# STATISTICAL ANALYSIS PLAN

**VERSION: 1.0**
**DATE:** 22 SEPTEMBER 2020

**STUDY DRUG:**

*DEFIBROTIDE (DEFIBROTIDE SODIUM)*

**PROTOCOL/STUDY NUMBER:**

*JZP963-201 Protocol Amendment 1 (19 JUNE 2018)*

**STUDY TITLE:**

*A Phase 2, Prospective, Randomized, Open-label Study on the Efficacy of Defibrotide Added to Standard of Care Immunoprophylaxis for the Prevention of Acute Graft-versus-Host-Disease in Adult and Pediatric Patients After Allogeneic Hematopoietic Stem Cell Transplant*

**SPONSOR:**

*Jazz Pharmaceuticals*

*3170 Porter Dr., Palo Alto, CA 94304*

This study is being conducted in compliance with Good Clinical Practice guidelines, including the archiving of essential documents.

# SIGNATURE PAGE

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# 1. LIST OF ABBREVIATIONS

**Table 1: List of Abbreviations**

| Abbreviation | Term |
|---|---|
| AE | Adverse event |
| aGvHD | Acute graft-versus-host disease |
| ATG | Anti-thymocyte globulin |
| BMT | Bone marrow transplantation |
| BMTS | Bone Marrow Transplantation Subscale |
| cGvHD | Chronic graft-versus-host disease |
| CI | Confidence interval |
| CMV | Cytomegalovirus |
| CRF | Case report form |
| CSA | Cyclosporine A |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EDC | Electronic data capture |
| EQ-5D | EuroQol-5D health questionnaire |
| EQ-5D-5L | 5-Level EuroQol-5D health questionnaire |
| EQ-5D-Y | EuroQol-5D health questionnaire for youth |
| FACT | Functional Assessment of Cancer Therapy |
| FACT-BMT-TOI | Functional Assessment of Cancer Therapy-Bone Marrow Transplant-Trial Outcomes Index |
| FACT-G | General FACT total score |
| GI | Gastrointestinal |
| GvHD | Graft-versus-host disease |
| HLA | Human leukocyte antigen |
| HRQoL | Health-related quality of life |
| HSCT | Hematopoietic stem cell transplant |
| IBMTR | International Bone Marrow Transplant Registry |
| ICH | International Conference on Harmonisation |
| ICU | Intensive care unit |

| | |
|---|---|
| IRT | Interactive response technology |
| ITT | Intent-to-treat |
| IV | Intravenous |
| IWRS | Interactive web response system |
| MAGIC | Mount Sinai Acute Graft-versus-Host Disease International Consortium |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intent-to-treat |
| MMF | Mycophenolate mofetil |
| MTX | Methotrexate |
| NIH | National Institutes of Health |
| PT | Preferred term |
| QoL | Quality of life |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAS | Statistical Analysis System |
| SMQ | Standardised MedDRA Query |
| SOC | System organ class |
| TAC | Tacrolimus |
| TA-TMA | Transplant-associated thrombotic microangiopathy |
| TBI | Total body irradiation |
| TEAE | Treatment-emergent adverse event |
| TOI | Trial outcomes index |
| VAS | Visual analogue scale |
| VOD | Veno-occlusive disease |

## 2. MODIFICATION HISTORY

Version History:

| Version | Date | Description |
|---|---|---|
| Original | *22 September 2020* | |

# 3. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses for Protocol JZP963-201 for inclusion in the clinical study report (CSR). Mock tables, listings, and figure shells will be provided in a separate supporting document.

This SAP complies with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. The current version of the SAP is based on the following study documents:

- Protocol Amendment 1 dated 19 June 2018
- Case Report Form (CRF), Version 4.0 dated 28 June 2019

Any additional analyses or deviation from the analyses outlined in this plan will be documented with rationale in the final CSR. All decisions regarding the final analysis of the study results, as defined in this SAP, have been made prior to database lock of the study data.

# 4. STUDY OBJECTIVES AND ENDPOINTS

## 4.1. Study Objectives

### 4.1.1. Primary Objective

The primary objective of the study is to compare the efficacy of defibrotide added to standard of care immunoprophylaxis versus standard of care immunoprophylaxis alone for the prevention of acute graft-versus-host disease (aGvHD) as measured by the cumulative incidence of Grade B-D aGvHD by Day +100 post-allogeneic hematopoietic stem cell transplant (HSCT) in adult and pediatric subjects.

### 4.1.2. Secondary Objectives

- To compare the efficacy of defibrotide added to standard of care immunoprophylaxis versus standard of care immunoprophylaxis alone on the following variables:
  - Grade B-D aGvHD-free survival by Days +100 and +180 post-HSCT
  - Cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT
  - Cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT
  - Cumulative incidence of relapse by Days +100 and +180 post-HSCT
    (Note: Disease relapse per local institutional guidelines)
- To evaluate systemic steroid use in the treatment of aGvHD by Day +180 post-HSCT
- To compare the health-related quality of life (HRQoL) using the following questionnaires:
  - Functional Assessment of Cancer Therapy-Bone Marrow Transplant-Trial Outcomes Index (FACT-BMT-TOI) (adults only)
  - EuroQol-5D (EQ-5D; version dependent on age group)
- To compare the safety of defibrotide added to standard of care immunoprophylaxis versus standard of care immunoprophylaxis alone, including adverse event (AE) profile, serious adverse event (SAE) profile, laboratory abnormalities, neutrophil and platelet engraftment, graft failure, and infectious disease occurrence

### 4.1.3. Exploratory Objectives

The exploratory objectives of the study are to evaluate the efficacy, hospital resource utilization, and potential biomarkers associated with defibrotide treatment:

- Graft-versus-host disease (GvHD)-free, relapse-free survival (ie, subjects alive without relapse, without Grade B-D aGvHD and without chronic GvHD [cGvHD]) by Day +180 post-HSCT
- Grade C-D aGvHD-free survival by Days +100 and +180 post-HSCT
- Cumulative incidence of non-relapse mortality by Days +100 and +180 post-HSCT
- Cumulative incidence of cGvHD by Day +180 post-HSCT

- Overall survival by Day +180 post-HSCT
- Cumulative incidence of veno-occlusive disease (VOD) with or without multi-organ dysfunction by Days +30 and +100 post-HSCT
- Cumulative incidence of transplant-associated thrombotic microangiopathy (TA-TMA) by Day +180 post-HSCT
- To compare the hospital resource utilization for defibrotide prophylaxis and standard of care subjects
- To evaluate plasma concentrations of potential predictive and prognostic biomarkers of aGvHD and cGvHD

## 4.2. Study Endpoints

### 4.2.1. Primary Endpoint

The primary endpoint of the study is the cumulative incidence of Grade B-D aGvHD by Day +100 post-HSCT.

### 4.2.2. Secondary Endpoints

- Secondary efficacy endpoints include the following:
  - Grade B-D aGvHD-free survival by Days +100 and +180 post-HSCT
  - Cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT
  - Cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT
  - Cumulative incidence of relapse by Days +100 and +180 post-HSCT (Note: Disease relapse per institutional guidelines)
- Systemic steroid use in the treatment of aGvHD by Day +180 post-HSCT
- HRQoL endpoints:
  - Change between any of the post-HSCT assessments and baseline assessment on the physical well-being subscale using the FACT-BMT questionnaire (subjects with age $\geq$ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the social/family well-being subscale using the FACT-BMT questionnaire (subjects with age $\geq$ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the emotional well-being subscale using the FACT-BMT questionnaire (subjects with age $\geq$ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the functional well-being subscale using the FACT-BMT questionnaire (subjects with age $\geq$ 16 years at baseline)

  - Change between any of the post-HSCT assessments and baseline assessment on the Bone Marrow Transplantation Subscale (BMTS) using the FACT-BMT questionnaire (subjects with age ≥ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the general FACT total score (FACT-G, defined as the sum of the following subscale scores: physical well-being, social/family well-being, emotional well-being, and functional well-being) using the FACT-BMT questionnaire (subjects with age ≥ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the FACT-BMT total score (defined as the sum of FACT-G and BMTS) using the FACT-BMT questionnaire (subjects with age ≥ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the FACT-BMT-TOI (defined as the sum of the following subscale scores: physical well-being, functional well-being, and BMTS) using the FACT-BMT questionnaire (subjects with age ≥ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) based on the descriptive system of the 5-Level EQ-5D (EQ-5D-5L) (subjects with age ≥ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the EQ-5D-5L index value for health states (subjects with age ≥ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the EQ visual analogue scale (VAS) (subjects with age ≥ 16 years at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on each dimension (mobility, taking care of him/herself, doing usual activities, having pain or discomfort, and feeling worried, sad or unhappy) based on the descriptive system of the EQ-5D for youth (EQ-5D-Y), proxy version 1 (pediatric subjects 4 to 7 years of age at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the EQ VAS (pediatric subjects 4 to 7 years of age at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on each dimension (mobility, taking care of him/herself, doing usual activities, having pain or discomfort, and feeling worried, sad or unhappy) based on the descriptive system of the EQ-5D-Y, self-report version (pediatric subjects 8 to 15 years of age at baseline)
  - Change between any of the post-HSCT assessments and baseline assessment on the EQ VAS (pediatric subjects 8 to 15 years of age at baseline)

- Safety endpoints:
  - AEs

- Clinical laboratory results
- Graft failure and time to neutrophil and platelet engraftment
- Karnofsky and Lansky performance scores
- Incidence of infectious disease marker by Days +100 and +180 post-HSCT
- Concomitant medications

### 4.2.3. Exploratory Endpoints

- GvHD-free, relapse-free survival (ie, subjects alive without relapse, without Grade B-D aGvHD and without cGvHD) by Day +180 post-HSCT
- Grade C-D aGvHD-free survival by Days +100 and +180 post-HSCT
- Cumulative incidence of non-relapse mortality by Days +100 and +180 post-HSCT
- Cumulative incidence of cGvHD by Day +180 post-HSCT
- Overall survival by Day +180 post-HSCT
- Cumulative incidence of VOD with or without multi-organ dysfunction by Days +30 and +100 post-HSCT
- Cumulative incidence of TA-TMA by Day +180 post-HSCT
- Hospital resource utilization
- Plasma concentrations as potential predictive and prognostic biomarkers of aGvHD and cGvHD

# 5. STUDY DESIGN

## 5.1. Summary of Study Design

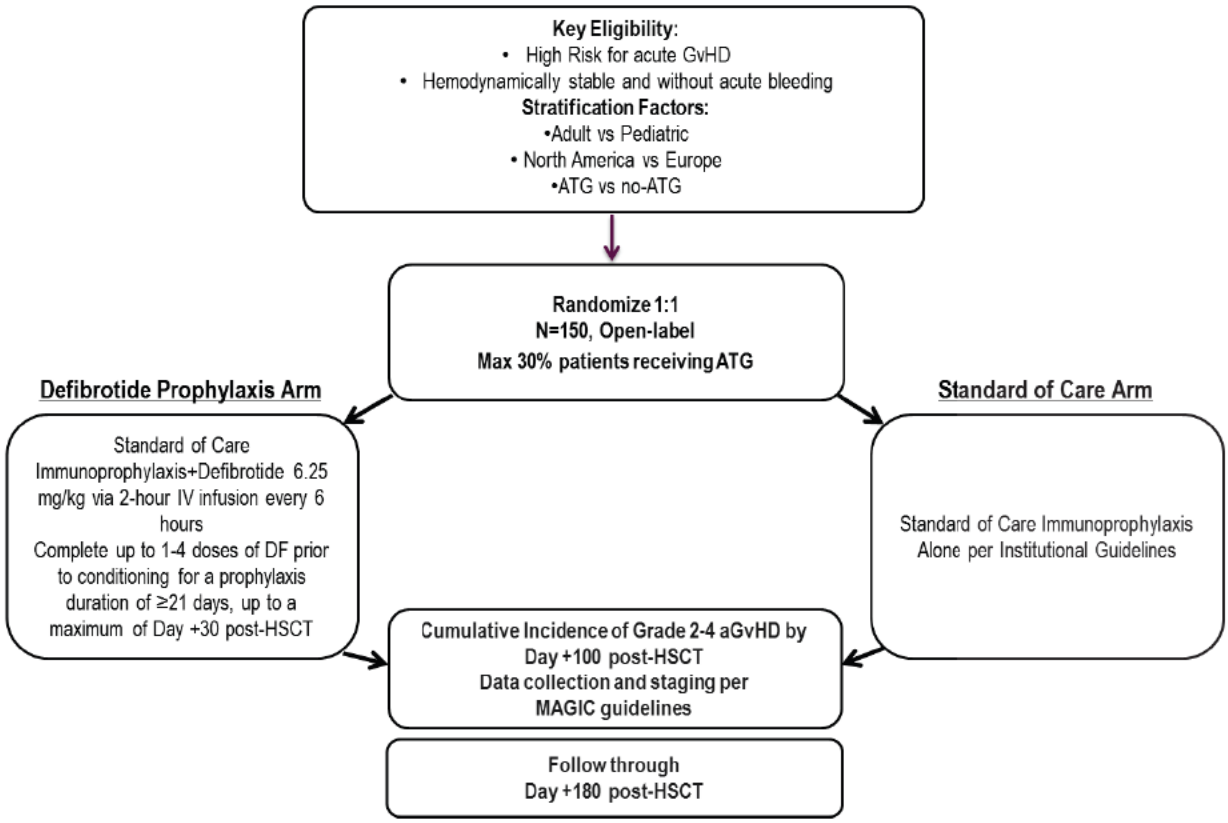
This is a phase 2, prospective, randomized, open-label study comparing the efficacy and safety of defibrotide added to standard of care immunoprophylaxis (defibrotide prophylaxis arm) versus standard of care immunoprophylaxis alone (standard of care arm) for the prevention of aGvHD as measured by the cumulative incidence of Grade B-D aGvHD by Day +100 post-HSCT in adult and pediatric subjects who are at high risk of developing aGvHD. The trial is hypothesis generating and is not powered to detect minimal clinically meaningful differences between the 2 treatment arms at a significant Type I error rate of 0.05.

An overview of the study design is illustrated in Figure 1.

A total of 150 subjects are planned for enrollment in the study. After informed consent and/or assent is obtained from patients, parents/legal guardians or representatives, as applicable, screening procedures will be performed within 28 days of the scheduled start of the subject's HSCT conditioning regimen. Eligible subjects will be randomly assigned to receive defibrotide prophylaxis 25 mg/kg/day in addition to standard of care immunoprophylaxis or standard of care immunoprophylaxis alone in a 1:1 ratio. Standard of care immunoprophylaxis will consist of methotrexate (MTX) or mycophenolate mofetil (MMF) + calcineurin inhibitor (cyclosporine A [CSA] or tacrolimus [TAC]) ± anti-thymocyte globulin (ATG), with dosing and treatment schedules per local institutional guidelines, physician preference, and patient need. Randomization will be stratified by age (< 17 versus ≥ 17 years), geographical region (North America versus Europe), and intent to use ATG (ATG versus No ATG) using an interactive web response system (IWRS). Intent to use ATG will be limited to 30% of subjects (45 subjects).

Subjects will be monitored for the primary endpoint through Day +100 post-HSCT and secondary endpoints through Day +180 post-HSCT.

**Figure 1: Study Diagram**




ATG = anti-thymocyte globulin; DF = defibrotide; GvHD = graft-versus-host disease; HSCT = hematopoietic stem cell transplant; IV = intravenous; MAGIC = Mount Sinai Acute Graft-versus-Host Disease International Consortium.

Investigative site clinical diagnosis of aGvHD will be based on clinical, laboratory, and histological assessments on site. Collection of data for determination of clinical diagnosis of aGvHD and clinical staging of aGvHD will be based on the recommendations of Mount Sinai Acute Graft-versus-Host Disease International Consortium (MAGIC; Harris 2016). Grading of aGvHD for assessment of the primary and secondary efficacy endpoints will be based on the International Bone Marrow Transplant Registry (IBMTR) Severity Index (Rowlings 1997). As sensitivity analyses, all aGvHD-related efficacy endpoints will also be analyzed using the modified Consensus Criteria detailed in the aGvHD grading system from MAGIC (Harris 2016). Grading of cGvHD will be based on the National Institutes of Health (NIH) criteria (Jagasia 2015). Subjects who develop clinical signs and symptoms of aGvHD after hospital discharge or Day +30 post-HSCT may require more frequent monitoring, and re-admission to the hospital will be at the investigator's discretion.

For both treatment arms of the study, subjects who develop aGvHD should be treated for aGvHD based on local institutional guidelines, physician preference, and patient need. Subjects in the defibrotide prophylaxis arm diagnosed with aGvHD prior to Day +30 post-HSCT and receiving defibrotide prophylaxis at the time of diagnosis may continue to receive defibrotide at the discretion of their physician up to a maximum of Day +30 post-HSCT. Subjects in the standard of care arm will not receive defibrotide for the treatment of aGvHD.

If a subject in either the defibrotide prophylaxis arm or standard of care arm develops VOD during the course of the study, the investigator may treat with Defitelio (commercially available defibrotide) if clinically indicated. Investigators should not use the study drug (defibrotide) for treatment of VOD. If subjects in the defibrotide prophylaxis arm are diagnosed with VOD prior to Day +30 post-HSCT and are receiving defibrotide prophylaxis at the time of diagnosis, they may continue to receive defibrotide up to Day +30 post-HSCT and start Defitelio treatment thereafter. They will need to clearly demonstrate the diagnosis of VOD and the use of Defitelio should be clearly stated as for use in VOD. Details of VOD diagnosis will be captured as per the schedule of procedures and assessments.

Efficacy will also be assessed through monitoring for aGvHD-free survival, GvHD-free and relapse-free survival, relapse of disease, cGvHD, and overall survival.

Other assessments include HRQoL and hospital resource utilization. Measurement of biomarkers in blood for assessment of their potential as predictive or diagnostic biomarkers of GvHD and response to defibrotide prophylaxis will also be performed.

Safety will be assessed throughout the study. Safety will be assessed through monitoring of AEs, SAEs, vital signs, physical examination, clinical laboratory tests, and Karnofsky/Lansky performance scales. In addition, the following parameters will be assessed for safety:

- Time to neutrophil and platelet engraftment and cumulative incidence of graft failure by Day +100 post-HSCT
- Incidence of infectious disease marker by Day +180 post-HSCT

## 5.2. Study Treatment

### 5.2.1. Defibrotide Administration

#### 5.2.1.1. Defibrotide Prophylaxis

For subjects randomized to receive defibrotide prophylaxis, defibrotide will be administered prior to the start of the conditioning regimen (may have completed 1 to 4 doses of defibrotide prior to conditioning) for a recommended prophylaxis duration of $\geq$ 21 days and ending no later than Day +30 post-HSCT. Subjects in this arm of the study should also receive standard of care immunoprophylaxis, with dosing and duration of therapy based on local institutional guidelines, physician preference, and patient need. Subjects must undergo Day +14 post-HSCT assessments before hospital discharge. If a subject is discontinued from study/study drug prior to Day +14 post-HSCT, the Day +14 post-HSCT assessments must be completed on the day of study/study drug discontinuation (± 2 days).

#### 5.2.1.2. Extended Defibrotide Administration in the Defibrotide Prophylaxis Arm for Subjects who Develop aGvHD

Subjects in the defibrotide prophylaxis arm diagnosed with aGvHD prior to Day +30 post-HSCT and receiving defibrotide prophylaxis at the time of diagnosis may continue to receive defibrotide at the discretion of their physician up to Day +30 post-HSCT.

Note that there are no known benefits in the use of defibrotide as treatment for aGvHD. Subjects in the defibrotide prophylaxis arm who have discontinued defibrotide prophylaxis and are

subsequently diagnosed with aGvHD prior to Day +30 may not re-start defibrotide as treatment for aGvHD.

