10.5.1. Based on (Van Groningen 2016), the durable ORR at Day 56 in the BAT arm is expected to be approximately 35%. The stratum specific rates (Grade II 45%, Grade III 36%, Grade IV 30%) are obtained assuming that the ratio of aGvHD Grade II: III: IV is 0.2:0.4:0.4. It is expected that treatment with ruxolitinib will result in a 20% increase in the ORR, i.e., an expected odds ratio of 2.25 (which corresponds to an increase in durable ORR to 55%). With these assumptions and sample size of 308 patients, the power for the key secondary endpoint is at least 90%.

With sample size 154 patients in each treatment arm, an observed odds ratio greater than or equal to 1.59 for durable ORR at Day 56 would achieve statistical significance. Assuming that the observed durable response rates in Grades II/III/IV in BAT arm are 45%/36%/30% (overall 35%), observed durable response rates ≥ 57%/47%/41% (overall 47%) in the ruxolitinib arm would achieve statistical significance.

# 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 providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

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

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) 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 Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

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.

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.

According to Novartis policy, authors of publication 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.

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 patients. 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, patients' 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 Novartis. 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: Acute GvHD Staging Criteria (Harris 2016)

Organ staging will be performed according to updated NIH criteria as described by Harris et al in Table 14-1.

**Table 14-1 Acute GvHD Staging Criteria (Harris 2016)**

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

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or stage 2-3 lower GI with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver or lower GI involvement, with stage 0-1 upper GI.

## 14.2 Appendix 2: Infection Severity Grading

**Table 14-2 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<br>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.<br>*Pneumocystis jiroveci* pneumonia (regardless of PaO2 level) |
| Viral infections | Mucous HSV infection | | |

| Type of Infection/ Severity Grade | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| | 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 |
| | | 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 (or per Table 14-3)
- Pressors at any dose
- Two of the following:
  - Capillary refill > 5 secs
  - Core to peripheral temperature gap > 3oC
  - Urine output < 0.5 mL/kg/hr
  - Unexplained metabolic acidosis (Base deficit > 5.0 mEq/L)
  - Blood lactate > 2 x ULN

**Respiratory**:

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

**Neurological**:

- Glasgow Coma Score < 11 or

- Acute change in mental status with a decrease in GSC >3 pts from abnormal baseline

**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 14-3 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:

1. CMV, HSV, EBV, HHV6: 2 months (< 60 days)
2. VZV, HZV: 2 weeks (< 14 days)
3. Bacterial, non-C. difficile: 1 week (< 7 days)
4. Bacterial, C. difficile: 1 month (< 30 days)
5. Yeast: 2 weeks (< 14 days)
6. Molds: 3 months (< 90 days)
7. Helicobacter: 1 year (< 365 days)
8. Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (< 14 days)
9. Polyomavirus (BK virus): 2 months (< 60 days)

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

## 14.3 Appendix 3: Grading of Chronic GvHD (NIH Criteria)

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

| | | | | |
|---|---|---|---|---|
| **MOUTH**<br>*Lichen planus-like features present:*<br>☐ **Yes**<br>☐ **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):* | | | | |

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **PERFORMANCE SCORE:** ☐<br>**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†** ☐<br>**SCORE % BSA**<br>*GVHD features to be scored by BSA:*<br>**Check all that apply:**<br>☐ Maculopapular rash/erythema<br>☐ Lichen planus-like features<br>☐ Sclerotic features<br>☐ Papulosquamous lesions or ichthyosis<br>☐ 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:**<br>☐ Deep sclerotic features<br>☐ "Hidebound" (unable to pinch)<br>☐ Impaired mobility<br>☐ 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.

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **EYES**<br><br>*Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:*<br>☐ **Yes**<br>☐ **No**<br>☐ **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**<br>***Check all that apply:***<br>☐ Esophageal web/ proximal stricture or ring<br>☐ Dysphagia<br>☐ Anorexia<br>☐ Nausea<br>☐ Vomiting<br>☐ Diarrhea<br>☐ Weight loss ≥5%*<br>☐ 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:**<br>% FEV1 ☐ | ☐ FEV1≥80% | ☐ FEV1 60-79% | ☐ FEV1 40-59% | ☐ FEV1 ≤39% |
| *Pulmonary function tests*<br>☐ Not performed | | | | |
| ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____ | | | | |

