STATISTICAL ANALYSIS PLAN

VERSION: 2.0
DATE: 24NOV2020

STUDY DRUG:
Defibrotide (defibrotide sodium)

PROTOCOL/STUDY NUMBER:
15-007 Protocol Amendment 3 v4.0 (20-AUG-2018)

STUDY TITLE:
A Phase 3, Randomized, Adaptive Study Comparing the Efficacy and Safety of Defibrotide vs Best Supportive Care in the Prevention of Hepatic Veno-Occlusive Disease in Adult and Pediatric Patients Undergoing Hematopoietic Stem Cell Transplant

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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1 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
AUC	Area under the curve
BLQ	Below the limit of quantitation
BMI	Body mass index
BSC	Best supportive care
CDISC	Clinical Data Interchange Standards Consortium
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DP	Defibrotide prophylaxis
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EPAC	Endpoint Adjudication Committee
FDA	Food and Drug Administration
GvHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplant
ICH	International Council for Harmonisation
IRT	Interactive response technology
ISC	Independent Statistical Center
ITT	Intent-to-treat
IWRS	Interactive web response system
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MOD	Multi-organ dysfunction
NRM	Non-relapse mortality
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
VOD	Hepatic veno-occlusive disease
WHO	World Health Organization

2 MODIFICATION HISTORY

Version	Date	Description
Original 1.0	*15MAY2020*	
2.0	*24NOV2020*	Section 5 was updated to describe the following changes in conduct of the planned analysis: • Clarify censoring rules for subjects who do not undergo HSCT • Add censoring rules for subjects who are diagnosed with VOD prior to HSCT • Clarify the definition of Baseline Section 10.1.2 was updated to correct the criteria for determining prior liver disease by removing the criterion of advanced stage neuroblastoma requiring myeloablative conditioning. Section 16 was updated to account for differences in PK timepoints across protocol amendments for samples taken in subjects who developed VOD and received defibrotide rescue treatment.

3 PURPOSE

This Statistical Analysis Plan (SAP) provides a detailed and complete description of the planned statistical analyses for the final analysis of Study 15-007 to support the Clinical Study Report (CSR). Mock tables, listings, and figures shells will be provided in a separate supporting document.

This SAP complies with the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. The current version is based on Protocol version *4.0* dated *20 August 2018*.

Biomarker and immunogenicity analysis plans and results will be provided in separate documents.

All decisions regarding the final analysis of the study results, as defined in this SAP document, will be made prior to database freeze of the study data.

4 STUDY DESIGN

4.1 Study Design

This is a Phase 3, open-label, randomized study to compare the efficacy and safety of defibrotide prophylaxis (DP) *vs.* best supportive care (BSC) in the prevention of hepatic veno-occlusive disease (VOD) as diagnosed using the modified Seattle criteria in adult and pediatric subjects undergoing hematopoietic stem cell transplant (HSCT) who are at high risk or very high risk of developing VOD. This study has an adaptive design with 1 interim analysis which has been detailed in a separate interim SAP.

A total of 400 subjects are planned for enrollment to ensure completion of approximately 360 subjects. An interim analysis overseen by an independent Data Monitoring Committee (DMC) is planned when 70% of subjects are evaluable for the primary efficacy endpoint (ie, VOD-free survival by Day +30 post-HSCT), with prespecified rules for efficacy stop, futility stop, and possible sample size re-estimation up to a maximum of 600 subjects total.

After informed consent or assent has been obtained from subjects, or legal parent/guardians or representatives, as applicable, screening procedures will be performed within 14 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 BSC (DP arm) or BSC alone (BSC arm) in a 1:1 ratio.

All subjects enrolled in the study will receive individualized standard of care therapy based on local institutional guidelines and subject need. This standard of care therapy or BSC is intended to serve as a study control for comparison with those subjects randomized to receive defibrotide prophylaxis. Subjects randomized to the BSC arm will receive standard of care therapy per institutional guidelines and subject need; subjects randomized to the defibrotide prophylaxis arm (DP arm) will also receive standard of care therapy based on local institutional guidelines and

subject need plus defibrotide prophylaxis. Prophylactic use of defibrotide added to BSC (DP arm) will be compared to BSC (BSC arm).

Administration of defibrotide to subjects in the DP arm will begin within 24 hours of the first dose of conditioning regimen, and will continue (for those subjects without a VOD diagnosis) for a recommended minimum of 21 days and end no later than Day +30 post-HSCT. For subjects in the BSC arm, administration of BSC according to institutional guidelines and subject need will begin on the first day of conditioning and continue until Day +30 post-HSCT or hospital discharge, whichever is sooner, or diagnosis of VOD, if applicable.

If subjects in either the DP or BSC arm develop VOD, per the modified Seattle criteria, they may receive rescue defibrotide treatment for VOD as prespecified in the informed consent and/or assent forms. For subjects in either arm who develop VOD, defibrotide for treatment of VOD should be administered until resolution of VOD or hospital discharge.

Subjects will continue to be monitored for development of late-onset VOD through Day +180 post-HSCT. Subjects who develop clinical signs and symptoms of VOD after hospital discharge/Day +30 post-HSCT will require more frequent monitoring (refer to specific instructions within schedule of assessments in the protocol), and re-admission to the hospital will be at the investigator's discretion.