#### 5.2.1.3. Defitelio Rescue Treatment for Subjects who Develop VOD

If a subject in either the defibrotide prophylaxis arm or standard of care arm develops VOD during the course of the study, the investigator may treat with Defitelio (commercially available defibrotide) if clinically indicated. Investigators should not use the study drug (defibrotide) for the treatment of VOD. If subjects in the defibrotide prophylaxis arm are diagnosed with VOD prior to Day +30 post-HSCT and are receiving defibrotide prophylaxis at the time of diagnosis, they may continue to receive defibrotide up to Day +30 post-HSCT and start Defitelio treatment thereafter. The subject must have a documented diagnosis of VOD and the use of Defitelio as treatment for VOD must be clearly indicated on the appropriate page of the CRF. Details of the criteria used to diagnose VOD must be captured on the appropriate page of the CRF. Defitelio may be administered as treatment for VOD until resolution of VOD or hospital discharge, whichever is sooner, and may continue beyond Day +30 post-HSCT. Subjects must be hemodynamically stable and not at risk of bleeding, to receive Defitelio as treatment for VOD.

### 5.2.2. Reference Therapy

Subjects randomized to the standard of care arm should receive standard of care immunoprophylaxis therapy according to local institutional guidelines, physician preference, and patient need. The standard of care options available are intended to serve as study control for comparison with those subjects randomized to receive defibrotide prophylaxis in addition to standard of care immunoprophylaxis. Administration of standard of care immunoprophylaxis should be based on local institutional guidelines, physician preference, and patient need regarding dosing and duration of each immunosuppressive agent.

## 5.3. Power and Sample Size Considerations

The sample size of 150 subjects (75 subjects per treatment arm) will provide a 90% confidence interval (CI) of -0.28, -0.03 for the treatment difference of the primary endpoint (ie, cumulative incidence of Grade B-D aGvHD by Day +100 post-HSCT), assuming the cumulative incidence of 28.6% and 44% for the defibrotide prophylaxis arm and standard of care arm, respectively. The calculation of the CI is based on the large sample normal approximation. The 44% cumulative incidence for the standard of care arm is based on published studies and results from a previously conducted study (Study 2004-000592-33). The 28.6% cumulative incidence for the defibrotide prophylaxis arm is projected based on a relative 35% improvement from the standard of care arm.

## 5.4. Randomization and Blinding

Subjects will be randomly assigned to receive defibrotide prophylaxis in addition to standard of care immunoprophylaxis or standard of care immunoprophylaxis alone in a 1:1 ratio in an open-label fashion after they qualify for participation in the study. Randomization will be stratified by age (< 17 years versus ≥ 17 years), geographical region (North America versus Europe), and intent to use ATG (ATG versus no-ATG) using an IWRS. Intent to use ATG will be limited to 30% of subjects (45 subjects). Intent to use ATG specified at the time of screening will be closely monitored throughout the conduct of the study. When the number of subjects with

intent use to ATG gets to 40, approval from the Sponsor is required when a site is enrolling a subject who specified intent to use ATG at the time of screening. When the number of subjects with intent to use ATG reaches 45, any further enrollment of subjects who specified intent to use ATG at the time of screening will be disapproved.

Blinding is not applicable in this open-label study.

## 5.5. Interim Analysis

Not applicable.

# 6. ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined:

| Analysis Set | Description |
|---|---|
| Enrolled | All subjects who signed the informed consent form and met all eligibility criteria for the study |
| Intent-to-treat (ITT) | The ITT Analysis Set includes all randomized subjects. Subjects will be analyzed according to the treatment arm to which they were randomized. This is the primary analysis set for efficacy analyses. |
| Modified ITT (mITT) | The mITT Analysis Set includes all subjects in the ITT Analysis Set who underwent HSCT. This will be used in some of the sensitivity analyses. |
| mITT2 | The mITT2 Analysis Set includes all randomized subjects who did not have any scheduled aGvHD assessment during country-specific lockdowns due to COVID-19. |
| Safety | The Safety Analysis Set includes all subjects in the ITT Analysis Set who either received at least 1 dose of defibrotide or 1 dose of the conditioning therapy with no defibrotide received. Subjects will be analyzed according to the treatment they actually received. This is the primary analysis set for safety analyses. |

# 7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

The statistical principles applied in the design and planned analyses of this study are consistent with ICH E9 guidelines (ICH 1998).

## 7.1. General Methods

All study data will be summarized using descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for continuous variables (eg, age, weight) and using the number and percentage of subjects for categorical variables (eg, gender, race), unless otherwise specified. Data listings will be organized by treatment arm and then by subject within each treatment arm. Dates will be presented in the YYYY-MM-DD format.

All summaries, statistical analyses, data listings and figures described below will be completed using Version 9.4 of the Statistical Analysis System (SAS Institute, Inc., Cary, NC). All figures will be generated with high resolution in black and white. Each summary, figure or data listing will include the data cutoff date in addition to the production date.

## 7.2. Baseline and Study Day Definitions

### 7.2.1. Baseline

Baseline is defined as the date defibrotide prophylaxis starts for subjects who receive defibrotide in addition to standard of care prophylaxis, and the date conditioning therapy starts for subjects who receive standard of care prophylaxis alone. If a subject receives conditioning therapy prior to receiving defibrotide, baseline is the date conditioning therapy starts.

### 7.2.2. Day +0 Post-HSCT

Day +0 post-HSCT is defined as the day of HSCT. For subjects in the ITT Analysis Set who did not have HSCT, Day +0 post-HSCT is the day of randomization. For the analyses of all efficacy endpoints, duration calculations will start at Day +0 post-HSCT.

### 7.2.3. Day +X Post-HSCT

Day +X post-HSCT is defined as the Xth day after the date of Day +0 post-HSCT, where X is a positive integer representing the number of days to an event. For subjects who did not undergo HSCT, Day +X post-HSCT is the Xth day after the date of randomization. Day +X post-HSCT for an event is calculated as the following,

**X** = [Date of the event] – [Date of Day +0 post-HSCT].

### 7.2.4. Visit Windows

#### 7.2.4.1. HRQoL Assessments

HRQoL assessments will be completed at baseline, then weekly starting at Day +7 post-HSCT to Day +28 post-HSCT, and then at Days +100 and +180 post-HSCT (end of study), or at early termination. The table below provides the analysis windows for the purpose of identifying the HRQoL assessments to be used in the analyses.

| Visit Identifier | Nominal Day | Lower Limit: HSCTSTDY | Upper Limit: HSCTSTDY |
|---|---|---|---|
| Baseline | | The last available assessment on or prior to the date of baseline | |
| Day +7 post-HSCT | HSCTSTDY = 8 | 5 | 11 |
| Day +14 post-HSCT | HSCTSTDY = 15 | 12 | 18 |
| Day +21 post-HSCT | HSCTSTDY = 22 | 19 | 25 |
| Day +28 post-HSCT | HSCTSTDY = 29 | 26 | 32 |
| Day +100 post-HSCT | HSCTSTDY = 101 | 91 | 111 |
| Day +180 post-HSCT | HSCTSTDY = 181 | 166 | 196 |

Note: HSCTSTDY = DATE – (Date of Day +0 post-HSCT) + 1, where DATE is the date of the HRQoL assessment.

If multiple valid non-missing assessments (including unscheduled assessments) exist in an analysis window, then the following rules will be used to choose the assessment for the analyses:

- The assessment on the date closest to the nominal day of that visit will be selected.
- If there are 2 assessments with equal distance from the nominal day, the one on the latest date will be selected.
- If there are repeated assessments on the selected date, the one indicating the poorest quality of life will be used for the analyses. For any of the FACT-BMT subscales, FACT-G, FACT-BMT total score, FACT-BMI-TOI, EQ-5D-5L index value, and EQ VAS score, the assessment indicating the poorest quality of life is the one with the lowest score. For any of the EQ-5D-5L dimensions and EQ-5D-Y dimensions, the assessment indicating the poorest quality of life is the one with the highest level of problems.

#### 7.2.4.2. Laboratory Tests

For the laboratory (hematology, coagulation, and chemistry) tests, the table below provides the analysis windows for the purpose of identifying the assessments to be used in the analyses.

| Visit Identifier | Nominal Day | Lower Limit: HSCTSTDY | Upper Limit: HSCTSTDY |
|---|---|---|---|
| Baseline | | The last available assessment on or prior to the date of baseline | |

| | | | |
|---|---|---|---|
| Day +0 post-HSCT | HSCTSTDY = 1 | 1 | 1 |
| Day +7 post-HSCT | HSCTSTDY = 8 | 5 | 11 |
| Day +14 post-HSCT | HSCTSTDY = 15 | 12 | 18 |
| Day +21 post-HSCT | HSCTSTDY = 22 | 19 | 25 |
| Day +28 post-HSCT | HSCTSTDY = 29 | 26 | 32 |
| Day +35 post-HSCT | HSCTSTDY = 36 | 33 | 39 |
| Day +42 post-HSCT | HSCTSTDY = 43 | 40 | 46 |
| Day +49 post-HSCT | HSCTSTDY = 50 | 47 | 53 |
| Day +56 post-HSCT | HSCTSTDY = 57 | 54 | 60 |
| Day +63 post-HSCT | HSCTSTDY = 64 | 61 | 67 |
| Day +70 post-HSCT | HSCTSTDY = 71 | 68 | 74 |
| Day +77 post-HSCT | HSCTSTDY = 78 | 75 | 81 |
| Day +84 post-HSCT | HSCTSTDY = 85 | 82 | 88 |
| Day +91 post-HSCT | HSCTSTDY = 92 | 89 | 95 |
| Day +100 post-HSCT | HSCTSTDY = 101 | 96 | 106 |
| Day +180 post-HSCT | HSCTSTDY = 181 | 171 | 191 |

Note: HSCTSTDY = DATE – (Date of Day +0 post-HSCT) + 1, where DATE is the date of the lab assessment.

If multiple valid non-missing assessments (including unscheduled assessments) exist in an analysis window, then the following rules will be used to choose the assessment for the analyses:

- The assessment on the date closest to the nominal day of that visit will be selected.
- If there are 2 assessments with equal distance from the nominal day, the one on the latest date will be selected.
- If there is more than 1 assessment on the selected date, the average will be taken and used for the analyses.

#### 7.2.4.3. Vital Signs

For the vital signs, the table below provides the analysis windows for the purpose of identifying the assessments to be used in the analyses.

| Visit Identifier | Nominal Day | Lower Limit: HSCTSTDY | Upper Limit: HSCTSTDY |
|---|---|---|---|
| Baseline | | The last available assessment on or prior to the date of baseline | |
| Day +0 post-HSCT | HSCTSTDY = 1 | 1 | 1 |
| Day +7 post-HSCT | HSCTSTDY = 8 | 5 | 11 |
| Day +14 post-HSCT | HSCTSTDY = 15 | 12 | 18 |
| Day +21 post-HSCT | HSCTSTDY = 22 | 19 | 25 |
| Day +28 post-HSCT | HSCTSTDY = 29 | 26 | 32 |
| Day +35 post-HSCT | HSCTSTDY = 36 | 33 | 39 |
| Day +42 post-HSCT | HSCTSTDY = 43 | 40 | 46 |
| Day +49 post-HSCT | HSCTSTDY = 50 | 47 | 53 |
| Day +56 post-HSCT | HSCTSTDY = 57 | 54 | 60 |
| Day +63 post-HSCT | HSCTSTDY = 64 | 61 | 67 |
| Day +70 post-HSCT | HSCTSTDY = 71 | 68 | 74 |
| Day +77 post-HSCT | HSCTSTDY = 78 | 75 | 81 |
| Day +84 post-HSCT | HSCTSTDY = 85 | 82 | 88 |
| Day +91 post-HSCT | HSCTSTDY = 92 | 89 | 95 |
| Day +100 post-HSCT | HSCTSTDY = 101 | 96 | 106 |
| Day +180 post-HSCT | HSCTSTDY = 181 | 171 | 191 |

Note: HSCTSTDY = DATE – (Date of Day +0 post-HSCT) + 1, where DATE is the date of the vital sign assessment.

Note that the analysis windows for visits after Day +63 post-HSCT are only applicable for weight. If multiple valid non-missing assessments (including unscheduled assessments) exist in an analysis window, then the following rules will be used to choose the assessment for the analyses:

- The assessment on the date closest to the nominal day of that visit will be selected.

- If there are 2 assessments with equal distance from the nominal day, the one on the latest date will be selected.
- If there is more than 1 assessment on the selected date, the average will be taken and used for the analyses.

#### 7.2.4.4. Infectious Disease Markers

For the infectious disease markers, the table below provides the analysis windows for the purpose of identifying the assessments to be used in the analyses.

| Visit Identifier | Nominal Day | Lower Limit: HSCTSTDY | Upper Limit: HSCTSTDY |
|---|---|---|---|
| Screening | | The last available assessment on or prior to the date of randomization | |
| Day +100 post-HSCT | HSCTSTDY = 101 | 96 | 106 |
| Day +180 post-HSCT | HSCTSTDY = 181 | 171 | 191 |

Note: HSCTSTDY = DATE – (Day +0 post-HSCT) + 1, where DATE is the date of the marker assessment.

If multiple valid non-missing assessments (including unscheduled assessments) exist in an analysis window, then the one indicating presence of infectious disease marker, if any, will be used for the analyses.

### 7.2.5. Missing Data

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a "blank" in subject listing displays. Note that if any missing data is imputed, the imputed data will only be used in summaries, and will not be included in any listing. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should not be displayed as missing.

#### 7.2.5.1. Incomplete and Missing AE Start Date

For this study, the first dose date is defined the same as baseline. The following imputation rules will be followed, when the AE start date is incomplete (eg, only *year* is present, but *month* and *day* are missing) or completely missing:

- If *year* is missing (including the situation where the start date is completely missing), set the date to the first dose date.
- If *year* is present, and *month* and *day* are missing, or *year* and *day* are present, and *month* is missing,
  - if *year* = year of first dose, set the date to the first dose date;
  - if *year* < year of first dose, set *month* and *day* to December 31st;

  - if *year* > year of first dose, set *month* and *day* to January 1st.
- If *year* and *month* are present, and *day* is missing,
  - if *year* = year of first dose, and
    - if *month* = month of first dose, set *day* to day of first dose;
    - if *month* < month of first dose, set *day* to the last day of *month*;
    - if *month* > month of first dose, set *day* to the first day of *month*;
  - if *year* < year of first dose, set *day* to the last day of *month*;
  - if *year* > year of first dose, set *day* to the first day of *month*.
- For all other cases that are not covered above, set the date to the first dose date.

#### 7.2.5.2. Incomplete and Missing Prior and Concomitant Medication Start Date

The following imputation rules will be followed, when the prior and concomitant medication start date is incomplete (eg, only *year* is present, but *month* and *day* are missing) or completely missing:

- If *year* is missing (including the situation where the start date is completely missing), do not impute, and the start date will be treated as missing in the analysis.
- If *year* is present, and *month* and *day* are missing, or *year* and *day* are present, and *month* is missing, set *month* and *day* to January 1st.
- If *year* and *month* are present, and *day* is missing, set *day* to the first day of *month*.

#### 7.2.5.3. Incomplete and Missing Prior and Concomitant Medication End Date

The following imputation rules will be followed, when the prior and concomitant medication end date is incomplete (eg, only *year* is present, but *month* and *day* are missing) or completely missing:

- If it is indicated that the medication is ongoing (ie, "Yes" is checked for the question "Ongoing?" in the CRF), do not impute, since there should not be an end date for this medication.
- If *year* is missing (including the situation where the end date is completely missing), do not impute, and the end date will be treated as missing in the analysis.
- If *year* is present, and *month* and *day* are missing, or *year* and *day* are present, and *month* is missing, set *month* and *day* to December 31st.
- If *year* and *month* are present, and *day* is missing, set *day* to the last day of *month*.

#### 7.2.5.4. Missing HRQoL Data from the FACT-BMT Questionnaire

For any of the items on the FACT-BMT questionnaire, it is considered to have a valid response if one of the following options is checked in the CRF: "Not at all", "A little bit", "Some-what", "Quite a bit", and "Very much". If the option of "Question not completed" is checked in the CRF, the item is NOT considered to have a valid response.

For the analyses on the HRQoL endpoints using the FACT-BMT questionnaire, the following imputation rules will be followed when the response is missing for any of the items on the questionnaire:

- For any of the subscales (physical well-being, social/family well-being, emotional well-being, functional well-being, and BMTS),
  - if more than 50% of the items were answered with valid responses, the subscale score can be prorated using the formula below:

**Prorated subscale score** = [Sum of item scores] × [N of items in subscale] ÷ [N of items answered]

  - if less than or equal to 50% of the items were answered with valid response, prorating the subscale score in the way mentioned above is not acceptable, and the subscale will not be considered to have a valid score. Do not impute the subscale score in this case, and the subscale score will be treated as missing in the analysis.
- For the FACT-G and the FACT-BMT total scores, in addition to the rules on the subscale scores mentioned above, the following rules will be followed:
  - a total score should only be calculated as long as the overall item response rate is greater than 80% (eg, at least 22 of the 27 FACT-G items completed with valid responses);
  - a total score should NOT be calculated if the overall item response rate is less than or equal to 80% (eg, 29 or fewer of the 37 items for the FACT-BMT total score completed with valid responses), since in this case the scale is not considered to be an acceptable indicator of subject quality of life. Do not impute the total score in this case, and the total score will be treated as missing in the analyses.
- For the FACT-BMT-TOI, there is no additional rule other than the ones on the relevant subscale scores as mentioned above.

#### 7.2.5.5. Missing HRQoL Data from the EQ-5D Questionnaires

For any of the 5 dimensions on the EQ-5D questionnaires (EQ-5D-5L and EQ-5D-Y), it is considered to have a valid response, if a meaningful health status is provided in the CRF. If the option of "Question not completed" is checked in the CRF, the dimension is NOT considered to have a valid response.

For the analyses on the HRQoL endpoints using the EQ-5D questionnaires, the following rules will be followed, when the response is missing or ambiguous (eg, 2 boxes are ticked for a single dimension) for any of the 5 dimensions on the questionnaires:

- For each dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression for EQ-5D-5L, and mobility, taking care of him/herself, doing usual activities, having pain or discomfort, and feeling worried, sad or unhappy for EQ-5D-Y),
  - if the response is missing, or the option of "Question not completed" is checked in the CRF, do not impute;

  - if the response is ambiguous, this dimension is considered not to have a valid response.

- For the EQ-5D-5L index value, it can only be calculated if all of the 5 dimensions are completed with no ambiguity and have valid responses. If any of the 5 dimensions has missing or ambiguous response, or the option of "Question not completed" is checked in the CRF for any of the 5 dimensions, the EQ-5D-5L index value cannot be calculated, and will be treated as having a missing value in the analysis.
- For the EQ VAS score (corresponding to the question on "Your Health TODAY" for the EQ-5D-5L and the EQ-5D-Y, self-report version questionnaires, and the question on "Describing the child's health TODAY" for the EQ-5D-Y, proxy version 1 questionnaire in the CRF), if the response is missing, do not impute, and the EQ VAS score will be treated as missing in the analyses.

#### 7.2.5.6. Missing Treatment Relationship for AEs and SAEs

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst case scenario assumed to impute the relationship. For subjects who received defibrotide, if relationship to the study drug (defibrotide) is missing, the event will be assumed to be related to defibrotide.

## 7.3. Hypotheses Testing

The primary objective of the study is to compare the efficacy of defibrotide added to standard of care immunoprophylaxis versus standard of care immunoprophylaxis alone for the prevention of aGvHD as measured by the cumulative incidence of Grade B-D aGvHD by Day +100 post-HSCT in adult and pediatric subjects. The trial is hypothesis generating and is not powered to detect minimal clinically meaningful differences between the 2 treatment arms. The trial is designed to obtain meaningful estimates of the treatment difference of the cumulative incidence rates between the 2 treatment arms.