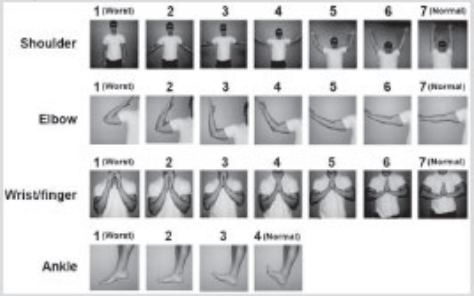
| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **JOINTS AND FASCIA**<br><br>P-ROM score<br>*(see below)*<br>Shoulder (1-7):___<br>Elbow (1-7): ____<br>Wrist/finger (1-7):___<br>Ankle (1-4):___ | ☐ No symptoms | ☐ Mild tightness of arms or legs, normal or mild decreased range of motion (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**<br>(*See Supplemental figure*‡)<br>☐ Not examined<br>*Currently sexually active*<br>☐ Yes<br>☐ 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)**



## 14.4 Appendix 4: Hematologic Disease Relapse/Progression definitions

**Malignancy relapse/progression is defined as follows:**

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

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

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

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

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

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

The reappearance of cytogenetic abnormalities present prior to transplantation

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

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

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

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

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

**Non-Malignant Hematologic Disease progression is defined as follows:**

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

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

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

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

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

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

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

## 14.5 Appendix 5: HCT Specific Comorbidity Index Score

The HCT-Specific Comorbidity Index Score is described in Table 14-4 below.

**Table 14-4 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<br>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<br>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<br>Dyspnea at rest or requiring oxygen | 3 |

Total score is the sum of all comorbidities present at time of transplantation.

AST: aspartate aminotransferase; ALT; alanine aminotransferase; CTD: connective tissue disease; DLCO: diffusing capacity of the lung for carbon monoxide; EF: ejection fraction; FEV1: forced expiratory volume in 1 second; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ULN: upper limit of normal.

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

## 14.6 Appendix 6: CIMBTR classification

CIBMTR risk assessment should be performed as described in Table 14-5.

**Table 14-5 CIBTMR disease risk index**

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| **AML and ALL**<br>precursor B-lymphoblastic lymphoma/leukemia {per W.H.O. reclassified from lymphoma}<br>precursor T-lymphoblastic lymphoma/leukemia | **Low risk:**<br>CR 1 | **First complete remission (CR1**):A treatment response where all of the following criteria are met for at least four weeks*†:<br>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<br>Platelets ≥ 100,000/µL*†<br>Transfusion independent<br>No other signs or symptoms of disease, including extramedullary disease(e.g., central nervous system or soft tissue involvement)<br>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.<br>*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.<br>**NOTE: Recipients with MDS that transformed to AML**<br>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:**<br>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. |

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| **AML and ALL (con"t)** | **High risk (not in remission):**<br>Never treated<br><br>Primary Induction Failure (PIF)<br>Relapse | **Never treated:** The recipient was diagnosed with acute leukemia and never treated.<br>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.<br><br>**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.<br><br>**Relapse:** Recurrence of disease after CR. Relapse is defined as:<br>≥ 5% blasts in the marrow<br>Extramedullary disease<br>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.<br>Although CIBMTR collects information upon the number of the relapse, this information is not needed for the ASBMT RFI |
| **CML** | **Low risk:**<br>Hematologic CR1<br>CP1 | Hematologic CR 1 deriving from first Chronic Phase (never in AP or BP).<br>A treatment response where all of the following criteria are met:<br>White blood count is less than 10 x 109/L, without immature granulocytes and with less than 5% basophils<br>Platelet count less than 450 x 109/L<br>Non-palpable spleen<br>**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:<br>Relatively few blasts (<10%) present in the blood and bone marrow.<br>Symptoms are often not present.<br>The chronic phase may last several months to years depending on the individual recipient and the treatment received.<br>Although CIBMTR collects additional information regarding cytogenetic and molecular response, this information is not needed to complete the RFI. |
| **CML (con't)** | **Intermediate risk:**<br>CP2<br>Hematologic CR2<br>Hematologic CR deriving from AP or BP<br>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.<br>**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).<br>**Hematologic CR deriving from AP or BP**: Hematologic CR occurring after treatment for a **single** previous episode of AP or BP. |

