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.