As part of the primary efficacy endpoint analysis, the difference in the cumulative incidence of Grade B-D aGvHD between the 2 treatment arms will be tested. The hypotheses for this test are expressed as follows:

- $H_0$: the cumulative incidence rates of Grade B-D aGvHD for the 2 treatment arms are the same

  versus

- $H_a$: the cumulative incidence rates of Grade B-D aGvHD for the 2 treatment arms are significantly different.

The null hypothesis will be tested using a 2-sided stratified Gray's test (Gray 1988) with a Type I error rate of 0.1 (see Section 9.1.1 for details).

## 7.4. Level of Significance & Multiplicity Adjustment

The primary efficacy endpoint will be tested for differences between the 2 treatment arms, as described in Section 7.3.. Nominal p-value will be reported. There will be no adjustments for multiple testing in the analyses for this study.

## 7.5. Subgroups and Subgroup Analyses

Exploratory analyses of the primary efficacy and secondary efficacy endpoints will be conducted for the following subgroups of interest:

- Pediatric subjects (age < 17 years at the time of screening)
- Adult subjects (age ≥ 17 years at the time of screening)
- Subjects stratified at randomization to ATG use
- Subjects stratified at randomization to no ATG use
- Subjects actually treated with ATG as part of the standard of care prophylaxis (regardless of the stratification factor level of ATG use selected at randomization)
- Subjects not treated with ATG as part of the standard of care prophylaxis (regardless of the stratification factor level of ATG use selected at randomization)

For any of the subgroups, if the number of subjects is no more than 10% of all randomized subjects, the corresponding subgroup analyses will not be performed. If the discrepancy between the subgroups by ATG use at randomization and the subgroups by the actual ATG use is no more than 5 subjects and they are fairly evenly distributed between the 2 treatment arms, all subgroup analyses by the actual ATG use specified in this document will not be performed.

## 7.6. Changes to Planned Analyses

Neither secondary nor exploratory endpoints are specifically defined in the protocol. They are defined in this document to be corresponding to the secondary and exploratory objectives of this study (see Section 4.2).

In the protocol, the Safety Analysis Set is defined based on randomization, as follows:

*The Safety Analysis Set will include all subjects randomized to the defibrotide prophylaxis arm who received at least 1 dose of defibrotide and all subjects randomized to the standard of care arm.*

The definition of the Safety Analysis Set has been changed in this document to reference the treatment that subjects actually received (see Section 6).

For the primary efficacy and all aGvHD-related secondary efficacy endpoints, sensitivity analyses with all randomized subjects who underwent HSCT (the mITT Analysis Set) have been added.

For the primary efficacy and the following aGvHD-related secondary efficacy endpoints: cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT, and cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT, sensitivity analyses with disease relapse treated as a competing risk have been added.

For the primary efficacy endpoint, a sensitivity analysis that excludes all subjects with any aGvHD assessment scheduled during country lockdowns due to COVID-19 has been added.

For the purpose of planning the potential confirmatory phase 3 trial strategically, additional analyses have been added, while several analyses have been dropped for the final CSR. With these changes, the grading of aGvHD under both the IBMTR Severity Index and the modified Consensus Criteria from MAGIC will be evaluated comprehensively. The analyses that have been added are the following:

- GvHD-free (free of Grade II-IV aGvHD and cGvHD), Relapse-free Survival (Section 9.3.1)
- GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival (Section 9.3.2)
- Grade III-IV aGvHD-free Survival (Section 9.3.3)
- Cumulative Incidence of Stage 3-4 Skin aGvHD (Section 9.3.4)
- Cumulative Incidence of Stage 3-4 Lower GI aGvHD (Section 9.3.5)
- Cumulative Incidence of Stage 3-4 Liver aGvHD (Section 9.3.6)

The analyses that have been dropped are the following:

- Grade B-D aGvHD-free Survival with Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation
- GvHD-free (free of Grade B-D aGvHD and cGvHD), Relapse-free Survival
- Grade C-D aGvHD-free Survival
- Cumulative Incidence of Non-relapse Mortality

# 8. STUDY POPULATION SUMMARIES

Summaries will be produced by treatment arm and overall using the ITT Analysis Set, unless otherwise specified. There will be no statistical comparison between the 2 treatment arms for any of the measures in this section.

## 8.1. Analysis Sets

All analysis sets will be summarized. The ITT Analysis Set will be further summarized by randomization stratum. The number of randomized subjects by country and site will also be summarized. The following summaries will be provided:

- Analysis Sets by Treatment Arm and Overall
- Randomized Subjects by Country and Site and by Treatment Arm and Overall

If there are discrepancies between the interactive response technology (IRT) and electronic data capture (EDC) stratifications (eg, subject stratified at randomization to ATG use at the time of screening did not receive any treatment with ATG), a listing of the discrepancies will be provided:

- Discrepancies between IRT stratifications and stratification factor levels reported in the EDC

## 8.2. Disposition

### 8.2.1. Subject Disposition

A summary of subject disposition, including study completion, study withdrawal, and primary reason for study withdrawal, will be provided:

- Study Disposition by Treatment Arm and Overall

Every category will be kept in the summary even if it has 0 subjects. The following listing will be provided with date of screening, date of randomization, date of HSCT, study completion (Yes or No), the last on-study date/Day +X post-HSCT and primary reason for study withdrawal (if No to study completion):

- Study Disposition

If a subject completes the study per protocol, the last on-study date is the last visit date for this subject; if a subject terminates the study early, the date entered in the early termination folder in EDC is the last on-study date for this subject. For randomized subjects who did not undergo HSCT and discontinued the study after randomization, date of HSCT will be left blank.

### 8.2.2. Defibrotide Disposition

A summary of defibrotide disposition, including defibrotide completion, defibrotide discontinuation, and primary reason for defibrotide discontinuation, will be provided for the defibrotide prophylaxis arm using the Safety Analysis Set:

- Defibrotide Disposition

Every category will be kept in the summary even if it has 0 subjects. The following listing will be provided with the first dose date of Defibrotide, date of HSCT, the last dose date of Defibrotide/Day +X post-HSCT, defibrotide completion as specified per protocol (Yes or No), and primary reason for defibrotide discontinuation (if No to defibrotide completion):

- Defibrotide Disposition

## 8.3. Demographic and Baseline Disease Characteristics

Summaries of demographic and baseline disease characteristics (including stratification factors) will be provided using the ITT Analysis Set by treatment arm and overall, as well as the Safety Analysis Set by treatment arm and overall:

- Demographic and Baseline Disease Characteristics by Treatment Arm and Overall (using the ITT Analysis Set)
- Demographic and Baseline Disease Characteristics by Treatment Arm and Overall (using the Safety Analysis Set)

The following demographic and baseline disease characteristics will be included in the summary mentioned above:

- Sex
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, or Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, or Unknown)
- Age at screening (as a continuous variable)
- Age group at screening ($< 17$ or $\geq 17$ years)
- Weight at baseline
- Geographical location (North America or Europe)
- Primary disease
- Time in days between the date of primary disease diagnosis and baseline
- Disease evaluations prior to HSCT:
  - Bone marrow biopsy
  - Bone marrow aspirate
  - Cytogenetics
- Information pertaining to current HSCT:
  - Source of graft
  - Degree of human leukocyte antigen (HLA) mismatching
- Intent to use ATG (ATG or no ATG)

For race, if multiple options are checked for a subject, the subject will be categorized under "Multiple". See the Conditioning Regimen Log page of the CRF for primary disease; if multiple

primary diseases are reported for a subject, the subject will be categorized under "Multiple". See the Primary Disease Diagnosis page of the CRF for date of primary disease diagnosis. See the Disease Evaluation (Screening) page of the CRF for disease evaluations prior to HSCT. See the HSCT Day 0 page of the CRF for information pertaining to current HSCT; subjects who did not undergo HSCT will be categorized under "No HSCT".

For each subgroup of interest (see Section 7.5), summaries of demographic and baseline disease characteristics will also be provided as described in the following.

For the pediatric and adult subgroups, summaries of demographic and baseline disease characteristics, including all of the demographic and baseline disease characteristics specified above except age group at screening, will be provided:

- Demographic and Baseline Disease Characteristics by Age Group at Screening (< 17 or ≥ 17 years) and by Treatment Arm and Overall (using the ITT Analysis Set)
- Demographic and Baseline Disease Characteristics by Age Group at Screening (< 17 or ≥ 17 years) and by Treatment Arm and Overall (using the Safety Analysis Set)

and each summary will include the following sections:

- Demographic and baseline disease characteristics for pediatric subjects
- Demographic and baseline disease characteristics for adult subjects

For the subgroups of subjects stratified at randomization to ATG and no ATG use, summaries of demographic and baseline disease characteristics, including all of the demographic and baseline disease characteristics specified above except intent to use ATG, will be provided:

- Demographic and Baseline Disease Characteristics by ATG Use Specified at Randomization (ATG or No ATG) and by Treatment Arm and Overall (using the ITT Analysis Set)
- Demographic and Baseline Disease Characteristics by ATG Use Specified at Randomization (ATG or No ATG) and by Treatment Arm and Overall (using the Safety Analysis Set)

and each summary will include the following sections:

- Demographic and baseline disease characteristics for ATG subjects
- Demographic and baseline disease characteristics for no ATG subjects

In addition, for the subgroups of subjects who are actually treated with ATG and those who are not (regardless of the stratification factor level of ATG use selected at randomization), summaries of demographic and baseline disease characteristics, including all of the demographic and baseline disease characteristics specified above, will be provided:

- Demographic and Baseline Disease Characteristics by Actual ATG Use (ATG or No ATG) and by Treatment Arm and Overall (using the ITT Analysis Set)
- Demographic and Baseline Disease Characteristics by Actual ATG Use (ATG or No ATG) and by Treatment Arm and Overall (using the Safety Analysis Set)

and each summary will include the following sections:

- Demographic and baseline disease characteristics for subjects receiving ATG as part of the standard of care prophylaxis
- Demographic and baseline disease characteristics for subjects not receiving ATG as part of the standard of care prophylaxis

For all of the summaries of demographic and baseline disease characteristics, every category will be kept in the summary even if it has 0 subjects.

The following listing of all demographic and baseline disease characteristics specified in this section will be provided for all subjects in the ITT Analysis Set with treatment arm according to the Safety Analysis Set and a flag for actual ATG use as part of the standard of care prophylaxis:

- Demographic and Baseline Disease Characteristics

### 8.3.1. Age Summary for Public Disclosure

For the purpose of submitting the trial results to *EudraCT*, the following summary of age at screening will be provided:

- Age at Screening by Age Group by Treatment Arm and Overall

The following age groups according to the requirement of *EudraCT* will be included in the summary:

- Infant and toddlers (28 days-23 months)
- Children (2-11 years)
- Adolescents (12-17 years)
- From 18 to 64 years
- From 65 to 84 years

## 8.4. Medical/Surgical History

Medical conditions and surgical events collected on the Medical/Surgical History page of the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 21.1. Summary of medical/surgical history by system organ class (SOC) and preferred term (PT) will be provided using the Safety Analysis Set by treatment arm and overall:

- Medical/Surgical History by SOC and PT and by Treatment Arm and Overall

System organ classes will be ordered alphabetically, with PTs within an SOC sorted in descending order of incidence in overall. The following listing of medical/surgical history will be provided with the start date, ongoing (Yes or No), and the end date, if not ongoing:

- Medical/Surgical History

## 8.5. Prior and Concomitant Medications

Prior medications include those current at screening (the time period from the date informed consent is signed to the date of randomization) up to but not including baseline, and all prior therapies for the malignant disease. Concomitant medications are those taken between baseline

and Day +63 post-HSCT, unless otherwise specified, and include conditioning regimen for HSCT, medications and therapies administered as standard of care prophylaxis, concomitant medications of special interest, and other concomitant medications. Medications taken at baseline are counted as concomitant medications. For reporting purpose, the following approach will be used to determine prior or concomitant medications in case that the start date or end date is missing, after the imputation rules for all incomplete and missing start and end dates (Section 7.2.5.2 and Section 7.2.5.3) are applied:

| **Start Date** | **End Date** | **Decision** |
|---|---|---|
| Before baseline | Before baseline | Prior medication |
| Missing | Before baseline | Prior medication |
| Before baseline | On or after baseline | Prior and concomitant medication |
| Baseline to Day +63 post-HSCT | On or after baseline | Concomitant medication |
| Baseline to Day +63 post-HSCT | Missing | Concomitant medication |
| Before baseline | Missing, but Ongoing = No at or before baseline | Prior medication |
| Before baseline | Missing, but Ongoing = No after baseline | Prior and concomitant medication |
| Before baseline | Missing, but Ongoing = Yes | Prior and concomitant medication |
| Before baseline | Missing, and Ongoing (Yes or No) not answered | Prior and concomitant medication |
| Missing | On or after baseline | Prior and concomitant medication |
| Missing | Missing, but Ongoing = No at or before baseline | Prior medication |
| Missing | Missing, but Ongoing = No after baseline | Prior and concomitant medication |
| Missing | Missing, but Ongoing = Yes | Prior and concomitant medication |

| | | |
|---|---|---|
| Missing | Missing, and Ongoing (Yes or No) not answered | Prior and concomitant medication |

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHODRUG B3 Global [March 2019]), and summarized separately by the generic name using the Safety Analysis Set by treatment arm and overall. Medications that are not coded will only be listed.

### 8.5.1. Prior Medications

Information on prior medications is collected on the Prior and Concomitant Medications page of the CRF. A summary of prior medications will be provided:

- Prior Medications by Treatment Arm and Overall

Subjects reporting medications with the same generic name 2 or more times will be counted only once for that generic name. Subjects reporting more than 1 prior medication will be counted only once in the total number of subjects taking a prior medication. Prior medications will be sorted in descending order of incidence in overall. The following listing of prior medications will be provided with indication, the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route:

- Prior Medications

### 8.5.2. Concomitant Medications (excluding Concomitant Medications of Special Interest)

Concomitant medications will be summarized separately for conditioning regimen for HSCT, medications and therapies administered as standard of care prophylaxis, and other concomitant medications. Note that this section does not apply to the concomitant medications of special interest. For each summary, subjects reporting medications with the same generic name 2 or more times will be counted only once for that generic name, and subjects reporting more than 1 medication will be counted only once in the total number of subjects taking a concomitant medication.

#### 8.5.2.1. Conditioning Regimen for HSCT

Information on conditioning regimen for HSCT is collected on the Conditioning Regimen Log page of the CRF. A summary of conditioning regimen for HSCT will be provided:

- Concomitant Medications: Conditioning Regimen for HSCT by Treatment Arm and Overall

The following categories of conditioning regimen will be included in the summary:

- Total body irradiation (TBI) based regimen:
  - TBI + cyclophosphamide (± etoposide, ± cytarabine, ± thiotepa)
  - TBI + fludarabine (± etoposide, ± cytarabine, ± thiotepa)
- Busulfan based regimen

  - busulfan + cyclophosphamide + fludarabine (± etoposide, ± cytarabine, ± thiotepa)
  - busulfan + cyclophosphamide (with no fludarabine) (± etoposide, ± cytarabine, ± thiotepa)
  - busulfan + fludarabine (with no cyclophosphamide) + thiotepa (with no cytarabine) (± etoposide)
  - busulfan + fludarabine (with no cyclophosphamide) + cytarabine (with no thiotepa) (± etoposide)
  - busulfan + fludarabine (with no cyclophosphamide, cytarabine, or thiotepa) (± etoposide)
- Regimen with no TBI or busulfan:
  - melphalan + fludarabine (± etoposide, ± cytarabine, ± thiotepa)
- Other

In addition, type of conditioning regimen (myeloablative or reduced intensity conditioning) will also be included in the summary as a separate item.

The following listing of conditioning regimen for HSCT will be provided with type of conditioning regimen, conditioning start date, conditioning end date, primary disease, dose (unit), frequency, route, and total dose (unit):

- Concomitant Medications: Conditioning Regimen for HSCT

#### 8.5.2.2. Medications and Therapies Administered as Standard of Care Prophylaxis

Medications and therapies administered as standard of care prophylaxis include ATG, CSA, MTX, MMF, and TAC with indication specified as GvHD prophylaxis (taken between baseline and Day +180 post-HSCT [end of study] or early termination) and with route specified as either intravenous or oral. Information on medications and therapies administered as stand of care prophylaxis is collected on the Medications of Special Interest (Immunosuppressant) page of the CRF (with indication of "GVHD Prophylaxis"). A summary of medications and therapies administered as standard of care prophylaxis will be provided:

- Concomitant Medications: Medications and Therapies (Immunosuppressants) Administered as Standard of Care Prophylaxis by Treatment Arm and Overall

The following categories will be included in the summary:

| Category | MMF/MTX | TAC/CSA | ATG/No ATG |
|---|---|---|---|
| MTX + TAC + ATG | MTX | TAC | ATG |
| MTX + TAC, with no ATG | MTX | TAC | No ATG |
| MTX + CSA + ATG | MTX | CSA | ATG |

| | | | |
|---|---|---|---|
| MTX + CSA, with no ATG | MTX | CSA | No ATG |
| MTX + ATG | MTX | Neither | ATG |
| MTX only | MTX | Neither | No ATG |
| MMF + TAC + ATG | MMF | TAC | ATG |
| MMF + TAC, with no ATG | MMF | TAC | No ATG |
| MMF + CSA + ATG | MMF | CSA | ATG |
| MMF + CSA, with no ATG | MMF | CSA | No ATG |
| MMF + ATG | MMF | Neither | ATG |
| MMF only | MMF | Neither | No ATG |
| TAC + ATG | Neither | TAC | ATG |
| TAC only | Neither | TAC | No ATG |
| CSA + ATG | Neither | CSA | ATG |
| CSA only | Neither | CSA | No ATG |
| ATG only | Neither | Neither | ATG |
| None | Neither | Neither | No ATG |

In addition, the actual use of ATG as part of the standard of care prophylaxis, regardless of use of other standard of care prophylaxis, will also be included in the summary as a separate item.

The following listing of medications and therapies administered as standard of care will be provided with the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), and route:

- Concomitant Medications: Medications and Therapies (Immunosuppressants) Administered as Standard of Care Prophylaxis

#### 8.5.2.3. Other Concomitant Medications

Other concomitant medications include concomitant medications other than conditioning regimen for HSCT, medications and therapies administered as standard of care prophylaxis, and concomitant medications of special interest. Information on other concomitant medications is collected on the Prior and Concomitant Medications page of the CRF. A summary of other concomitant medications will be provided:

- Concomitant Medications: Other by Treatment Arm and Overall

Medications will be sorted in descending order of incidence in overall. The following listing of other concomitant medications will be provided with indication, the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route:

- Concomitant Medications: Other

### 8.5.3. Concomitant Medications of Special Interest

Concomitant medications of special interest include steroid medication and therapies, treatment and prophylaxis for GvHD other than the standard of care prophylaxis, and Defitelio (taken between baseline and Day +180 post-HSCT [end of study] or early termination). Concomitant medications of special interest will be summarized separately for the 3 types of medications mentioned above.