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| | | **Accelerated phase 1 (AP1):** One or more of the following must be present (WHO definition):<br>10-19% blasts in blood or marrow<br>≥ 20% basophils in peripheral blood<br>Clonal cytogenetic abnormalities in addition to the single Philadelphia chromosome (clonal evolution)<br>Increasing spleen size, unresponsive to therapy<br>Increasing WBC, unresponsive to therapy<br>Thrombocytopenia (platelets < 100,000) unrelated to therapy<br>Thrombocytosis (platelets > 1,000,000) unresponsive to therapy |
| **CML (con't)** | **High risk:**<br>CP3/+,<br>Hematologic CR3/+ AP2/+<br>BP (Blast phase) | • **Third chronic phase (CP3):** Recipients had two or more AP/BP and was treated back into CP or hematologic CR<br>**Hematologic CR3:** Recipients who have achieved two prior hematologic CRs, progressed, and achieved a third hematologic CR after treatment.<br>**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.<br>**Blast Phase/Crisis (BP):**<br>≥ 20% blasts (formerly ≥ 30%) in the peripheral blood or bone marrow<br>Extramedullary blastic infiltrates (i.e., myeloid sarcoma, granulocytic sarcoma, or chloroma) |
| **CLL (includes PLL)**<br>**(report Hairy Cell Leukemia as „other", see last row of table)** | **Low risk:**<br>CR (includes CR2 or subsequent CR)<br>nPR | **Complete remission (CR):** The disease is completely absent and no relapse occurred prior to the preparative regimen. Requires all the following:<br>No lymphadenopathy<br>No organomegaly<br>Neutrophils > 1.5 x $10^9$/L<br>Platelets > 100 x $10^9$/L<br>Hemoglobin 11g/dL<br>Lymphocytes < 4 x $10^9$/L/L<br>Bone marrow < 30% lymphocytes<br>Absence of constitutional symptoms<br><br>**Nodular Partial Remission (nPR)** complete response with persistent lymphoid nodules in bone marrow. |
| **CLL (con't)** | **Intermediate risk:**<br>PR<br>Never treated<br>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:<br>50% decrease in peripheral blood lymphocyte count from pretreatment value<br>50% reduction in lymphadenopathy if present pretreatment<br>50% reduction in liver and spleen size if enlarged pretreatment |

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|---|---|---|
| | | **AND one or more** of the following:<br>Neutrophils ≥ $2.5x10^9$/L or 50% above baseline<br>Platelets > $100x10^9$/L or 50% improvement over baseline<br>Hemoglobin > 11.0 g/dL or 50% improvement over baseline<br><br>**Never Treated:** The recipient was diagnosed with leukemia and never treated.<br><br>**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:**<br>NR/SD<br>Progression | **No Response/Stable disease (NR/SD):** No change OR Less than 50% change in disease.Not complete response, partial response, or progressive disease.<br><br>**Progression:** Increase in disease burden or new sites of disease. Requires one or more of the following:<br>≥ 50% increase in the sum of the products of ≥ 2 lymph nodes (≥ 1 node must be ≥ 2 cm) or new nodes<br>≥ 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly<br>≥ 50% increase in absolute lymphocyte count to ≥ 5 x $10^9$/L<br>Transformation to a more aggressive histology, e.g. transform to diffuse large B-cell lymphoma known as Richter's transformation. |
| **MDS**<br>(Note all MPD are reported as "other". JMML has its own category on the ASBMT RFI Outcomes Data table) | **Low risk:**<br>RA<br>RARS<br>RCMD<br>RCMD/RS<br>MDS Unclassifiable isolated 5q- syndrome | **RA/RARS/RCMD/RS/ MDS-NOS** and <5% blasts, isolated 5q-syndrome/ |
| **MDS (con't)** | **High risk:**<br>RAEB<br>RAEB-T<br>RAEB-1<br>RAEB-2<br>CMML | RAEB/RAEB-T/RAEB-1/RAEB-2/ **CMML**<br><br>NOTE: RAEB and RAEB-T have been replaced in current WHO nomenclature by RAEB-1 or RAEB-2 |