#### 8.5.3.1. Steroids

Information on steroids is collected on the Medications of Special Interest (Systemic/Non-Systemic Steroid) page of the CRF. A summary of steroid use will be provided:

- Concomitant Medications of Special Interest: Steroids by Treatment Arm and Overall

The summary will include the following sections:

- Systemic steroid
- Non-systemic steroid

For each of the 2 types of steroid, subjects reporting steroid use with the same generic name 2 or more times will be counted only once for that generic name, and subjects reporting steroid use with more than 1 generic name will be counted only once in the total number of subjects taking that type of steroid. The following listing of steroid use will be provided with steroid type (systemic or non-systemic), indication, the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route, with separate sections for systemic and non-systemic steroid:

- Concomitant Medications of Special Interest: Steroids

#### 8.5.3.2. Immunosuppressants

Information on immunosuppressants is collected on the Medications of Special Interest (Immunosuppressant) page of the CRF. Immunosuppressants other than medications and therapies administered as standard of care prophylaxis will be summarized by indication (GvHD treatment, GvHD prophylaxis, cytokine storm/engraftment syndrome, idiopathic pneumonia syndrome, and other):

- Concomitant Medications of Special Interest: Immunosuppressants Excluding Standard of Care Prophylaxis by Treatment Arm and Overall

For each indication, subjects reporting immunosuppressant use with the same generic name 2 or more times will be counted only once for that generic name, and subjects reporting immunosuppressant use with more than 1 generic name will be counted only once in the total number of subjects taking immunosuppressant for that indication. The following listing of immunosuppressant will be provided along indication, the start date, ongoing (Yes or No), the

end date, if not ongoing, dose (unit), and route, with separate sections for the indications mentioned above:

- Concomitant Medications of Special Interest: Immunosuppressants Excluding Standard of Care Prophylaxis

#### 8.5.3.3. Defitelio

Information on Defitelio use is collected on the Medications of Special Interest (Defitelio) page of the CRF. A summary of Defitelio use will be provided:

- Concomitant Medications of Special Interest: Defitelio by Treatment Arm and Overall

The summary will include the number of subjects with Defitelio used to treat VOD. The following listing of Defitelio will be provided with indication, the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route:

- Concomitant Medications of Special Interest: Defitelio

## 8.6. Protocol Deviations

Major protocol deviations will be summarized:

- Major Protocol Deviations by Treatment Arm and Overall

The summary will include but not be limited to the following subtypes:

- Inclusion criteria
- Exclusion criteria
- Informed consent
- Concomitant medication
- Withdrawals/termination criteria
- Study treatment admin/dispense
- Study procedures/assessments
- Other

Every subtype will be kept in the summary even if it has 0 subjects. Subjects with more than 1 major protocol deviation will be counted only once in the total number of subjects with major protocol deviations. The following listing of all protocol deviations will be provided with deviation subtype, description, and a flag for major protocol deviation:

- All Protocol Deviations

# 9. EFFICACY

All efficacy analyses will be performed using the ITT Analysis Set, unless otherwise specified.

## 9.1. Primary Efficacy Endpoint and Analysis

### 9.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the cumulative incidence rate of Grade B-D aGvHD by Day +100 post-HSCT. Grading of aGvHD for this analysis will be based on the IBMTR Severity Index (Rowlings 1997). The onset of Grade B-D aGvHD is the event of interest. Death without experiencing Grade B-D aGvHD is the competing risk. The time to the onset of Grade B-D aGvHD is the number of days from the date of Day +0 post-HSCT to the date of the first onset of Grade B-D aGvHD, calculated as the following:

**Time to the onset of Grade B-D aGvHD** = [Date of the first onset of Grade B-D aGvHD] – [Date of Day +0 post-HSCT].

The time to death is the number of days from the date of Day +0 post-HSCT to the date of death, calculated as the following:

**Time to death** = [Date of death] – [Date of Day +0 post-HSCT].

If a subject who has had HSCT does not experience Grade B-D aGvHD or die, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and thus is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT.

For each treatment arm, the cumulative incidence rate of Grade B-D aGvHD by Day +100 post-HSCT will be estimated using the cumulative incidence competing risk estimator, as described by Marubini and Valsecchi (1995). The difference in the cumulative incidence rate of Grade B-D aGvHD by Day +100 post-HSCT between the 2 treatment arms will be estimated and presented along with a 2-sided 90% CI (Zhang and Fine 2008). The treatment comparison on the cumulative incidence of Grade B-D aGvHD will be conducted using a stratified Gray's test (Gray 1988). If a stratification factor has a category that includes less than 20% of all randomized subjects, that factor will not be used in the stratified test. The cumulative incidence rates of Grade B-D aGvHD will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade B-D aGvHD based on the IBMTR Severity Index
- Figure of the Cumulative Incidence of Grade B-D aGvHD based on the IBMTR Severity Index

The following listing of all aGvHD assessments for all subjects in the ITT Analysis Set will be provided including treatment arm, age group at screening ($< 17$ or $\geq 17$ years), intent to use ATG at randomization (ATG or no ATG), a flag for actual ATG use as part of the standard of care prophylaxis, date of HSCT, date of death/Day +X post-HSCT, date of aGvHD assessment/Day +X post-HSCT, skin stage, liver stage, upper GI stage, lower GI stage, grade of

aGvHD based on the IBMTR Severity Index, and grade of aGvHD based on the modified Consensus Criteria from MAGIC:

- All aGvHD Assessments

All aGvHD assessments that are reported on the MAGIC Weekly GVHD page, the MAGIC GVHD Diagnosis page and the MAGIC GVHD Treatment page of the CRF will be included in this listing.

### 9.1.2. Grading of aGvHD Using the IBMTR Severity Index

The grading of aGvHD using the IBMTR Severity Index is based on staging the skin, liver and gastrointestinal (GI) involvements. The following table provides the categorization of the skin, liver and GI stages:

| Stage | Skin (Extent of rash) | Liver (Total bilirubin) | GI* (Volume of diarrhea) |
|---|---|---|---|
| 0 | No GVHD rash | < 2.0 mg/dL or non-GvHD jaundice | < 500 mL/day or non-GvHD diarrhea (for adult);<br>< 10 mL/kg/day or non-GvHD diarrhea (for pediatric) |
| 1 | < 25% BSA | 2.0 to 3.0 mg/dL | 500 to 999 mL/day (for adult);<br>10 to 19.9 mL/kg/day (for pediatric) |
| 2 | 25 to 50% BSA | 3.1 to 6.0 mg/dL | 1000 to 1500 mL/day (for adult);<br>20 to 30 mL/kg/day (for pediatric) |
| 3 | > 50% BSA | 6.1 to 15.0 mg/dL | > 1500 mL/day (for adult);<br>> 30 mL/kg/day (for pediatric) |
| 4 | Generalized rash with bullous formation and/or desquamation | > 15.0 mg/dL | Severe abdominal pain with or without ileus, or grossly bloody stool (volume independent) (for adult and pediatric) |

* For GI involvement under the IBMTR Severity Index, refer to the Lower GI section of the MAGIC GVHD Diagnosis page and the MAGIC Weekly GVHD page of the CRF.

For each of the system organs, the following rules should be followed when applicable for the analyses:

- If the leading question is answered "No" and the corresponding stage information is missing, set the stage to 0.

- If the confidence level is answered "Possible" or "Negative" and the corresponding stage information is not 0, set the stage to 0.

Based on the skin, liver, and GI stages, the grade of aGvHD according to the IBMTR Severity Index will be assigned as follows:

| Grade | Criteria according to the IBMTR Severity Index |
|---|---|
| A | Skin stage = 1 AND liver stage = 0 AND GI stage = 0 |
| B | Skin stage = 2 OR liver stage = 1 to 2 OR GI stage = 1 to 2 |
| C | Skin stage = 3 OR liver stage = 3 OR GI stage = 3 |
| D | Skin stage = 4 OR liver stage = 4 OR GI stage = 4 |

If aGvHD cannot be graded due to missing stage information for a particular assessment, it is assumed that no aGvHD is diagnosed at this assessment.

### 9.1.3. Analysis of the Primary Efficacy Endpoint

For each treatment arm, the Kaplan-Meier estimator for the overall survival distribution, $S(t)$ is given by,

$$\hat{S}(t) = \prod_{t_j \le t} \left\{ 1 - \frac{r_j + d_j}{Y_j} \right\}$$

and the Nelson-Aalen estimator for the cumulative hazard function of the event of interest (the onset of Grade B-D aGvHD under the IBMTR Severity Index), $\Lambda^1(t)$ is given by,

$$\hat{\Lambda}^1(t) = \sum_{t_j \le t} \frac{r_j}{Y_j}$$

where $t_j, j = 1, 2, \cdots, D$ are the distinct times where the event of interest occurs, $Y_j$ is the number of subjects at risk at time $t_j$, $r_j$ is the number of events at time $t_j$, and $d_j$ is the number of competing risk events at time $t_j$. Then, for each treatment arm, the cumulative incidence rates of Grade B-D aGvHD can be estimated using the following nonparametric estimator,

$$\hat{F}_1(t) = \sum_{t_j \le t} \hat{S}(t_{j-1}) d\hat{\Lambda}^1(t_j) = \sum_{t_j \le t} \hat{S}(t_{j-1}) \frac{r_j}{Y_j} \quad (1)$$

as described by Marubini and Valsecchi (1995). For the analysis of the primary efficacy endpoint, the analysis dataset should include the following variables:

- Treatment arm: indicating the treatment arm a subject was randomized to (the defibrotide prophylaxis arm or the standard of care arm)
- Status: an indicator with the value 0 for censoring, 1 for the onset of Grade B-D aGvHD, or 2 for death without experiencing Grade B-D aGvHD

– Time-to-event: the time in days after the date of Day +0 post-HSCT (if Status is 0, it is the number of days from the date of Day +0 post-HSCT to the date of the last available evaluation of aGvHD; if Status is 1, it is the time to the first onset of Grade B-D aGvHD; if Status is 2, it is the time to death [see Section 9.1.1])

For the difference of the cumulative incidence rates by a given time, $t$ between the 2 treatment arms, a $(1-\alpha)\times 100\%$ confidence interval is given by,

$$\left\{\hat{F}_{T1}(t)-\hat{F}_{R1}(t)\right\} \pm Z_{\alpha/2}\left\{\left[SE(\hat{F}_{T1}(t))\right]^2+\left[SE(\hat{F}_{R1}(t))\right]^2\right\}^{1/2} \qquad (2)$$

where $\hat{F}_{T1}(t)$ and $\hat{F}_{R1}(t)$ are the estimators of the cumulative incidence rates of Grade B-D aGvHD for the defibrotide prophylaxis arm and the standard of care arm, respectively, $SE$ stands for standard error, and $Z_\alpha$ is the $(1-\alpha)$th quantile of the standard normal distribution (Zhang and Fine 2008). The 2-sided 90% CI of the difference in the cumulative incidence rate of Grade B-D aGvHD by Day +100 post-HSCT between the 2 treatment arms can be calculated using formula (2) and the SAS outputs of the cumulative incidence rates of Grade B-D aGvHD for the 2 treatment arms.

The calculation of the cumulative incidence rates and the stratified Gray's test can be carried out using the LIFETEST procedure in SAS version 9.4.

### 9.1.4. Sensitivity Analyses

The sensitivity analyses will be conducted using the same methods as the primary efficacy endpoint analysis described in Section 9.1.1, except that no hypothesis testing will be performed.

#### 9.1.4.1. Sensitivity Analysis: aGvHD Graded using the Modified Consensus Criteria from MAGIC

The cumulative incidence rate of Grade II-IV aGvHD by Day +100 post-HSCT will be analyzed with aGvHD graded using the modified Consensus Criteria detailed in the aGvHD grading system from MAGIC. The onset of Grade II-IV aGvHD under the modified Consensus Criteria from MAGIC is the event of interest for this sensitivity analysis, instead of the onset of Grade B-D aGvHD under the IBMTR Severity Index. The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade II-IV aGvHD based on the Modified Consensus Criteria from MAGIC
- Figure of the Cumulative Incidence of Grade II-IV aGvHD based on the Modified Consensus Criteria from MAGIC

For the listing of aGvHD assessments corresponding to this sensitivity analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

The grade of aGvHD using the modified Consensus Criteria by MAGIC is based on staging the skin, liver, upper and lower GI involvements according to the following table:

| Stage | Skin | Liver | Upper GI | Lower GI |
|---|---|---|---|---|

| | (Active erythema only) | (Bilirubin) | | (Stool Output/Day) |
|---|---|---|---|---|
| 0 | No GVHD rash | < 2.0 mg/dL or non-GvHD jaundice | No nausea, vomiting, or anorexia, or nausea, vomiting, or anorexia from non-GvHD causes | < 500 mL/day or non-GvHD diarrhea (for adult);<br>< 10 mL/kg/day or non-GvHD diarrhea (for pediatric) |
| 1 | < 25% BSA | 2.0 to 3.0 mg/dL | Nausea, vomiting, or anorexia | 500 to 999 mL/day (for adult);<br>10 to 19.9 mL/kg/day (for pediatric) |
| 2 | 25 to 50% BSA | 3.1 to 6.0 mg/dL | | 1000 to 1500 mL/day (for adult);<br>20 to 30 mL/kg/day (for pediatric) |
| 3 | > 50% BSA | 6.1 to 15.0 mg/dL | | > 1500 mL/day (for adult);<br>> 30 mL/kg/day (for pediatric) |
| 4 | Generalized rash with bullous formation and/or desquamation | > 15.0 mg/dL | | Severe abdominal pain with or without ileus, or grossly bloody stool (volume independent) (for adult and pediatric) |

For each of the system organs, the following rules should be followed when applicable for the analyses:

- If the leading question is answered "No" and the corresponding stage information is missing, set the stage to 0.
- If the confidence level is answered "Possible" or "Negative" and the corresponding stage information is not 0, set the stage to 0.

Based on the skin, liver, upper GI and lower GI stages, the grade of aGvHD according to the modified Consensus Criteria by MAGIC will be assigned as follows:

| Grade | Criteria according to the Modified Consensus Criteria by MAGIC |
|---|---|
| 0 | Skin stage = 0 AND liver stage = 0 AND upper GI stage = 0 AND lower GI = 0 |

| | |
|---|---|
| I | Skin stage = 1 to 2 AND liver stage = 0 AND upper GI stage = 0 AND lower GI = 0 |
| II | Skin stage = 3 OR liver stage = 1 OR upper GI stage = 1 OR lower GI stage = 1 |
| III | [Liver stage = 2 to 3 OR lower GI stage = 2 to 3] AND [skin stage = 0 to 3 OR upper GI stage = 0 to 1] |
| IV | [Skin stage = 4 OR liver stage = 4 OR lower GI stage = 4] AND [upper GI stage = 0 to 1] |

If aGvHD cannot be graded due to missing stage information for a particular assessment, it is assumed that no aGvHD is diagnosed at this assessment.

#### 9.1.4.2. Sensitivity Analysis: Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation

The primary efficacy endpoint will be analyzed (with aGvHD graded using the IBMTR Severity Index) with subjects in the standard of care arm who received Defitelio for the treatment of VOD censored at the time of Defitelio initiation. Note that for the standard of care arm,

- if a subject experienced the event of interest and later received Defitelio for the treatment of VOD, the subject is considered as having experienced the event of interest in the analysis, and the first occurrence of the event of interest will be used to calculate the time-to-event variable;
- if a subject received Defitelio for the treatment of VOD and later experienced the event of interest, the subject will be censored on the date of Defitelio initiation;
- if a subject received Defitelio for the treatment of VOD and did not experience the event of interest, the subject will be censored on the date of Defitelio initiation.

The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade B-D aGvHD with Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation
- Figure of the Cumulative Incidence of Grade B-D aGvHD with Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation

For the listing of aGvHD assessments corresponding to this sensitivity analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1. For subjects in the standard of care arm receiving Defitelio for VOD, all aGvHD assessments prior to Defitelio initiation will be flagged; for the other subjects, all aGvHD assessments will be flagged.

#### 9.1.4.3. Sensitivity Analysis: Randomized Subjects who Underwent HSCT

The primary efficacy endpoint will be analyzed (with aGvHD graded using the IBMTR Severity Index) using the mITT Analysis Set. The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade B-D aGvHD for Randomized Subjects who Underwent HSCT
- Figure of the Cumulative Incidence of Grade B-D aGvHD for Randomized Subjects who Underwent HSCT

For the listing of aGvHD assessments corresponding to this sensitivity analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1. All aGvHD assessments for subjects in the mITT Analysis Set will be flagged.

#### 9.1.4.4. Sensitivity Analysis: Disease Relapse Treated as a Competing Risk

The primary efficacy endpoint will be analyzed (with aGvHD graded using the IBMTR Severity Index) with disease relapse as a competing risk in addition to death without experiencing Grade B-D aGvHD. The time to competing risk event is the number of days from the date of Day +0 post-HSCT to the date of disease relapse or death, whichever occurs first, calculated as the following:

**Time to competing risk event** = [The earlier of date of disease relapse and date of death] – [Date of Day +0 post-HSCT].

If a subject who has had HSCT does not experience Grade B-D aGvHD, have disease relapse, or die, the subject will be censored at the date of the last available evaluation of aGvHD. Note that,

- if a subject experienced the event of interest and later experienced disease relapse, the subject is considered as having experienced the event of interest in the analysis, and the first occurrence of the event of interest will be used to calculate the time-to-event variable;
- if a subject experienced disease relapse and later experienced the event of interest, the subject is considered as having experienced the competing risk event, and the date of disease relapse will be used to calculate the time-to-event variable based on the formula specified above;
- if a subject experienced disease relapse and did not experience the event of interest, the subject is considered as having experienced the competing risk event, and the date of disease relapse will be used to calculate the time-to-event variable based on the formula specified above.

The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade B-D aGvHD with Disease Relapse as a Competing Risk
- Figure of the Cumulative Incidence of Grade B-D aGvHD with Disease Relapse as a Competing Risk

For the listing of aGvHD assessments corresponding to this sensitivity analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1. For subjects who experienced disease relapse, all aGvHD assessments prior to the first occurrence of disease relapse will be flagged; for the other subjects, all aGvHD assessments will be flagged.

#### 9.1.4.5. Sensitivity Analysis: Excluding Subjects with Any aGvHD Assessment Scheduled during Country Lockdowns due to COVID-19

The primary efficacy endpoint will be analyzed (with aGvHD graded using the IBMTR Severity Index) using the mITT2 Analysis Set. Subjects with any aGvHD assessment scheduled during country-specific lockdowns due to COVID-19 will be excluded. Those subjects will be identified based on the randomization and HSCT information and country-specific lockdown durations due to COVID-19. The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade B-D aGvHD with Subjects Having Any aGvHD Assessment Scheduled during Country Lockdowns due to COVID-19 Excluded
- Figure of the Cumulative Incidence of Grade B-D aGvHD with Subjects Having Any aGvHD Assessment Scheduled during Country Lockdowns due to COVID-19 Excluded

### 9.1.5. Subgroup Analyses

The primary efficacy endpoint will be analyzed for each of the subgroups specified in Section 7.5. The subgroup analyses will be conducted using the same methods as the primary efficacy endpoint analysis described in Section 9.1.1, except that no hypothesis testing will be performed. The following summaries and figures will be provided:

- Analysis of the Cumulative Incidence of Grade B-D aGvHD for Pediatric and Adult Subjects
- Figure of the Cumulative Incidence of Grade B-D aGvHD for Pediatric Subjects
- Figure of the Cumulative Incidence of Grade B-D aGvHD for Adult Subjects
- Analysis of the Cumulative Incidence of Grade B-D aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Grade B-D aGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Grade B-D aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Grade B-D aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade B-D aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade B-D aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the cumulative incidence of Grade II-IV aGvHD based on the modified Consensus Criteria from MAGIC specified in Section 9.1.4.1, subgroup analyses by ATG use at randomization and by the actual ATG use will be performed. The following summaries and figures will be provided:

- Analysis of the Cumulative Incidence of Grade II-IV aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Grade II-IV aGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Grade II-IV aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Grade II-IV aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade II-IV aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade II-IV aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the listings of aGvHD assessments corresponding to these subgroup analyses, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

## 9.2. Secondary Endpoints and Analyses

### 9.2.1. Secondary Efficacy Endpoints

#### 9.2.1.1. Grade B-D aGvHD-free Survival by Days +100 and +180 Post-HSCT

Both the onset of Grade B-D aGvHD based on the IBMTR Severity Index and death are the events of interest for this analysis. The time to event is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of Grade B-D aGvHD or death, whichever occurs first, calculated as the following:

**Time to event** = [The earlier of date of the first onset of Grade B-D aGvHD and date of death] – [Date of Day +0 post-HSCT].

If a subject does not experience Grade B-D aGvHD or die, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and thus is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT. The Kaplan-Meier estimates of the Grade B-D aGvHD-free survival rates by Days +100 and +180 post-HSCT will be presented. The median survival times of Grade B-D aGvHD-free survival will be presented. A stratified Cox proportional hazards model will be used to estimate the hazard ratio of the defibrotide prophylaxis arm with respect to the standard of care arm, which will be presented along with a 90% CI. If a stratification factor has a category that includes less than 20% of all randomized subjects, that factor will not be used in the stratified model. The Kaplan-Meier curves on Grade B-D aGvHD-free survival will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of Grade B-D aGvHD-free Survival based on the IBMTR Severity Index
- Figure of Grade B-D aGvHD-free Survival based on the IBMTR Severity Index

For the listing of assessments corresponding to this analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

#### 9.2.1.2. Cumulative Incidence of Grade B-D aGvHD by Day +180 Post-HSCT

This secondary efficacy endpoint will be analyzed using the same methods as the primary efficacy endpoint. The results of this analysis will be included in following summary specified in Section 9.1.1: Analysis of the Cumulative Incidence of Grade B-D aGvHD based on the IBMTR Severity Index. The listing of aGvHD assessments corresponding to this analysis is the same as the listing of All aGvHD Assessments specified in Section 9.1.1.

#### 9.2.1.3. Cumulative Incidence of Grade C-D aGvHD by Days +100 and +180 Post-HSCT

The onset of Grade C-D aGvHD based on the IBMTR Severity Index is the event of interest for this analysis. Death without experiencing Grade C-D aGvHD is the competing risk. The time to the onset of Grade C-D aGvHD is the number of days from the date of Day +0 post-HSCT to the date of the first onset of Grade C-D aGvHD, calculated as the following:

**Time to the onset of Grade C-D aGvHD** = [Date of the first onset of Grade C-D aGvHD] – [Date of Day +0 post-HSCT].

The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If a subject who has had HSCT does not experience Grade C-D aGvHD or die, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and, thus, is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT. For each treatment arm, the cumulative incidence rates of Grade C-D aGvHD by Days +100 and +180 post-HSCT will be estimated using the cumulative incidence competing risk estimator (Marubini and Valsecchi 1995). The difference between the 2 treatment arms, in the respective cumulative incidence rates by Days +100 and +180 post-HSCT, will be estimated and presented along with a 2-sided 90% CI (Zhang and Fine 2008). The cumulative incidence rates of Grade C-D aGvHD will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100 and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade C-D aGvHD based on the IBMTR Severity Index
- Figure of the Cumulative Incidence of Grade C-D aGvHD based on the IBMTR Severity Index

For the listing of aGvHD assessments corresponding to this analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

#### 9.2.1.4. Cumulative Incidence of Relapse by Days +100 and +180 Post-HSCT

Disease relapse is the event of interest for this analysis. Death without disease relapse is the competing risk. The time to disease relapse is defined as the number of days from the date of Day +0 post-HSCT to the date of disease relapse, calculated as the following:

**Time to disease relapse** = [Date of disease relapse] – [Date of Day +0 post-HSCT].

The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If a subject does not experience disease relapse or die, the subject will be censored at the last on-study date. If a subject did not undergo HSCT, the subject will be censored at the date of Day +1 post-HSCT. For each treatment arm, the cumulative incidence rates of relapse by Days +100 and +180 post-HSCT will be estimated using the cumulative incidence competing risk estimator (Marubini and Valsecchi 1995). The difference between the 2 treatment arms, in the respective cumulative incidence rates by Days +100 and +180 post-HSCT, will be estimated and presented along with a 2-sided 90% CI (Zhang and Fine 2008). The cumulative incidence rates of relapse will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Disease Relapse
- Figure of the Cumulative Incidence of Disease Relapse

The following listing of all disease relapse evaluations will be provided with treatment arm, age group at screening (< 17 or ≥ 17 years), ATG use at randomization (ATG or no ATG), a flag for actual ATG use as part of the standard of care prophylaxis, date of HSCT, date of death/Day +X post-HSCT, did the patient experience a relapse (Yes or No), date of relapse/Day +X post-HSCT, and criteria for relapse:

- All Disease Relapse Evaluations

For each event of disease relapse, all reported criteria for relapse will be included in this listing.

### 9.2.2. Steroid Use in the Treatment of aGvHD by Day +180 Post-HSCT

The initiation of systemic steroid with the indication of aGvHD is the event of interest (the initiation of systemic steroid has to be for the treatment of aGvHD, for it to be the event of interest) for this analysis. The time to the event of interest for this analysis is defined as the number of days from the date of Day +0 post-HSCT to the date of the initiation of systemic steroid with the indication of aGvHD, calculated as the following:

**Time to the initiation of systemic steroid for the treatment of aGvHD** = [Date of systemic steroid initiation to treat aGvHD] – [Date of Day +0 post-HSCT].

Death without use of systemic steroid for treating aGvHD is a competing risk. The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If a subject, diagnosed with aGvHD, received treatment other than systemic steroid before or without receiving systemic steroid for treating aGvHD, the initiation of the other-than-systemic-steroid aGvHD treatment is also a competing risk, and the time to this competing risk event is defined as the number of days from the date of Day +0 post-HSCT to the date of the initiation of the other-than-systemic-steroid aGvHD treatment. If a subject who has had HSCT does not experience aGvHD or die, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and thus is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT. Note that,

– if a subject received systemic steroid for treating aGvHD and later received treatment other than systemic steroid for treating aGvHD, the subject is considered as having

experienced the event of interest, and the date of the systemic steroid initiation will be used to calculate the time-to-event variable;

- if a subject received treatment other than systemic steroid for treating aGvHD and later received systemic steroid for treating aGvHD, the subject is considered as having experienced the competing risk event, and the initiation date of the other-than-systemic-steroid aGvHD treatment will be used to calculate the time-to-event variable;
- if a subject received treatment other than systemic steroid for treating aGvHD and did not receive systemic steroid for treating aGvHD, the subject is considered as having experienced the competing risk event, and the initiation date of the other-than-systemic-steroid aGvHD treatment will be used to calculate the time-to-event variable.

For each treatment arm, the cumulative incidence rate of systemic steroid use for the treatment of aGvHD by Day +180 post-HSCT will be estimated using the cumulative incidence competing risk estimator (Marubini and Valsecchi 1995). The difference between the 2 treatment arms will be estimated and presented along with a 2-sided 90% CI (Zhang and Fine 2008). The cumulative incidence rates of systemic steroid use for the treatment of aGvHD will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD
- Figure of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD

The following listing of all medications of special interest for the treatment of aGvHD will be provided with treatment arm, age group at screening (< 17 or ≥ 17 years), ATG use at randomization (ATG or no ATG), a flag for actual ATG use as part of the standard of care prophylaxis, date of HSCT, date of death/Day +X post-HSCT, medication category (Systemic Steroid, Non-Systemic Steroid, or Immunosuppressant), medication name (systemic steroid name, if medication category is Systemic Steroid; non-systemic steroid name, if medication category is Non-Systemic Steroid; medication name, if medication category is Immunosuppressant), indication (aGvHD or GvHD treatment) and the start date of the medication/Day +X post-HSCT:

- All Medications of Special Interest for the Treatment of aGvHD

All medications of special interest for the treatment of aGvHD that are reported on the Medications of Special Interest (Systemic/Non-Systemic Steroid) page, and the Medications of Special Interest (Immunosuppressant) page of the CRF will be included in this listing.

### 9.2.3. HRQoL Endpoints based on the FACT-BMT Questionnaire

All HRQoL endpoints will be analyzed and presented using the Safety Analysis Set by treatment arm. Only subjects with age ≥ 16 years at baseline will be included in the analyses of the HRQoL endpoints based on the FACT-BMT questionnaire. The analyses will be performed after all of

the imputation rules specified in Section 7.2.5.4 are applied. See Section 7.2.4.1 for the identification of the assessments used in the analyses. Means and medians will be rounded to 2 decimal places, standard deviations 3 decimal places, and minimums and maximums 1 decimal place. There will be no statistical comparison between the 2 treatment arms.

The following summary of missing data will be provided by assessment, for each of the FACT-BMT subscales, FACT-G, FACT-BMT total score, and FACT-BMT-TOI:

- Missing HRQoL Data by Assessment and by Treatment Arm – FACT-BMT Questionnaire

#### 9.2.3.1. FACT-BMT Subscales

For each of the 5 FACT-BMT subscales, namely physical well-being, social/family well-being, emotional well-being, functional well-being, and BMTS, the subscale score at a given assessment can be calculated according to FACT-BMT Scoring Guidelines, Version 4 (Appendix 1). For each subscale, a higher score represents better quality of life (QoL). The subscale score at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. For each of the post-HSCT assessments, change between baseline and that assessment in the subscale score will be calculated as follows for a specific subject,

**Change in subscale score** = [Subscale score at the post-HSCT assessment] – [Subscale score at baseline],

so that a positive value represents improved QoL, and will be summarized and presented using descriptive statistics. If the subscale score is missing at either baseline or a specific post-HSCT assessment for a subject, change between baseline and that assessment will be treated as unknown. The following summary will be provided:

- FACT-BMT Subscales and Change in FACT-BMT Subscales from Baseline by Assessment and by Treatment Arm

#### 9.2.3.2. FACT-G

FACT-G is defined as the sum of the subscale scores of the following subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. FACT-G at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. For each of the post-HSCT assessments, change between baseline and that assessment in FACT-G will be calculated similarly to the subscale scores for a specific subject, and will be summarized and presented using descriptive statistics. The following summary will be provided:

- FACT-G and Change in FACT-G from Baseline by Assessment and by Treatment Arm

#### 9.2.3.3. FACT-BMT Total Score

The FACT-BMT total score is defined as the sum of the subscale scores of all 5 FACT-BMT subscales. The FACT-BMT total score at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. For each of the post-HSCT

assessments, change between baseline and that assessment in the FACT-BMT total score will be calculated similarly to the subscale scores for a specific subject, and will be summarized and presented using descriptive statistics. The following summary will be provided:

- FACT-BMT Total Score and Change in FACT-BMT Total Score from Baseline by Assessment and by Treatment Arm

#### 9.2.3.4. FACT-BMT-TOI

FACT-BMT-TOI is defined as the sum of the subscale scores of the following subscales: physical well-being, functional well-being, and BMTS. FACT-BMT-TOI at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. For each of the post-HSCT assessments, change between baseline and that assessment in FACT-BMT-TOI will be calculated similarly to the subscale scores for a specific subject, and will be summarized and presented using descriptive statistics. The following summary will be provided:

- FACT-BMT-TOI and Change in FACT-BMT-TOI from Baseline by Assessment and by Treatment Arm

#### 9.2.3.5. Listing of All HRQoL Assessments based on the FACT-BMT Questionnaire

The following listing of all HRQoL assessments based on the FACT-BMT questionnaire for subjects with age ≥ 16 years at baseline will be provided with treatment arm, date of baseline, date of HSCT, date of assessment/Day +X post-HSCT, response of each individual item, physical well-being subscale score, social/family well-being subscale score, emotional well-being subscale score, functional well-being subscale score, BMTS score, FACT-G, FACT-BMT-TOI, and FACT-BMT total score:

- All HRQoL Assessments based on the FACT-BMT Questionnaire for Subjects with Age ≥ 16 Years at Baseline

Day +X post-HSCT will be provided for all post-HSCT assessments.

### 9.2.4. HRQoL Endpoints based on the EQ-5D Questionnaires

All HRQoL endpoints will be analyzed and presented using the Safety Analysis Set by treatment arm. The EQ-5D-5L questionnaire is used for subjects with age ≥ 16 years at baseline. The EQ-5D-Y, self-report version is used for pediatric subjects with age ≥ 8 and ≤ 15 years at baseline. The EQ-5D-Y, proxy version 1 is used for pediatric subjects with age ≥ 4 and ≤ 7 years at baseline. Analyses will be performed for the 3 age groups separately, after all of the imputation rules specified in Section 7.2.5.5 are applied as necessary. For any of the 3 age groups, if the number of subjects is no more than 10, the analyses corresponding to that subgroup will not be performed. See Section 7.2.4.1 for the identification of the assessments used in the analyses. There will be no statistical comparison between the 2 treatment arms in any of the age groups.

The following summary of missing data will be provided by assessment, for EQ-5D-5L index value, EQ VAS score for subjects with age ≥16 years, EQ VAS score for pediatric subjects with age ≥8 and ≤15 years, and EQ VAS score for pediatric subjects with age ≥4 and ≤7 years:

- Missing HRQoL Data by Assessment and by Treatment Arm – EQ-5D Questionnaires

#### 9.2.4.1. EQ-5D-5L

##### 9.2.4.1.1. EQ-5D-5L Dimension

For each of the 5 dimensions based on the descriptive system of the EQ-5D-5L, the numbers and percentages of subjects for all categories (the 5 levels of reported problems and question not completed) and with missing data at baseline and each of the post-HSCT assessments will be presented. For each of the post-HSCT assessments, change between baseline and that assessment in each dimension will be categorized as follows for a specific subject,

- Condition improved, if the reported level of problem is lower at that assessment than at baseline
- Condition unchanged, if the reported level of problem remains the same
- Condition deteriorated, if the reported level of problem is higher at that assessment than at baseline
- Unknown, if the reported level of problem is not completed or missing either at baseline or at that assessment

The numbers and percentages of subjects for all the above-mentioned categories will be presented for each dimension at each of the post-HSCT assessments. The following summaries will be provided:

- EQ-5D-5L Dimensions for Subjects with Age ≥16 years by Assessment and by Treatment Arm
- Change in EQ-5D-5L Dimensions from Baseline for Subjects with Age ≥ 16 years by Assessment and by Treatment Arm

##### 9.2.4.1.2. EQ-5D-5L Index Value

The EQ-5D-5L index value can be calculated based on the EQ-5D-5L health states, defined by the 5 dimensions of the EQ-5D-5L descriptive system, described in Section 9.2.4.1.1. According to the EQ-5D User Guide, the index value "reflects how good or bad a health state is according to the preferences of the general population of a country/region". The conversion from EQ-5D-5L health states to an index value is country specific. Therefore, the index values for subjects from different countries, if available, should be analyzed separately. For this study, only subjects from US will be included in this analysis. The conversion from EQ-5D-5L health states to an index value for US is provided in a separate document downloaded from the EuroQol official website. The EQ-5D-5L index value at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. A higher EQ-5D-5L index value represents better QoL. For each of the post-HSCT assessments, change between baseline and that assessment in the EQ-5D-5L index value will be calculated as follows for a specific subject,

**Change in the EQ-5D-5L index value** = [Index value at the post-HSCT assessment] – [Index value at baseline],

so that a positive value represents improved QoL, and will be summarized and presented using descriptive statistics. If the EQ-5D-5L index value is missing at either baseline or a specific post-HSCT assessment for a subject, change between baseline and that assessment will be treated as unknown. Means and medians will be rounded to 4 decimal places, standard deviations 5 decimal places, and minimums and maximums 3 decimal place. The following summary will be provided:

- EQ-5D-5L Index Value and Change in EQ-5D-5L Index Value from Baseline for US Subjects with Age ≥ 16 years by Assessment and by Treatment Arm

#### 9.2.4.1.3. EQ VAS Score

The EQ VAS score at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. Similar to the EQ-5D-5L index value, a higher EQ VAS score represents better QoL. For each of the post-HSCT assessments, change between baseline and that assessment in the EQ VAS score will be calculated similarly to the EQ-5D-5L index value for a specific subject (see Section 9.2.4.1.2), and will be summarized and presented using descriptive statistics. Means and medians will be rounded to 1 decimal place, standard deviations 2 decimal places, and minimums and maximums the nearest integer. The following summary will be provided:

- EQ VAS Score and Change in EQ VAS Score from Baseline for Subjects with Age ≥ 16 years by Assessment and by Treatment Arm

### 9.2.4.2. EQ-5D-Y, Self-report Version

#### 9.2.4.2.1. EQ-5D-Y Dimension

For each of the 5 dimensions based on the descriptive system of the EQ-5D-Y, self-report version, the numbers and percentages of subjects for all categories (the 3 levels of reported problems and question not completed) and with missing data at baseline and each of the post-HSCT assessments will be presented. For each subject at a specific post-HSCT assessment, change between baseline and that assessment in each dimension will be categorized similarly to the change in each of the 5 dimensions in EQ-5D-5L (see Section 9.2.4.1.1). The numbers and percentages of subjects for all categories in change between baseline and each of the post-HSCT assessments will be presented for each dimension. The following summaries will be provided:

- EQ-5D-Y Dimensions for Pediatric Subjects (Age ≥ 8 and ≤ 15 years) by Assessment and by Treatment Arm
- Change in EQ-5D-Y Dimensions from Baseline for Pediatric Subjects (Age ≥ 8 and ≤ 15 years) by Assessment and by Treatment Arm

#### 9.2.4.2.2. EQ VAS Score

The EQ VAS score at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. For each of the post-HSCT assessments, change between baseline and that assessment in the EQ VAS score will be calculated as mentioned in Section 9.2.4.1.3 for a specified subject, and will be summarized and presented using descriptive statistics. Means and medians will be rounded to 1 decimal place, standard deviations 2 decimal

places, and minimums and maximums the nearest integer. The following summary will be provided:

- EQ VAS Score and Change in EQ VAS Score from Baseline for Pediatric Subjects (Age ≥ 8 and ≤ 15 years) by Assessment and by Treatment Arm

#### 9.2.4.3. EQ-5D-Y, Proxy Version 1

##### 9.2.4.3.1. EQ-5D-Y Dimension

For each of the 5 dimensions based on the descriptive system of the EQ-5D-Y, proxy version 1, the numbers and percentages of subjects for all categories (the 3 levels of reported problems and question not completed) and with missing data at baseline and each of the post-HSCT assessments will be presented. For each subject at a specific post-HSCT assessment, change between baseline and that assessment in each dimension will be categorized similarly to the change in each of the 5 dimensions in EQ-5D-5L (see Section 9.2.4.1.1). The numbers and percentages of subjects for all categories in change between baseline and each of the post-HSCT assessments will be presented for each dimension. The following summaries will be provided:

- EQ-5D-Y Dimensions for Pediatric Subjects (Age ≥ 4 and ≤ 7 years) by Assessment and by Treatment Arm
- Change in EQ-5D-Y Dimensions from Baseline for Pediatric Subjects (Age ≥ 4 and ≤ 7 years) by Assessment and by Treatment Arm

##### 9.2.4.3.2. EQ VAS Score

The EQ VAS score at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. For each of the post-HSCT assessments, change between baseline and that assessment in the EQ VAS score will be calculated as mentioned in Section 9.2.4.1.3 for a specific subject, and will be summarized and presented using descriptive statistics. Means and medians will be rounded to 1 decimal place, standard deviations 2 decimal places, and minimums and maximums the nearest integer. The following summary will be provided:

- EQ VAS Score and Change in EQ VAS Score from Baseline for Pediatric Subjects (Age ≥ 4 and ≤ 7 years) by Assessment and by Treatment Arm

#### 9.2.4.4. Listing of All HRQoL Assessments based on the EQ-5D Questionnaires

The following listing of all HRQoL assessments based on the EQ-5D questionnaires for subjects with age ≥ 4 years at baseline will be provided with treatment arm, date of baseline, date of HSCT, date of assessment/Day +X post-HSCT, response of each dimension, EQ-5D-5L index value, and EQ VAS score:

- All HRQoL Assessments based on the EQ-5D Questionnaires for Subjects with Age ≥ 4 Years at Baseline

Day +X post-HSCT will be provided for all post-HSCT assessments. EQ-5D-5L index value is only applicable for subjects with age ≥ 16 years at baseline. For each treatment arm, subjects will be ordered by age at baseline in this listing.