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| **Hodgkin Disease/Hodgkin Lymphoma†** | **Low Risk:**<br>CR1<br>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.<br><br>**CR1 Unconfirmed (CRU1):** Complete disappearance of all known disease for ≥ 4 weeks with the exception of persistent scan abnormalities of unknown significance†.<br>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:**<br>CR2/+<br>CRU2/+<br>PR without prior CR (PR1)<br>PR with prior CR (PR2+)<br>(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†.<br><br>**CR2+ Unconfirmed (CRU2+):** The recipient has achieved a second or subsequent complete response but has persistent radiographic abnormalities of unknown significance<br><br>**Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites.<br>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. |
| **Hodgkin Disease/Hodgkin Lymphoma† (con't)** | **High risk:**<br>Never treated<br>Primary Refractory (PIF res)<br>Relapse untreated (any number)<br>Relapse resistant (any number) | **Never Treated**: The recipient was diagnosed with lymphoma and never treated.<br><br>**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.<br><br>**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) †**<br>Includes the following diseases: splenic marginal zone B-cell lymphoma, extranodal marginal | **Low risk:**<br>CR1<br>CRU1 | **CR1 Confirmed**: Complete disappearance of all known disease for ≥ 4 weeks†. The term "confirmed" is defined as a laboratory and/or pathological or radiographic determination. |

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|---|---|---|
| zone B-cell lymphoma of MALT type,<br>nodal marginal zone B-cell lymphoma, follicular lymphoma (Grade I-III and unknown)<br>**Waldenstrom macroglobulinemia (lymphoplasmacytic lymphoma**) should be reported as 'Other' | | **CR1 Unconfirmed (CRU1):** Complete disappearance of all known disease for ≥ 4 weeks with the exception of persistent scan abnormalities of unknown significance†. The term "unconfirmed" is defined as scan abnormalities of unknown significance that are not biopsied or otherwise evaluated. |
| | **Intermediate risk:**<br>CR2/+,<br>CRU2/+<br>PR with prior CR<br>PR without prior CR (includes any sensitive relapse)<br>Never Treated | **CR2+ Confirmed:** The recipient relapsed, then achieved complete absence of disease for at least one month without radiographic evidence of disease†.<br><br>**CR2+ Unconfirmed (CRU2+):** The recipient has achieved a second or subsequent complete response but has persistent radiographic abnormalities of unknown significance.<br><br>**Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites.<br>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.<br><br>**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**:<br>Primary Refractory<br>Relapse untreated (any number)<br>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.<br><br>**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. |

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| **NHL (Aggressive/ Intermediate andHigh Grade)** Includes the following diseases: mantle cell lymphoma, diffuse large B-cell lymphoma, Burkitt's lymphoma/Burkitt cell leukemia, high grade B-cell lymphoma, Burkitt- like (provisional entity), adult T-cell lymphoma/leukemia (HTLV1+), aggressive NK-cell leukemia, extranodal NK/T-cell 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 | **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.<br><br>**CR1 Unconfirmed (CRU1):** Complete disappearance of all known disease for ≥ 4 weeks with the exception of persistent scan abnormalities of unknown significance†. The term "unconfirmed" is defined as scan abnormalities of unknown significance that are not biopsied or otherwise evaluated. |
| **NHL (Aggressive/ Intermediate and High Grade) (con't)** | **Intermediate risk:** CR2/+, CRU2/+ PR with prior CR PR without prior CR (includes any sensitive relapse) | **CR2+ Confirmed**: The recipient relapsed, then achieved complete absence of disease for at least one month without radiographic evidence of disease†.<br><br>**CR2+ Unconfirmed (CRU2+):** The recipient has achieved a second or subsequent complete response but has persistent radiographic abnormalities of unknown significance<br><br>**Partial remission- (PR):** Reductions of ≥ 50% in greatest diameter of all sites of known disease and no new sites.<br>Partial response may be represented as PR1, PR2, etc. There are differing interpretations of what |

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| | | 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. |
| **NHL (Aggressive/ Intermediate and High Grade) (con't)** | **High risk:**<br>Primary refractory<br>Relapse untreated (any number)<br>Relapse resistant (any number)<br>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.<br><br>**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.<br><br>**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:**<br>CR1 (includes first sCR) VGPR 1 (eg VGPR without prior CR)<br>PR1 (eg PR without prior CR) | CR1, (**CR**) A treatment response where all of the following criteria are met:<br>Negative immunofixation on serum and urine samples<br>Disappearance of any soft tissue plasmacytomas<br>< 5% plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed)<br><br>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.<br>Stringent Complete Remission (sCR) Follow criteria for CR as defined above PLUS Normal free light chain ratio AND<br>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)<br><br>**Very Good Partial Response (VGPR)** Serum and urine M protein detectable by immunofixation but not on electrophoresis, or >= 90% reduction in serum M-protein and urine M protein level < 100 mg/24h<br>**PR without prior CR (PR1)**<br>Both of the following must be present:<br>≥ 50% reduction in serum M-protein |

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|---|---|---|
| | | Reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours.<br>If the serum and urine M-protein are not measurable (i.e., do not meet any of the following criteria:<br>Serum M-protein ≥ 1 g/dL,<br>Urine M-protein ≥ 200 mg/24 hours;<br>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)**<br>CR1 (includes first sCR)<br>VGPR 1 (eg VGPR without prior CR)<br>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%.<br>In addition to the above listed criteria, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required, if present at baseline.<br>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.<br>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:**<br>Relapse from CR (untreated)<br>CR2/+<br>sCR2/+<br>VGPR2/+<br>PR2/+ (with prior CR)<br>SD<br>Progression<br>Never treated<br>PR2/+ | **Relapse from CR (untreated)** Requires one or more of the following:<br>Reappearance of serum or urine M-protein by immunofixation or electrophoresis<br>Development of ≥ 5% plasma cells in the bone marrow (relapse from CR has a 5% cutoff vs. 10% for other categories of relapse)<br>Appearance of any other sign of progression (e.g., new plasmacytoma, lytic bone lesion, hypercalcemia)<br>**Relapse requires two consecutive assessments made at any time before classification as relapse, and/or the institution of any new therapy†**<br><br>**CR2/+:** Same criteria as „Myeloma low risk CR", except a relapse must have occurred and recipient was treated back into CR.<br><br>**sCR2/+:** see sCR definition for MM, except a relapse must have occurred and recipient was treated back into sCR<br><br>**VGPR2/+:** See VGPR definition.<br>**PR2/+ (with prior CR):**<br>Same criteria as 'Myeloma low risk PR', except a relapse must have occurred and treatment back into PR. |

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| **Multiple Myeloma (con't)** | **High risk (Con't):**<br>Relapse from CR (untreated) CR2/+<br>sCR2/+VGPR2/+ PR2/+ (with prior CR)<br>SD Progression Never treated PR2/+ | **SD:**<br>Does not meet the criteria for CR, VGPR, PR, or PD.<br><br>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<br><br>**Progression:** Requires one or more of the following:<br>Increase of ≥ 25% from the lowest response value achieved:<br>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)<br>Urine M-component with an absolute increase ≥ 200 mg/24 hours<br>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<br>Bone marrow plasma cell percentage with absolute percentage ≥ 10%<br>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<br>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<br>PD requires two consecutive assessments made at any time before classification as disease progression, and/or the institution of any new therapy†. |
| **Solid Tumors:**<br>**Adult** Includes: breast cancer, Ewings sarcoma, germ cell cancers, neuroblastoma, ovarian cancer, rhabdomyosarcoma, testicular cancer, renal cell carcinoma and any other solid tumors | All clinical status at HCT | |
| **Solid Tumors:**<br>**Pediatric**<br>Neuroblastoma | **Intermediate Risk**<br>CR1<br>CRU1<br>VGPR1<br>PR1 (PR without prior CR)<br>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.**<br><br>**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* |

| ASBMT Diagnosis Category | ASBMT RFI Classification | CIBMTR Classification^ |
|---|---|---|
| | | **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)<br><br>**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.<br><br>**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<br><br>**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:**<br>**Pediatric**<br>Neuroblastoma (con't) | **High Risk**<br>CR2/+<br>CRU2/+<br>PR2/+ (with prior CR)<br>NR/SD<br>PD<br>Relapse (untreated)<br>Never treated | Note CR definitions for Neuroblastoma above.<br><br>**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.<br>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<br><br>**Progressive Disease (PD)** Increase of ≥ 25% in the size of one or more measurable lesions, or the appearance of new lesions. RECIST: At least a 20% increase in the sum of the longest diameter of measured lesions (target lesions), taking as reference the smallest sum of the longest diameters recorded since the treatment started or the appearance of one or more new lesions<br><br>**Relapse (untreated)** The reappearance of disease after complete recovery. Should be determined by one or more diagnostic tests.<br><br>**Never Treated (upfront):** Recipient has not received any treatment for Neuroblastoma prior to the |