### 9.2.5. Sensitivity Analyses

Sensitivity analyses will be performed for the following secondary efficacy endpoints: Grade B-D aGvHD-free survival by Days +100 and +180 post-HSCT, cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT, and cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT, unless otherwise specified. No hypothesis testing will be performed for any of the sensitivity analyses.

#### 9.2.5.1. Sensitivity Analysis: aGvHD Graded using the Modified Consensus Criteria from MAGIC

The aGvHD-related secondary efficacy endpoints will be analyzed with aGvHD graded using the modified Consensus Criteria detailed in the aGvHD grading system from MAGIC (see Section 9.1.4.1). For the endpoints where the onset of Grade B-D aGvHD under the IBMTR Severity Index is an event of interest for the original analyses, the onset of Grade II-IV aGvHD under the modified Consensus Criteria from MAGIC is the event of interest instead for the sensitivity analyses. For the endpoint where the onset of Grade C-D aGvHD under the IBMTR Severity Index is the event of interest for the original analysis, the onset of Grade III-IV aGvHD under the modified Consensus Criteria from MAGIC is the event of interest instead for the sensitivity analysis. The results of the analysis of the cumulative incidence of Grade II-IV aGvHD by Day +180 post-HSCT will be included in the following summary specified in Section 9.1.4.1: Analysis of the Cumulative Incidence of Grade II-IV aGvHD based on the Modified Consensus Criteria from MAGIC. The listing of aGvHD assessments corresponding to this analysis is the same as the listing of aGvHD assessments specified in Section 9.1.4.1. The following summaries and figures will be provided:

- Analysis of Grade II-IV aGvHD-free Survival based on the Modified Consensus Criteria from MAGIC
- Figure of Grade II-IV aGvHD-free Survival based on the Modified Consensus Criteria from MAGIC
- Analysis of the Cumulative Incidence of Grade III-IV aGvHD based on the Modified Consensus Criteria from MAGIC
- Figure of the Cumulative Incidence of Grade III-IV aGvHD based on the Modified Consensus Criteria from MAGIC

For the listing of assessments corresponding to the Analysis of Grade II-IV aGvHD-free Survival based on the Modified Consensus Criteria from MAGIC, refer to the listing of All aGvHD Assessments specified in Section 9.1.1. For the listing of aGvHD assessments corresponding to the Analysis of the Cumulative Incidence of Grade III-IV aGvHD based on the Modified Consensus Criteria from MAGIC, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

#### 9.2.5.2. Sensitivity Analysis: Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation

The following secondary efficacy endpoints will be analyzed (with aGvHD graded using the IBMTR Severity Index) with subjects in the standard of care arm who received Defitelio for the treatment of VOD censored at the time of Defitelio initiation: cumulative incidence of Grade

B-D aGvHD by Day +180 post-HSCT, and cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT. The results of the sensitivity analysis of the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT will be included in the following summary specified in Section 0: Analysis of the Cumulative Incidence of Grade B-D aGvHD with Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation. The listing of aGvHD assessments corresponding to this analysis is the same as the listing of aGvHD assessments specified in Section 0. For the sensitivity analysis of the cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT, note that for the standard of care arm,

- if a subject experienced the event of interest and later received Defitelio for the treatment of VOD, the subject is considered as having experienced the event of interest in the analysis, and the first occurrence of the event of interest will be used to calculate the time-to-event variable;
- if a subject received Defitelio for the treatment of VOD and later experienced the event of interest, the subject will be censored on the date of Defitelio initiation;
- if a subject received Defitelio for the treatment of VOD and did not experience the event of interest, the subject will be censored on the date of Defitelio initiation.

The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade C-D aGvHD with Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation
- Figure of the Cumulative Incidence of Grade C-D aGvHD with Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation

For the listing of aGvHD assessments corresponding to the Analysis of the Cumulative Incidence of Grade C-D aGvHD with Subjects in the Standard of Care Arm Receiving Defitelio for VOD Censored at the Time of Defitelio Initiation, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

#### 9.2.5.3. Sensitivity Analysis: Randomized Subjects who Underwent HSCT

The aGvHD-related secondary efficacy endpoints will be analyzed (with aGvHD graded using the IBMTR Severity Index) using the mITT Analysis Set. The results of the sensitivity analysis of the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT will be included in the following summary specified in Section 9.1.4.3: Analysis of the Cumulative Incidence of Grade B-D aGvHD for Randomized Subjects who Underwent HSCT. The listing of aGvHD assessments corresponding to this analysis is the same as the listing of aGvHD assessments specified in Section 9.1.4.3. The following summaries and figures will be provided:

- Analysis of Grade B-D aGvHD-free Survival for Randomized Subjects who Underwent HSCT
- Figure of Grade B-D aGvHD-free Survival for Randomized Subjects who Underwent HSCT

- Analysis of the Cumulative Incidence of Grade C-D aGvHD for Randomized Subjects who Underwent HSCT
- Figure of the Cumulative Incidence of Grade C-D aGvHD for Randomized Subjects who Underwent HSCT

For the listing of all Grade B-D aGvHD-free survival events corresponding to the Analysis of Grade B-D aGvHD-free Survival for Randomized Subjects who Underwent HSCT, refer to the listing of All aGvHD Assessments specified in Section 9.1.1. For the listing of aGvHD assessments corresponding to the Analysis of the Cumulative Incidence of Grade C-D aGvHD for Randomized Subjects who Underwent HSCT, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

#### 9.2.5.4. Sensitivity Analysis: Disease Relapse Treated as a Competing Risk

Sensitivity analyses will be performed for the following secondary efficacy endpoints, with disease relapse treated as a competing risk (in addition to death without experiencing the event of interest): cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT, and cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT. The results of the sensitivity analysis of the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT will be included in the following summary specified in Section 9.1.4.4: Analysis of the Cumulative Incidence of Grade B-D aGvHD with Disease Relapse as a Competing Risk. The listing of aGvHD assessments corresponding to this analysis is the same as the listing of aGvHD assessments specified in Section 9.1.4.4. For the sensitivity analysis of the cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT, note that,

- if a subject experienced the event of interest and later experienced disease relapse, the subject is considered as having experienced the event of interest in the analysis, and the first occurrence of the event of interest will be used to calculate the time-to-event variable;
- if a subject experienced disease relapse and later experienced the event of interest, the subject is considered as having experienced the competing risk event, and the date of disease relapse will be used to calculate the time-to-event variable;
- if a subject experienced disease relapse and did not experience the event of interest, the subject is considered as having experienced the competing risk event, and the date of disease relapse will be used to calculate the time-to-event variable.

The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Grade C-D aGvHD with Disease Relapse as a Competing Risk
- Figure of the Cumulative Incidence of Grade C-D aGvHD with Disease Relapse as a Competing Risk

For the listing of aGvHD assessments corresponding to this analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

### 9.2.6. Subgroup Analyses

The secondary endpoints specified in Section 9.2.1 and Section 9.2.2 will be analyzed for the subgroups specified in Section 7.5. The subgroup analyses will be conducted using the corresponding methods for the analyses on the full population as described in Section 9.2.1 and Section 9.2.2, with no hypothesis testing performed. The results of the analysis of the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT for a specific subgroup will be included in the summary of the corresponding subgroup analysis of the cumulative incidence of Grade B-D aGvHD as specified in Section 9.1.5. The listings of aGvHD assessments corresponding to the subgroup analyses of the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT are the same as the listings of aGvHD assessments corresponding to the subgroup analyses of the cumulative incidence of Grade B-D aGvHD by Day +100 post-HSCT specified in Section 9.1.5. The following summaries and figures will be provided:

for Grade B-D aGvHD-free survival by Days +100 and +180 post-HSCT,

- Analysis of Grade B-D aGvHD-free Survival for Pediatric and Adult Subjects
- Figure of Grade B-D aGvHD-free Survival for Pediatric Subjects
- Figure of Grade B-D aGvHD-free Survival for Adult Subjects
- Analysis of Grade B-D aGvHD-free Survival for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of Grade B-D aGvHD-free Survival for Subjects Stratified at Randomization to ATG Use
- Figure of Grade B-D aGvHD-free Survival for Subjects Stratified at Randomization to No ATG Use
- Analysis of Grade B-D aGvHD-free Survival for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of Grade B-D aGvHD-free Survival for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of Grade B-D aGvHD-free Survival for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

for cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT,

- Analysis of the Cumulative Incidence of Grade C-D aGvHD for Pediatric and Adult Subjects
- Figure of the Cumulative Incidence of Grade C-D aGvHD for Pediatric Subjects
- Figure of the Cumulative Incidence of Grade C-D aGvHD for Adult Subjects
- Analysis of the Cumulative Incidence of Grade C-D aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Grade C-D aGvHD for Subjects Stratified at Randomization to ATG Use

- Figure of the Cumulative Incidence of Grade C-D aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Grade C-D aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade C-D aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade C-D aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

for cumulative incidence of relapse by Days +100 and +180 post-HSCT,

- Analysis of the Cumulative Incidence of Disease Relapse for Pediatric and Adult Subjects
- Figure of the Cumulative Incidence of Disease Relapse for Pediatric Subjects
- Figure of the Cumulative Incidence of Disease Relapse for Adult Subjects
- Analysis of the Cumulative Incidence of Disease Relapse for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Disease Relapse for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Disease Relapse for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Disease Relapse for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Disease Relapse for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Disease Relapse for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

for steroid use in the treatment of aGvHD by Day +180 post-HSCT,

- Analysis of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis

- Figure of the Cumulative Incidence of Systemic Steroid Use for the Treatment of aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the listings of assessments corresponding to the subgroup analyses of Grade B-D aGvHD-free survival by Days +100 and +180 post-HSCT, refer to the listing of All aGvHD Assessments specified in Section 9.1.1. For the listings of aGvHD assessments corresponding to the subgroup analyses of the cumulative incidence of Grade C-D aGvHD by Days +100 and +180 post-HSCT, refer to the listing of All aGvHD Assessments specified in Section 9.1.1. For the listings of disease relapse evaluations corresponding to the subgroup analyses of the cumulative incidence of relapse by Days +100 and +180 post-HSCT, refer to the listing of All Disease Relapse Evaluations specified in Section 9.2.1.4. For the listings of medications of special interest for the treatment of aGvHD corresponding to the subgroup analyses of the steroid use in the treatment of aGvHD by Day +180 post-HSCT, refer to the listing of All Medications of Special Interest for the Treatment of aGvHD specified in Section 9.2.2.

For the cumulative incidence of Grade III-IV aGvHD based on the modified Consensus Criteria from MAGIC specified in Section 9.2.5.1, subgroup analyses by ATG use at randomization and by the actual ATG use will be performed. The following summaries and figures will be provided:

- Analysis of the Cumulative Incidence of Grade III-IV aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Grade III-IV aGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Grade III-IV aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Grade III-IV aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade III-IV aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Grade III-IV aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the listings of aGvHD assessments corresponding to the subgroup analyses of the cumulative incidence of Grade III-IV aGvHD based on the modified Consensus Criteria from MAGIC, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

## 9.3. Exploratory Endpoints

No hypothesis testing will be performed for the analysis of any exploratory endpoint.

### 9.3.1. GvHD-free (free of Grade II-IV aGvHD and cGvHD), Relapse-free Survival by Day +180 Post-HSCT

The onset of Grade II-IV aGvHD, the onset of cGvHD, disease relapse, and death are the events of interest for this analysis. Grading of aGvHD will be based on the modified Consensus Criteria from MAGIC, and grading of cGvHD will be based on the NIH criteria. The time to event is

defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of Grade II-IV aGvHD, the first onset of cGvHD, disease relapse, or death, whichever occurs first. If a subject does not experience any of the events of interest, the subject will be censored at the earlier date of the last available evaluations of aGvHD and cGvHD. If a subject did not undergo HSCT and thus is not evaluable for GvHD, the subject will be censored at the date of Day +1 post-HSCT. The Kaplan-Meier estimates of the GvHD-free, relapse-free survival rate by Day +180 post-HSCT will be presented. The median survival times of GvHD-free, relapse-free survival will be presented. The Kaplan-Meier curves on GvHD-free, relapse-free survival will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of GvHD-free (free of Grade II-IV aGvHD and cGvHD), Relapse-free Survival
- Figure of GvHD-free (free of Grade II-IV aGvHD and cGvHD), Relapse-free Survival

For the listing of the assessments corresponding to this analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

### 9.3.2. GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival by Day +180 Post-HSCT

The onset of Grade III-IV aGvHD, the onset of moderate or severe cGvHD, disease relapse, and death are the events of interest for this analysis. Grading of aGvHD will be based on the modified Consensus Criteria from MAGIC, and grading of cGvHD will be based on the NIH criteria. The time to event is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of Grade III-IV aGvHD, the first onset of moderate or severe cGvHD, disease relapse, or death, whichever occurs first. If a subject does not experience any of the events of interest, the subject will be censored at the earlier date of the last available evaluations of aGvHD and cGvHD. If a subject did not undergo HSCT and thus is not evaluable for GvHD, the subject will be censored at the date of Day +1 post-HSCT. The Kaplan-Meier estimates of the GvHD-free, relapse-free survival rate by Day +180 post-HSCT will be presented. The median survival times of GvHD-free, relapse-free survival will be presented. The Kaplan-Meier curves on GvHD-free, relapse-free survival will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival
- Figure of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival

For this endpoint, subgroup analyses by ATG use at randomization and by the actual ATG use will be performed. The following summaries and figures will be provided:

- Analysis of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival for Subjects Stratified at Randomization to ATG Use
- Figure of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival for Subjects Stratified at Randomization to No ATG Use
- Analysis of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of GvHD-free (free of Grade III-IV aGvHD and moderate to severe cGvHD), Relapse-free Survival for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the listings of assessments corresponding to these analyses, refer to the listing of All aGvHD Assessments in Section 9.1.1.

### 9.3.3. Grade III-IV aGvHD-free Survival by Days +100 and +180 Post-HSCT

These endpoints will be analyzed using the same methods as the secondary efficacy endpoint on Grade B-D aGvHD-free survival by Days +100 and +180 post-HSCT as described in Section 9.2.1.1. The onset of Grade III-IV aGvHD based on the modified Consensus Criteria from MAGIC and death are the events of interest for this analysis. The time to event is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of Grade III-IV aGvHD or death, whichever occurs first. If a subject does not experience Grade III-IV aGvHD or die, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and thus is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT. The following summary and figure will be provided:

- Analysis of Grade III-IV aGvHD-free Survival
- Figure of Grade III-IV aGvHD-free Survival

For the listing of assessments corresponding to this analysis, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

### 9.3.4. Cumulative Incidence of Stage 3-4 Skin aGvHD by Day +180 Post-HSCT

This endpoint will be analyzed using the same methods as the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT as described in Section 9.2.1.2. The onset of Stage 3-4 skin aGvHD is the event of interest for this analysis, and death without experiencing Stage 3-4 skin aGvHD is the competing risk. The time to the onset of Stage 3-4 skin aGvHD is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of Stage 3-4 skin aGvHD. The time to death is the number of days from the date of Day +0 post-HSCT to the

date of death. If diagnosis of Stage 3-4 skin aGvHD or death is not reported for a subject, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and thus is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT. The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Stage 3-4 Skin aGvHD
- Figure of the Cumulative Incidence of Stage 3-4 Skin aGvHD

For this endpoint, subgroup analyses by ATG use at randomization and by the actual ATG use will be performed. The following summaries and figures will be provided:

- Analysis of the Cumulative Incidence of Stage 3-4 Skin aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Stage 3-4 Skin aGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Stage 3-4 Skin aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Stage 3-4 Skin aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Stage 3-4 Skin aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Stage 3-4 Skin aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the listings of assessments corresponding to these analyses, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

### 9.3.5. Cumulative Incidence of Stage 3-4 Lower GI aGvHD by Day +180 Post-HSCT

This endpoint will be analyzed using the same methods as the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT as described in Section 9.2.1.2. The onset of Stage 3-4 lower GI aGvHD is the event of interest for this analysis, and death without experiencing Stage 3-4 lower GI aGvHD is the competing risk. The time to the onset of Stage 3-4 lower GI aGvHD is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of Stage 3-4 lower GI aGvHD. The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If diagnosis of Stage 3-4 lower GI aGvHD or death is not reported for a subject, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and thus is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT. The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD
- Figure of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD

For this endpoint, subgroup analyses by ATG use at randomization and by the actual ATG use will be performed. The following summaries and figures will be provided:

- Analysis of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Stage 3-4 Lower GI aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the listings of assessments corresponding to these analyses, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

### 9.3.6. Cumulative Incidence of Stage 3-4 Liver aGvHD by Day +180 Post-HSCT

This endpoint will be analyzed using the same methods as the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT as described in Section 9.2.1.2. The onset of Stage 3-4 liver aGvHD is the event of interest for this analysis, and death without experiencing Stage 3-4 liver aGvHD is the competing risk. The time to the onset of Stage 3-4 liver aGvHD is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of Stage 3-4 liver aGvHD. The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If diagnosis of Stage 3-4 liver aGvHD or death is not reported for a subject, the subject will be censored at the date of the last available evaluation of aGvHD. If a subject did not undergo HSCT and thus is not evaluable for aGvHD, the subject will be censored at the date of Day +1 post-HSCT. The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of Stage 3-4 Liver aGvHD
- Figure of the Cumulative Incidence of Stage 3-4 Liver aGvHD

For this endpoint, subgroup analyses by ATG use at randomization and by the actual ATG use will be performed. The following summaries and figures will be provided:

- Analysis of the Cumulative Incidence of Stage 3-4 Liver aGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of Stage 3-4 Liver aGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of Stage 3-4 Liver aGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of Stage 3-4 Liver aGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis

- Figure of the Cumulative Incidence of Stage 3-4 Liver aGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of Stage 3-4 Liver aGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

For the listings of assessments corresponding to these analyses, refer to the listing of All aGvHD Assessments specified in Section 9.1.1.

### 9.3.7. Cumulative Incidence of cGvHD by Day +180 post-HSCT

This endpoint will be analyzed using the same methods as the cumulative incidence of Grade B-D aGvHD by Day +180 post-HSCT as described in Section 9.2.1.2. The onset of cGvHD is the event of interest for this analysis, and death without experiencing cGvHD is the competing risk. The time to the onset of cGvHD is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of cGvHD. The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If diagnosis of cGvHD or death is not reported for a subject, the subject will be censored at the date of the last available evaluation of cGvHD. If a subject did not undergo HSCT and thus is not evaluable for cGvHD, the subject will be censored at the date of Day +1 post-HSCT. The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of cGvHD
- Figure of the Cumulative Incidence of cGvHD

For this endpoint, subgroup analyses by ATG use at randomization and by the actual ATG use will be performed. The following summaries and figures will be provided:

- Analysis of the Cumulative Incidence of cGvHD for Subjects Stratified at Randomization to ATG and No ATG Use
- Figure of the Cumulative Incidence of cGvHD for Subjects Stratified at Randomization to ATG Use
- Figure of the Cumulative Incidence of cGvHD for Subjects Stratified at Randomization to No ATG Use
- Analysis of the Cumulative Incidence of cGvHD for Subjects by Treatment with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of cGvHD for Subjects Treated with ATG as Part of the Standard of Care Prophylaxis
- Figure of the Cumulative Incidence of cGvHD for Subjects Not Treated with ATG as Part of the Standard of Care Prophylaxis

Corresponding to these analyses, the following listing of all cGvHD assessments will be provided with treatment arm, age group at screening ($< 17$ or $\geq 17$ years), intent to use ATG at randomization (ATG or no ATG), a flag for actual ATG use as part of the standard of care prophylaxis, date of HSCT, date of death/Day +X post-HSCT, date of assessment/Day +X post-HSCT, does the patient have chronic GvHD (Yes or No), and the overall severity of cGvHD:

- All cGvHD Assessments

### 9.3.8. Overall Survival by Day +180 Post-HSCT

Death due to any cause is the event of interest. If death is not reported for a subject, the subject will be censored at the last on-study date. If a subject did not undergo HSCT, the subject will be censored at the date of Day +1 post-HSCT. The Kaplan-Meier estimates of the overall survival rate by Day +180 post-HSCT will be presented. The median survival times of overall survival will be presented. The Kaplan-Meier curves on overall survival will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of Overall Survival
- Figure of Overall Survival

The following listing of death will be provided with treatment arm, date of HSCT, date of death/Day +X post-HSCT, and primary cause of death:

- Death

### 9.3.9. Cumulative Incidence of VOD with or without Multi-organ Dysfunction by Days +30 and +100 Post-HSCT

The diagnosis of VOD is the event of interest for this analysis. Death without diagnosis of VOD is the competing risk. The time to the diagnosis of VOD is defined as the number of days from the date of Day +0 post-HSCT to the date of the first VOD diagnosis. The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If diagnosis of VOD or death is not reported for a subject, the subject will be censored at the date of the last available VOD assessment. If a subject did not undergo HSCT, the subject will be censored at the date of Day +1 post-HSCT. For each treatment arm, the cumulative incidence rates of VOD with or without multi-organ dysfunction by Days +30 and +100 post-HSCT will be estimated using the cumulative incidence competing risk estimator (Marubini and Valsecchi 1995). The difference between the 2 treatment arms, in the respective cumulative incidence rates by Days +30 and +100 post-HSCT, will be estimated and presented along with a 2-sided 90% CI (Zhang and Fine 2008). The cumulative incidence rates of VOD with or without multi-organ dysfunction will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +100 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30 and +100 post-HSCT). The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of VOD with or without Multi-organ Dysfunction
- Figure of the Cumulative Incidence of VOD with or without Multi-organ Dysfunction

The following listing of all VOD assessments will be provided with treatment arm, date of HSCT, date of death/Day +X post-HSCT, was VOD Diagnosis Assessment performed at this visit (Yes or No), date of VOD diagnosis assessment/Day +X post-HSCT, if Yes, has patient been diagnosed with VOD prior to or on this visit (Yes or No), date of VOD diagnosis/Day +X post-HSCT, if Yes, and VOD diagnosis criteria:

- All VOD Assessments

### 9.3.10. Cumulative Incidence of TA-TMA by Day +180 Post-HSCT

The onset of TA-TMA is the event of interest for this analysis. The following AE terms will be used to identify onset of TA-TMA: Thrombotic microangiopathy; Thrombotic thrombocytopenic purpura; Atypical thrombotic thrombocytopenic purpura; Haemolytic uraemic syndrome; Atypical haemolytic uraemic syndrome. Death without diagnosis of TA-TMA is the competing risk. The time to the onset of TA-TMA is defined as the number of days from the date of Day +0 post-HSCT to the date of the first onset of TA-TMA. The time to death is the number of days from the date of Day +0 post-HSCT to the date of death. If diagnosis of TA-TMA or death is not reported for a subject, the subject will be censored at the last on-study date. If a subject did not undergo HSCT, the subject will be censored at the date of Day +1 post-HSCT. For each treatment arm, the cumulative incidence rates of TA-TMA by Day +180 post-HSCT will be estimated using the cumulative incidence competing risk estimator (Marubini and Valsecchi 1995). The difference between the 2 treatment arms will be estimated and presented along with a 2-sided 90% CI (Zhang and Fine 2008). The cumulative incidence rates of TA-TMA will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT). The following summary and figure will be provided:

- Analysis of the Cumulative Incidence of TA-TMA
- Figure of the Cumulative Incidence of TA-TMA

The following listing of all diagnosis of TA-TMA will be provided with treatment arm, date of HSCT, date of death/Day +X post-HSCT, date of TA-TMA diagnosis/Day +X post-HSCT, and the SOC and PT of the TA-TMA event:

- All Diagnosis of TA-TMA

### 9.3.11. Hospital Resource Utilization

These endpoints will be analyzed based on the Safety Analysis Set. For the analyses, the following rules will be used to determine the hospitalization admission and discharge dates, and intensive care unit (ICU) admission and discharge dates under certain situations specified below:

- If the hospitalization admission date or ICU admission date is prior to the date of informed consent, use the date of informed consent as the hospitalization admission date or ICU admission date.
- If a subject is hospitalized or in the ICU at the time of study completion, study withdrawal, or death, use the date of study completion, study withdrawal, or death as the hospitalization discharge date or ICU discharge date.
- If the hospitalization admission and discharge dates are missing and the ICU admission and discharge dates are available for a subject, use the ICU admission and discharge dates to calculate both the days of hospital stay and the number of days in ICU.

The number of days for hospital stay will be calculated using the formula below:

**Days of hospital stay** = [Hospitalization discharge date] – [Hospitalization admission date] + 1.

If a subject is admitted to the hospital multiple times while on study, the number of days for hospital stay for this subject will be the sum of days of all hospital stays, and the overlapped days for hospital stay, if any, will be counted only once. The number of days for hospital stay will be summarized and presented using descriptive statistics. The number of days in ICU will be calculated using the formula below:

**The number of days in ICU** = [ICU discharge date] – [ICU admission date] + 1.

If a subject is admitted to ICU multiple times while on study, the number of days in ICU for this subject will be the sum of days of all ICU stays. The number of days in ICU will be summarized and presented using descriptive statistics. The following summary will be provided:

- Analysis of Hospital Resource Utilization by Treatment Arm

and the following sections will be included in the summary:

  - Hospital stay
  - ICU stay

The following listing of hospital resource utilization will be provided with treatment arm, date of HSCT, hospitalization admission date, hospitalization discharge date, ICU admission date, and ICU discharge date:

- Hospital Resource Utilization

For one hospital stay, if there is no ICU stay, ICU admission date and ICU discharge date will be left blank in the listing. For one hospital stay, if there are multiple ICU stays, the information will be listed in the following format:

| Trt. Arm | Subject Identifier/ Age/ Race | Date of HSCT | Hospitalization Admission Date | Hospitalization Discharge Date | ICU Admission Date | ICU Discharge Date |
|---|---|---|---|---|---|---|
| *Defibrotide Prophylaxis* | *10011001/ 17/ White* | *MMDD YYYY* | *Hospitalization Admission Date* | *Hospitalization Discharge Date* | *ICU Admission Date 1* | *ICU Discharge Date 1* |
| | | | | | *ICU Admission Date 2* | *ICU Discharge Date 2* |

# 10. SAFETY

Safety analyses will be performed by treatment arm based on the Safety Analysis Set.

## 10.1. Exposure

### 10.1.1. Extent of Exposure to Defibrotide

A summary of defibrotide exposure will be provided using descriptive statistics for the defibrotide prophylaxis arm:

- Defibrotide Exposure

The following information will be included in the summary:

- Days of defibrotide exposure: number of days on which a subject receive at least 1 dose of defibrotide
- Duration of defibrotide treatment in days:

  [Date of last dose of defibrotide] – [Date of first dose of defibrotide] + 1
- Total number of doses received
- Number of doses per day:

  [Total number of doses received] ÷ [Duration of defibrotide treatment in days]
- Total exposure in mg: total amount of defibrotide received by a subject
- Daily dose in mg/day:

  [Total exposure in mg] ÷ [Duration of defibrotide treatment in days]
- Daily dose in mg/kg/day:

  [Daily dose in mg/day] ÷ [Weight at baseline in kg]

The following listing of defibrotide administration will be provided including the information regarding dose number per 24 hours, was dose given (Yes or No), start date/time, end date/time, dose per administration (unit), was dose adjusted from plan (Yes or No), and reason for dose adjustment (if Yes to was dose adjusted from plan):

- Defibrotide Administration

### 10.1.2. Treatment Compliance

Not applicable.

## 10.2. Adverse Events

Adverse events recorded in the CRF will be coded to SOC and PT using MedDRA 21.1. Investigators will assess the relatedness of each AE to defibrotide and study procedures. The severity of AEs will be recorded using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The severity grade of events for which the severity was not recorded will be categorized as "missing" for summaries and listings, and will be considered the least severe for the purposes of sorting for data presentation.

Treatment-related AEs for defibrotide are those for which investigators answer "Yes" to the question "Was this adverse event related to study drug (Defibrotide)?" in the CRF. Events for which investigators do not record relationship to defibrotide will be considered as related to defibrotide for summary purpose (see Section 7.2.5.6). Listings will show treatment relationship as missing. AEs for which "Yes" is marked for the question "Was this adverse event related to a study procedure?" in the CRF will be identified and included in AE listings.

Serious AEs are those for which investigators answers "Yes" to the question "Was the adverse event serious?" in the CRF. The clinical database will be reconciled with the SAE database before the final database lock.

A treatment-emergent AE (TEAE) is defined as any event with a start date on or after baseline (see Section 7.2.1) through the end of the study, or any ongoing event that worsens in severity after baseline through the end of the study. For the purpose of determining treatment-emergent, incomplete and missing AE start dates will be imputed as specified in Section 7.2.5.1.

The following summaries of AEs will be provided:

- TEAEs by PT and by Treatment Arm
- Serious TEAEs by SOC and PT and by Treatment Arm
- Treatment-related TEAEs by SOC and PT (for the defibrotide prophylaxis arm only)
- Serious Treatment-related TEAEs by SOC and PT (for the defibrotide prophylaxis arm only)
- TEAEs Leading to Defibrotide Discontinuation by SOC and PT (for the defibrotide prophylaxis arm only)
- Treatment-related TEAEs Leading to Defibrotide Discontinuation by SOC and PT (for the defibrotide prophylaxis arm only)
- TEAEs Leading to Death by SOC and PT and by Treatment Arm
- Treatment-related TEAEs Leading to Death by SOC and PT (for the defibrotide prophylaxis arm only)
- TEAEs by SOC and PT, by Maximum Severity and by Treatment Arm
- Treatment-related TEAEs by SOC and PT and by Maximum Severity (for the defibrotide prophylaxis arm only)

All TEAEs with the onset date through the end of the AE reporting period as well as all serious TEAEs assessed as related to the study drug or a study procedure will be considered to be included in the summaries. The end of the AE reporting period is Day +63 post-HSCT for subjects who underwent HSCT, whereas for subjects who did not undergo HSCT, 70 days after baseline. Treatment-emergent AEs by treatment arm will be summarized by PT, sorted in descending order of incidence in the defibrotide prophylaxis arm. The other AE summaries will

be provided by SOC and PT, and SOCs will be ordered alphabetically, with PTs within an SOC sorted in descending order of incidence in the defibrotide prophylaxis arm. If a subject has more than 1 AE within a PT, the subject is counted only once at the maximum severity; if a subject has more than 1 AE within an SOC, the subject is counted once at the maximum severity when reporting results for that SOC.

The following listings will be provided with subject identifier, treatment arm, SOC, PT, start date, end date, severity grade, seriousness, relationship to defibrotide, relationship to a study procedure, action taken, and outcome of the AE:

- All AEs
- AEs Leading to Death
- CTCAE Grade 3 to 5 AEs
- Serious AEs

### 10.2.1. Adverse Events of Special Interest

As TEAEs of special interest, bleeding events will be summarized by SOC and PT and by age group at screening and overall. The MedDRA 21.1 Standardised MedDRA Query (SMQ) Haemorrhage terms (excl laboratory terms) will be used to search for bleeding events and is provided in **Appendix 2**. The following summary will be provided:

- TEAEs of Special Interest: Bleeding by Age Group, by SOC and PT and by Treatment Arm

For each of the subgroups defined by age and overall, SOCs will be ordered alphabetically, with PTs within an SOC sorted in descending order of incidence in the defibrotide prophylaxis arm; if a subject has more than 1 TEAE of special interest within a PT, the subject is counted only once at the maximum severity; if a subject has more than 1 TEAE of special interest within an SOC, the subject is counted once at the maximum severity when reporting results for that SOC.

The following listing of all TEAEs of special interest: bleeding will be provided with subject identifier, treatment arm, SOC, PT, start date, end date, severity grade, seriousness, relationship to defibrotide, relationship to a study procedure, action taken, and outcome of the AE:

- TEAEs of Special Interest: Bleeding

### 10.2.2. Adverse Event Summary for Public Disclosure

For the purpose of submitting the trial results to *ClinicalTrials.gov*, the following summary of non-serious TEAEs will be provided by SOC and PT:

- Non-serious TEAEs by SOC and PT and by Treatment Arm

with SOCs ordered alphabetically, and PTs within an SOC sorted in descending order of incidence in the defibrotide prophylaxis arm. If a subject has more than 1 AE within a PT, the subject is counted only once at the maximum severity; if a subject has more than 1 AE within an SOC, the subject is counted once at the maximum severity when reporting results for that SOC.

## 10.3. Laboratory Assessments

For all hematology, coagulation and chemistry tests, the lab values at baseline and each of the post-baseline assessments will be summarized and presented using descriptive statistics, along with the numbers and percentages of subjects with tests not done. See Section 7.2.4.2 for the identification of the assessments used in the analyses. For each of the post-baseline assessments, change between baseline and that assessment in a specific lab value will be calculated as follows,

**Change in lab value** = [Lab value at the post-baseline assessment] – [Lab value at baseline],

and will be summarized and presented using descriptive statistics. If the lab value is not done or missing at either baseline or a specific post-baseline assessment for a subject, change between baseline and that assessment will be treated as unknown. For each of the post-baseline assessments, the number and percentage of subjects with unknown changes between baseline and that assessment will also be presented. The following summary will be provided:

- Laboratory Results and Changes in Laboratory Results from Baseline by Assessment and by Treatment Arm

A listing of abnormal post-baseline lab values will be provided with corresponding normal ranges:

- Abnormal Post-baseline Laboratory Values

For each subject and each lab test, if there is at least one result with Grade 3 or 4 or at least one abnormal result, all results at all visits for that lab test will be included in the listing.

## 10.4. Vital Signs

Systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature and weight at baseline and each of the post-baseline assessments will be summarized and presented using descriptive statistics, along with the numbers and percentages of subjects with assessments not done. See Section 7.2.4.3 for the identification of the assessments used in the analyses. For each of the post-baseline assessments, change between baseline and that assessment in a specific vital sign will be calculated as follows,

**Change in vital sign** = [Vital sign at the post-baseline assessment] – [Vital sign at baseline],

and will be summarized and presented using descriptive statistics. If a specific type of vital signs is not done or missing at either baseline or a specific post-baseline assessment for a subject, change between baseline and that assessment will be treated as unknown. For each of the post-baseline assessments, the number and percentage of subjects with unknown changes between baseline and that assessment will also be presented. The following summary will be provided:

- Vital Signs and Changes in Vital Signs from Baseline by Assessment and by Treatment Arm

A listing abnormal post-baseline vital sign values will be provided:

- Abnormal Post-baseline Vital Signs

For each subject and each vital sign, if there is at least one abnormal result, all results at all visits for that vital sign will be included in the listing. The following values are considered to represent abnormal vital signs:

- Systolic blood pressure < 60 or > 160 mmHg
- Diastolic blood pressure < 50 or > 100 mmHg
- Pulse rate < 40 or > 120 beats per minute
- Respiratory rate < 10 or > 40 breaths per minute
- Temperature < 36 or > 39 degrees Centigrade

## 10.5. Graft Failure and Time to Neutrophil and Platelet Engraftment

Time to neutrophil and platelet engraftment is defined as the number of days from the date of Day +0 post-HSCT to the date that the criterion for neutrophil or platelet engraftment, respectively, is met. The date of neutrophil engraftment is defined as the first date after HSCT of an absolute neutrophil count > $0.5 \times 10^9$/L that is maintained for 3 consecutive days. The definition of "absolute neutrophil count" includes both segmented neutrophils and "bands", immature neutrophils. The date of platelet engraftment is defined as the first date after HSCT of a platelet count > $20 \times 10^9$/L without a platelet transfusion in the preceding 7 days.

Analyses on time to neutrophil and platelet engraftment will be performed separately.

Death without experiencing engraftment and disease relapse are the competing risks. Subjects who do not achieve engraftment, experience disease relapse, or die will be censored at the date of the last available engraftment assessment. Subjects with 'Unknown' engraftment status will be censored at the date of the last available engraftment assessment. Subjects with no engraftment status reported will be censored at the date of Day +1 post-HSCT. Subjects who do not have HSCT or who are reported as 'Never Below' on the engraftment status form will be excluded from this analysis. Note that,

- if a subject achieved engraftment and later experienced disease relapse, the subject is considered as having experienced the event of interest in the analysis, and the first date on which the engraftment criteria was met will be used to calculate the time-to-event variable;
- if a subject experienced disease relapse and later achieved engraftment, the subject is considered as having experienced the competing risk event, and the date of disease relapse will be used to calculate the time-to-event variable;
- if a subject experienced disease relapse and did not achieve engraftment, the subject is considered as having experienced the competing risk event, and the date of disease relapse will be used to calculate the time-to-event variable.

For each treatment arm, the cumulative incidence rates of engraftment by Days +30, +100, and +180 post-HSCT will be estimated using the cumulative incidence competing risk estimator, as described by Marubini and Valsecchi (1995). The respective differences in the cumulative incidence rates by Days +30, +100, and +180 post-HSCT between the 2 treatment arms will be estimated and presented along with 2-sided 90% CIs (Zhang and Fine 2008). The cumulative

incidence rates of engraftment will be plotted for both treatment arms in 1 figure, and presented with the numbers of subjects at risk up to Day +180 post-HSCT (including but not limited to the numbers of subjects at risk by Days +30, +100, and +180 post-HSCT).

Primary graft failure is defined as engraftment not achieved. Secondary graft failure is defined as engraftment achieved but not sustained. The numbers and percentages of subjects with primary and secondary graft failures, who do not have HSCT, who are reported as 'Never Below', and with engraftment and graft failure not assessed will be summarized.

The following summary and figures will be provided:

- Analysis of Graft Failure and Time to Neutrophil and Platelet Engraftment
- Figure of Time to Neutrophil Engraftment
- Figure of Time to Platelet Engraftment

The following sections will be included in the summary:

  - Time to neutrophil engraftment and neutrophil graft failure
  - Time to platelet engraftment and platelet graft failure

The following listing of all neutrophil and platelet engraftment assessments will be provided with treatment arm, date of HSCT, date of death/Day +X post-HSCT, date of disease relapse/Day +X post-HSCT, date of assessment/Day +X post-HSCT, absolute neutrophil count (ANC) recovery (No, Yes, Never Below, or Unknown), date of ANC recovery/Day +X post-HSCT, if Yes, was neutrophil graft failure (primary or secondary) observed (Yes or No), date of neutrophil graft failure/Day +X post-HSCT, if Yes, platelet recovery (No, Yes, Never Below, or Unknown), date of platelet recovery/Day +X post-HSCT, if Yes, was platelet graft failure (primary or secondary) observed (Yes or No), date of platelet graft failure/Day +X post-HSCT, if Yes, was there early graft loss (No, Yes, or Unknown), and date of early graft loss/Day +X post-HSCT, if Yes:

- All Neutrophil and Platelet Engraftment Assessments

If there are multiple disease relapses for a subject, only the date of the first disease relapse will be included in this listing.