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|---|---|---|
| | | preparative regimen. This disease status at transplant should rarely be used<br><br>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**<br>Includes all other solid tumors except neuroblastoma | **Intermediate Risk** – same as Neuroblastoma (above)<br>CR1<br>CRU1<br>VGPR1<br>PR1 (PR without prior CR)<br>Adjuvant | See Neuroblastoma above. |
| **All Other Solid Tumors – Pediatrics (con't)**<br>Includes all other solid tumors except neuroblastoma | **High Risk** – same as Neuroblastoma (above)<br>CR2/+ CRU2/+<br>PR with prior CR NR/SD<br>PD Relapse Never treated | See Neuroblastoma above. |
| **Non-Malignant Disease – Adults**<br>**Includes: severe aplastic anemia, and any other non-malignant diseases** | | |
| Non-Malignant Disease - Pediatrics<br>Includes: histiocytic disorders, Immunodeficiencies, Inborn errors of metabolism, congenital bone marrow failure, acquired aplastic anemia, thalassemia major, sickle cell anemia and any other non-cancerous diseases | | |
| Other<br>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 PR1/1$^{st}$ PR to PR without prior CR and PR2/2$^{nd}$ 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.

## 14.7 Appendix 7: List of CYP3A4 inhibitors and inducers

### Table 14-6 List of CYP3A4 inhibitors and inducers

Dual CYP2C9/CYP3A4 inhibitor:

| 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%.

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).

## 14.8 Appendix 8: FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quitea bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quitea bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| GS5 | I am satisfied with family communication about my illness ..... | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life ..... | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quitea bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad..... | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness ..... | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness ..... | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous ..... | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying..... | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse..... | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quitea bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home)..... | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling ..... | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life ..... | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness ..... | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quitea bit | Very much |
|---|---|---|---|---|---|---|
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| BMT1 | I am concerned about keeping my job (include work at home) | 0 | 1 | 2 | 3 | 4 |
| BMT2 | I feel distant from other people | 0 | 1 | 2 | 3 | 4 |
| BMT3 | I worry that the transplant will not work | 0 | 1 | 2 | 3 | 4 |
| BMT4 | The side effects of treatment are worse than I had imagined | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| C7 | I like the appearance of my body | 0 | 1 | 2 | 3 | 4 |
| BMT5 | I am able to get around by myself | 0 | 1 | 2 | 3 | 4 |
| BMT6 | I get tired easily | 0 | 1 | 2 | 3 | 4 |
| BL4 | I am interested in sex | 0 | 1 | 2 | 3 | 4 |
| BMT7 | I have concerns about my ability to have children | 0 | 1 | 2 | 3 | 4 |
| BMT8 | I have confidence in my nurse(s) | 0 | 1 | 2 | 3 | 4 |
| BMT9 | I regret having the bone marrow transplant | 0 | 1 | 2 | 3 | 4 |
| BMT10 | I can remember things | 0 | 1 | 2 | 3 | 4 |
| Br1 | I am able to concentrate | 0 | 1 | 2 | 3 | 4 |
| BMT11 | I have frequent colds/infections | 0 | 1 | 2 | 3 | 4 |
| BMT12 | My eyesight is blurry | 0 | 1 | 2 | 3 | 4 |
| BMT13 | I am bothered by a change in the way food tastes | 0 | 1 | 2 | 3 | 4 |
| BMT14 | I have tremors | 0 | 1 | 2 | 3 | 4 |
| B1 | I have been short of breath | 0 | 1 | 2 | 3 | 4 |
| BMT15 | I am bothered by skin problems (e.g., rash, itching) | 0 | 1 | 2 | 3 | 4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| BMT16 | I have trouble with my bowels..... | 0 | 1 | 2 | 3 | 4 |
| BMT17 | My illness is a personal hardship for my close family members | 0 | 1 | 2 | 3 | 4 |
| BMT18 | The cost of my treatment is a burden on me or my family.... | 0 | 1 | 2 | 3 | 4 |

## 14.9 Appendix 9: EQ-5D-5L Health Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY

**MOBILITY**

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

**SELF-CARE**

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

**ANXIETY / DEPRESSION**

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