## 10.6. Karnofsky and Lansky Performance Scores

Functional impairment will be assessed using the Karnofsky performance score for subjects ≥ 16 years of age and using the Lansky performance score for subjects < 16 years of age. The last available assessment on or prior to the date of baseline will be summarized with the number and percentage of subjects in each category and with missing data, for Karnofsky and Lansky performance scores separately:

- Karnofsky and Lansky Performance Scores at Baseline by Treatment Arm

The following listing of Karnofsky and Lansky performance scores at baseline with separate sections for Karnofsky and Lansky performance scores will be provided with treatment arm, date of assessment, date of baseline, age at baseline, and Karnofsky/Lansky score:

- Karnofsky and Lansky Performance Scores at Baseline

## 10.7. Incidence of Infectious Disease Marker by Days +100 and +180 Post-HSCT

The incidence of infectious disease marker during screening will be summarized for cytomegalovirus (CMV) and Hepatitis panel (HepB SAb, HepB SAg, HepB Core Ab, and HepC Ab), and the incidence of infectious disease marker by Days +100 and +180 post-HSCT will be summarized for CMV, with the number and percentage of subjects in each category and with missing data. See Section 7.2.4.4 for the identification of the assessments used in the analyses. The following summary will be provided:

- Incidence of Infectious Disease Marker by Assessment and by Treatment Arm

The following listing of infectious disease markers with separate sections for different markers will be provided with treatment arm, date of randomization date of HSCT, date of assessment/Day +X post-HSCT, and result:

- Infectious Disease Markers

For assessments during screening, Day +X post-HSCT are not applicable, and will be specified as such in this listing.

# 11. PHARMACOKINETIC ANALYSES

Not applicable.

# 12. PHARMACODYNAMIC ANALYSES

Not applicable.

## 13. COVID-19

Comments identifying missed visits, missed assessments, study drug discontinuation, and/or study participation termination due to COVID-19 will be captured in EDC. Additionally, comments will be captured in EDC if a visit is performed as a remote voice or video visit. Comments will specify if the study disruption was due to acquiring COVID-19 or due to other COVID-19 restrictions.

The following listing will be provided and will include all subjects affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered:

- Subjects Impacted by the COVID-19 Pandemic

## REFERENCES

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ICH. Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 05 February 1998.

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Zhang MJ and Fine J. Summarizing differences in cumulative incidence functions. Stat Med 2008; 27(24): 4939-4949.

# APPENDIX 1. FACT-BMT SCORING GUIDELINES (VERSION 4)

Instructions:
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-BMT).
5. **The higher the score, the better the QOL.**

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **PHYSICAL WELL-BEING (PWB)** | GP1 | 4 | - | _____ | =_____ |
| | GP2 | 4 | - | _____ | =_____ |
| | GP3 | 4 | - | _____ | =_____ |
| | GP4 | 4 | - | _____ | =_____ |
| *Score range:* 0-28 | GP5 | 4 | - | _____ | =_____ |
| | GP6 | 4 | - | _____ | =_____ |
| | GP7 | 4 | - | _____ | =_____ |
| | | | | ***Sum individual item scores:*** _____ | |
| | | | | ***Multiply by 7:*** _____ | |
| | | | | ***Divide by number of items answered:*** _____ | =**PWB subscale score** |

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **SOCIAL/FAMILY WELL-BEING (SWB)** | GS1 | 0 | + | _____ | =_____ |
| | GS2 | 0 | + | _____ | =_____ |
| | GS3 | 0 | + | _____ | =_____ |
| | GS4 | 0 | + | _____ | =_____ |
| *Score range:* 0-28 | GS5 | 0 | + | _____ | =_____ |
| | GS6 | 0 | + | _____ | =_____ |
| | GS7 | 0 | + | _____ | =_____ |
| | | | | ***Sum individual item scores:*** _____ | |
| | | | | ***Multiply by 7:*** _____ | |
| | | | | ***Divide by number of items answered:*** _____ | =**SWB subscale score** |

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **EMOTIONAL WELL-BEING (EWB)** | GE1 | 4 | - | _____ | =_____ |
| | GE2 | 0 | + | _____ | =_____ |
| | GE3 | 4 | - | _____ | =_____ |
| | GE4 | 4 | - | _____ | =_____ |
| *Score range:* 0-24 | GE5 | 4 | - | _____ | =_____ |
| | GE6 | 4 | - | _____ | =_____ |
| | | | | ***Sum individual item scores:*** _____ | |
| | | | | ***Multiply by 6:*** _____ | |
| | | | | ***Divide by number of items answered:*** _____ | =**EWB subscale score** |

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **FUNCTIONAL WELL-BEING (FWB)** | GF1 | 0 | + | _____ | =_____ |
| | GF2 | 0 | + | _____ | =_____ |
| | GF3 | 0 | + | _____ | =_____ |
| | GF4 | 0 | + | _____ | =_____ |
| *Score range:* 0-28 | GF5 | 0 | + | _____ | =_____ |
| | GF6 | 0 | + | _____ | =_____ |
| | GF7 | 0 | + | _____ | =_____ |
| | | | | ***Sum individual item scores:*** _____ | |
| | | | | ***Multiply by 7:*** _____ | |
| | | | | ***Divide by number of items answered:*** _____ | =**FWB subscale score** |

| Subscale | Item Code | Reverse item? | | Item response | Item Score |
|---|---|---|---|---|---|
| **BONE MARROW** | BMT1 | 4 | - | _____ | =_____ |
| **TRANSPLANT** | BMT2 | 4 | - | _____ | =_____ |
| **SUBSCALE** | BMT3 | 4 | - | _____ | =_____ |
| **(BMTS)** | BMT4 | 4 | - | _____ | =_____ |
| | C6 | 0 | + | _____ | =_____ |
| *Score range:* 0-40 | C7 | 0 | + | _____ | =_____ |
| | BMT5 | 0 | + | _____ | =_____ |
| | BMT6 | 4 | - | _____ | =_____ |
| | BL4 | 0 | + | _____ | =_____ |
| | BMT7 | NOT CURRENTLY SCORED | | | |
| | BMT8 | 0 | + | _____ | =_____ |
| | BMT9 | NOT CURRENTLY SCORED | | | |

***Sum individual item scores:*** _____
***Multiply by 10 :*** _____
***Divide by number of items answered:*** _____=**BMT Subscale score**

**To derive a FACT-BMT Trial Outcome Index (TOI):**
*Score range:* 0-96

_____ + _____ + _____ = _____ =**FACT-BMT TOI**
(**PWB** score) (**FWB** score) (**BMTS** score)

**To Derive a FACT-G total score:**
*Score range:* 0-108

_____ + _____ + _____ + _____ = _____ =**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

**To Derive a FACT-BMT total score:**
*Score range:* 0-148

_____ + _____ + _____ + _____ + _____ = _____ =**FACT-BMT Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**BMTS** score)

# APPENDIX 2. MEDDRA 21.1 SMQ HAEMORRHAGE TERMS (EXCL LABORATORY TERMS)

| | |
|---|---|
| Abdominal wall haematoma | Iris haemorrhage |
| Abdominal wall haemorrhage | Joint microhaemorrhage |
| Abnormal withdrawal bleeding | Kidney contusion |
| Achenbach syndrome | Lacrimal haemorrhage |
| Acute haemorrhagic leukoencephalitis | Large intestinal haemorrhage |
| Acute haemorrhagic ulcerative colitis | Large intestinal ulcer haemorrhage |
| Administration site bruise | Laryngeal haematoma |
| Administration site haematoma | Laryngeal haemorrhage |
| Administration site haemorrhage | Lip haematoma |
| Adrenal haematoma | Lip haemorrhage |
| Adrenal haemorrhage | Liver contusion |
| Anal fissure haemorrhage | Lower gastrointestinal haemorrhage |
| Anal haemorrhage | Lower limb artery perforation |
| Anal ulcer haemorrhage | Lymph node haemorrhage |
| Anastomotic haemorrhage | Mallory-Weiss syndrome |
| Anastomotic ulcer haemorrhage | Mediastinal haematoma |
| Aneurysm ruptured | Mediastinal haemorrhage |
| Angina bullosa haemorrhagica | Medical device site bruise |
| Anorectal varices haemorrhage | Medical device site haematoma |
| Aortic aneurysm rupture | Medical device site haemorrhage |
| Aortic dissection rupture | Melaena |
| Aortic intramural haematoma | Melaena neonatal |
| Aortic perforation | Meningorrhagia |
| Aortic rupture | Menometrorrhagia |
| Aponeurosis contusion | Menorrhagia |
| Application site bruise | Mesenteric haematoma |
| Application site haematoma | Mesenteric haemorrhage |
| Application site haemorrhage | Metrorrhagia |
| Application site purpura | Mouth haemorrhage |
| Arterial haemorrhage | Mucocutaneous haemorrhage |
| Arterial intramural haematoma | Mucosal haemorrhage |
| Arterial perforation | Muscle contusion |
| Arterial rupture | Muscle haemorrhage |
| Arteriovenous fistula site haematoma | Myocardial haemorrhage |
| Arteriovenous fistula site haemorrhage | Myocardial rupture |
| Arteriovenous graft site haematoma | Naevus haemorrhage |
| Arteriovenous graft site haemorrhage | Nail bed bleeding |
| Astringent therapy | Nasal septum haematoma |
| Atrial rupture | Neonatal gastrointestinal haemorrhage |
| Auricular haematoma | Nephritis haemorrhagic |
| Basal ganglia haematoma | Nipple exudate bloody |
| Basal ganglia haemorrhage | Ocular retrobulbar haemorrhage |
| Basilar artery perforation | Oesophageal haemorrhage |
| Bladder tamponade | Oesophageal intramural haematoma |

Bleeding varicose vein
Blood blister
Blood urine
Blood urine present
Bloody discharge
Bloody peritoneal effluent
Bone contusion
Bone marrow haemorrhage
Brain contusion
Brain stem haematoma
Brain stem haemorrhage
Brain stem microhaemorrhage
Breast haematoma
Breast haemorrhage
Broad ligament haematoma
Bronchial haemorrhage
Bronchial varices haemorrhage
Bursal haematoma
Cardiac contusion
Carotid aneurysm rupture
Carotid artery perforation
Catheter site bruise
Catheter site haematoma
Catheter site haemorrhage
Central nervous system haemorrhage
Cephalhaematoma
Cerebellar haematoma
Cerebellar haemorrhage
Cerebellar microhaemorrhage
Cerebral aneurysm perforation
Cerebral aneurysm ruptured syphilitic
Cerebral arteriovenous malformation haemorrhagic
Cerebral artery perforation
Cerebral haematoma
Cerebral haemorrhage
Cerebral haemorrhage foetal
Cerebral haemorrhage neonatal
Cerebral microhaemorrhage
Cervix haematoma uterine
Cervix haemorrhage uterine
Chest wall haematoma
Choroidal haematoma
Choroidal haemorrhage
Chronic gastrointestinal bleeding
Chronic pigmented purpura
Oesophageal ulcer haemorrhage
Oesophageal varices haemorrhage
Oesophagitis haemorrhagic
Optic disc haemorrhage
Optic nerve sheath haemorrhage
Oral contusion
Oral mucosa haematoma
Osteorrhagia
Ovarian haematoma
Ovarian haemorrhage
Palpable purpura
Pancreatic haemorrhage
Pancreatitis haemorrhagic
Papillary muscle haemorrhage
Paranasal sinus haematoma
Paranasal sinus haemorrhage
Parathyroid haemorrhage
Parotid gland haemorrhage
Pelvic haematoma
Pelvic haematoma obstetric
Pelvic haemorrhage
Penile contusion
Penile haematoma
Penile haemorrhage
Peptic ulcer haemorrhage
Pericardial haemorrhage
Perineal haematoma
Periorbital haematoma
Periorbital haemorrhage
Periosteal haematoma
Peripartum haemorrhage
Peripheral artery aneurysm rupture
Peripheral artery haematoma
Perirenal haematoma
Peritoneal haematoma
Peritoneal haemorrhage
Periventricular haemorrhage neonatal
Petechiae
Pharyngeal haematoma
Pharyngeal haemorrhage
Pituitary haemorrhage
Placenta praevia haemorrhage
Polymenorrhagia
Post abortion haemorrhage
Post procedural contusion

Ciliary body haemorrhage
Coital bleeding
Colonic haematoma
Conjunctival haemorrhage
Contusion
Corneal bleeding

Cullen's sign
Cystitis haemorrhagic
Deep dissecting haematoma
Diarrhoea haemorrhagic
Disseminated intravascular coagulation
Diverticulitis intestinal haemorrhagic
Diverticulum intestinal haemorrhagic
Duodenal ulcer haemorrhage
Duodenitis haemorrhagic
Dysfunctional uterine bleeding
Ear haemorrhage
Ecchymosis
Encephalitis haemorrhagic
Enterocolitis haemorrhagic
Epidural haemorrhage
Epistaxis
Exsanguination
Extra-axial haemorrhage
Extradural haematoma
Extravasation blood
Eye contusion
Eye haematoma
Eye haemorrhage
Eyelid bleeding
Eyelid contusion
Eyelid haematoma
Femoral artery perforation
Femoral vein perforation
Foetal-maternal haemorrhage
Fothergill sign positive
Gastric haemorrhage
Gastric ulcer haemorrhage
Gastric ulcer haemorrhage, obstructive
Gastric varices haemorrhage
Gastritis alcoholic haemorrhagic
Gastritis haemorrhagic
Gastroduodenal haemorrhage
Gastrointestinal haemorrhage
Gastrointestinal polyp haemorrhage
Post procedural haematoma
Post procedural haematuria
Post procedural haemorrhage
Post transfusion purpura
Postmenopausal haemorrhage
Postpartum haemorrhage
Post-traumatic punctate intraepidermal haemorrhage
Premature separation of placenta
Procedural haemorrhage
Proctitis haemorrhagic
Prostatic haemorrhage
Pulmonary alveolar haemorrhage
Pulmonary contusion
Pulmonary haematoma
Pulmonary haemorrhage
Puncture site haemorrhage
Purpura
Purpura fulminans
Purpura neonatal
Purpura non-thrombocytopenic
Purpura senile
Putamen haemorrhage
Radiation associated haemorrhage
Rectal haemorrhage
Rectal ulcer haemorrhage
Renal artery perforation
Renal cyst haemorrhage
Renal haematoma
Renal haemorrhage
Respiratory tract haemorrhage
Respiratory tract haemorrhage neonatal
Retinal aneurysm rupture
Retinal haemorrhage
Retinopathy haemorrhagic
Retroperitoneal haematoma
Retroperitoneal haemorrhage
Retroplacental haematoma
Ruptured cerebral aneurysm
Scleral haemorrhage
Scrotal haematocoele
Scrotal haematoma
Shock haemorrhagic
Skin haemorrhage
Skin neoplasm bleeding
Skin ulcer haemorrhage

Gastrointestinal ulcer haemorrhage
Gastrointestinal vascular malformation haemorrhagic
Genital contusion
Genital haemorrhage
Gingival bleeding
Graft haemorrhage
Grey Turner's sign
Haemarthrosis
Haematemesis
Haematochezia
Haematocoele
Haematoma
Haematoma evacuation
Haematoma infection
Haematosalpinx
Haematospermia
Haematotympanum
Haematuria
Haematuria traumatic
Haemobilia
Haemophilic arthropathy
Haemophilic pseudotumour
Haemoptysis
Haemorrhage
Haemorrhage coronary artery
Haemorrhage foetal
Haemorrhage in pregnancy
Haemorrhage intracranial
Haemorrhage neonatal
Haemorrhage subcutaneous
Haemorrhage subepidermal
Haemorrhage urinary tract
Haemorrhagic adrenal infarction
Haemorrhagic anaemia
Haemorrhagic arteriovenous malformation
Haemorrhagic ascites
Haemorrhagic breast cyst
Haemorrhagic cerebral infarction
Haemorrhagic cyst
Haemorrhagic diathesis
Haemorrhagic disease of newborn
Haemorrhagic disorder
Haemorrhagic erosive gastritis
Haemorrhagic hepatic cyst
Haemorrhagic infarction
Small intestinal haemorrhage
Small intestinal ulcer haemorrhage
Soft tissue haemorrhage
Spermatic cord haemorrhage
Spinal cord haematoma
Spinal cord haemorrhage
Spinal epidural haematoma
Spinal epidural haemorrhage
Spinal subarachnoid haemorrhage
Spinal subdural haematoma
Spinal subdural haemorrhage
Spleen contusion
Splenic artery perforation
Splenic haematoma
Splenic haemorrhage
Splenic varices haemorrhage
Splinter haemorrhages
Spontaneous haematoma
Spontaneous haemorrhage
Stoma site haemorrhage
Stomatitis haemorrhagic
Subarachnoid haematoma
Subarachnoid haemorrhage
Subarachnoid haemorrhage neonatal
Subchorionic haematoma
Subchorionic haemorrhage
Subclavian artery perforation
Subclavian vein perforation
Subcutaneous haematoma
Subdural haematoma
Subdural haematoma evacuation
Subdural haemorrhage
Subdural haemorrhage neonatal
Subgaleal haematoma
Subgaleal haemorrhage
Subretinal haematoma
Superior vena cava perforation
Testicular haemorrhage
Thalamus haemorrhage
Third stage postpartum haemorrhage
Thoracic haemorrhage
Thrombocytopenic purpura
Thrombotic thrombocytopenic purpura
Thyroid haemorrhage
Tongue haematoma

Haemorrhagic necrotic pancreatitis
Haemorrhagic ovarian cyst
Haemorrhagic stroke
Haemorrhagic thyroid cyst
Haemorrhagic transformation stroke
Haemorrhagic tumour necrosis
Haemorrhagic urticaria
Haemorrhagic vasculitis
Haemorrhoidal haemorrhage
Haemostasis
Haemothorax
Henoch-Schonlein purpura
Hepatic haemangioma rupture
Hepatic haematoma
Hepatic haemorrhage
Hereditary haemorrhagic telangiectasia
Hyperfibrinolysis
Hyphaema
Iliac artery perforation
Iliac artery rupture
Iliac vein perforation
Immune thrombocytopenic purpura
Implant site bruising
Implant site haematoma
Implant site haemorrhage
Incision site haematoma
Incision site haemorrhage
Increased tendency to bruise
Induced abortion haemorrhage
Inferior vena cava perforation
Infusion site bruising
Infusion site haematoma
Infusion site haemorrhage
Injection site bruising
Injection site haematoma
Injection site haemorrhage
Instillation site bruise
Instillation site haematoma
Instillation site haemorrhage
Internal haemorrhage
Intestinal haematoma
Intestinal haemorrhage
Intestinal varices haemorrhage
Intra-abdominal haematoma
Intra-abdominal haemorrhage
Intracerebral haematoma evacuation
Tongue haemorrhage
Tonsillar haemorrhage
Tooth pulp haemorrhage
Tooth socket haemorrhage
Tracheal haemorrhage
Traumatic haematoma
Traumatic haemorrhage
Traumatic haemothorax
Traumatic intracranial haematoma
Traumatic intracranial haemorrhage
Tumour haemorrhage
Ulcer haemorrhage
Umbilical cord haemorrhage
Umbilical haematoma
Umbilical haemorrhage
Upper gastrointestinal haemorrhage
Ureteric haemorrhage
Urethral haemorrhage
Urinary bladder haemorrhage
Urogenital haemorrhage
Uterine haematoma
Uterine haemorrhage
Vaccination site bruising
Vaccination site haematoma
Vaccination site haemorrhage
Vaginal haematoma
Vaginal haemorrhage
Varicose vein ruptured
Vascular access site bruising
Vascular access site haematoma
Vascular access site haemorrhage
Vascular access site rupture
Vascular graft haemorrhage
Vascular pseudoaneurysm ruptured
Vascular purpura
Vascular rupture
Vein rupture
Venous haemorrhage
Venous perforation
Ventricle rupture
Vertebral artery perforation
Vessel puncture site bruise
Vessel puncture site haematoma
Vessel puncture site haemorrhage
Vitreous haematoma
Vitreous haemorrhage

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| Intracranial haematoma | Vulval haematoma |
| Intracranial tumour haemorrhage | Vulval haematoma evacuation |
| Intraocular haematoma | Vulval haemorrhage |
| Intrapartum haemorrhage | Withdrawal bleed |
| Intraventricular haemorrhage | Wound haematoma |
| Intraventricular haemorrhage neonatal | Wound haemorrhage |