An independent Endpoint Adjudication Committee (EPAC) blinded to study treatment assignment will be established to determine whether a subject meets the criteria for VOD by Day +30 post-HSCT and by Day +100 post-HSCT, using the modified Seattle criteria. The EPAC will review relevant electronic case report forms (eCRFs), results of diagnostic procedures, and ultrasound results; alternate etiology (eg, cholecystitis, viral hepatitis, acute graft-versus-host disease [GvHD]) will also be considered during review of subject data.

4.2 Study Objectives

4.2.1 Primary Objective

The primary objective of the study is to compare the efficacy of defibrotide prophylaxis in addition to BSC (DP arm) vs BSC alone (BSC arm) for the prevention of VOD as measured by VOD-free survival by Day +30 post-HSCT in subjects who are at high risk or very high risk for developing VOD.

4.2.2 Secondary Objectives

The key secondary objective of the study is to compare the efficacy of defibrotide prophylaxis in addition to BSC (DP arm) vs BSC alone (BSC arm) for the prevention of VOD as measured by VOD-free survival by Day +100 post-HSCT in subjects who are at high risk or very high risk for developing VOD.

Other secondary objectives of the study are as follows:

- To further compare the efficacy of defibrotide prophylaxis in addition to BSC (DP arm) vs BSC alone (BSC arm) on additional variables as follows:
    - Incidence of VOD by Day +30 post-HSCT
    - VOD-free survival by Day +180 post -HSCT
    - Non-relapse mortality (NRM) by Days +100 and +180 post-HSCT
    - Incidence of VOD-associated multi-organ dysfunction (MOD) (ie, severe VOD) by Days +30 and +100 post-HSCT (in those subjects who develop VOD)
    - Resolution of VOD by Day +180 post-HSCT and time to resolution of VOD (in those subjects who develop VOD)
    - Incidence of VOD after Day +30 post-HSCT up to Days +100 and +180 post-HSCT
- To compare the health-related quality of life using the following questionnaires:
    - 5-Level EuroQol-5D (EQ-5D-5L) (adults only)
    - EuroQol-5D for Youth (EQ-5D-Y), proxy version 1 (pediatric subjects 4 to 7 years of age)
    - EQ-5D-Y, self-report version 1 (pediatric subjects 8 to <16 years of age)
- To characterize the pharmacokinetics of defibrotide
- To compare the overall safety of defibrotide in addition to BSC vs BSC alone, including adverse event (AE) profile, serious adverse event (SAE) profile, laboratory abnormalities, and vital signs (including peri-infusional vital signs for subjects who receive defibrotide)
- To compare the overall safety of defibrotide in addition to BSC vs BSC alone by comparing the incidence of Grades 2, 3, and 4 acute GvHD by Days +30, +100, and +180 post-HSCT, and the incidence of chronic GvHD by Day +180 post-HSCT
- To compare graft failure and time to neutrophil and platelet engraftment

4.2.3 Exploratory Objectives

The exploratory objectives of this study are as follows:

- To compare the hospital resource utilization for subjects in the DP and BSC arms.
- To evaluate plasma concentration of potential predictive or prognostic VOD biomarkers (which may include, but will not be limited to vascular cell adhesion molecule 1 [VCAM1], von Willebrand factor [vWF], L-ficolin, plasminogen activator inhibitor [PAI-1], thrombomodulin, C-reactive protein [CRP], angiopoietin 2 [ANG2]) and/or GvHD biomarkers (which may include, but will not be limited to tumor necrosis factor receptor 1 [TNFR1], interleukin-1 receptor-like-1 [IL1RL1, also known as ST2], and regenerating islet-derived 3-alpha [REG3α])
- To evaluate immunogenicity of defibrotide in subjects who receive defibrotide for treatment or prophylaxis

4.3 Study Endpoints

4.3.1 Primary Endpoint

The primary efficacy endpoint is VOD-free survival at Day +30 post-HSCT as adjudicated by the independent EPAC. An event for the primary efficacy endpoint is defined as a VOD diagnosis (as assessed by the EPAC) or death, whichever is earlier, up to and including Day +30 post-HSCT.

4.3.1.1 Primary Study Hypothesis

The primary efficacy endpoint is a time-to-event endpoint. The statistical hypothesis for the primary endpoint is as follows:

- Null hypothesis (H_0): There is no difference in VOD-free survival by Day +30 post-HSCT between the DP and the BSC arms.

- Alternative hypothesis (H_1): There is a difference in VOD-free survival by Day +30 post-HSCT in favor of the DP arm over the BSC arm.

Superiority will be assessed using data from the intent-to-treat (ITT) analysis set. The study is designed with both an interim and a final analysis. To maintain an overall significance level at 1-sided alpha of 0.025, the incremental alpha is specified at 1-sided 0.0005 for the interim analysis and 1-sided 0.0245 for final analysis (the corresponding nominal alpha is 1-sided 0.0005 for interim analysis and 1-sided 0.02498 for final analysis).

4.3.2 Secondary Endpoints

4.3.2.1 Key Secondary Endpoint

The key secondary efficacy endpoint is VOD-free survival by Day +100 post-HSCT as adjudicated by the independent EPAC.

4.3.2.2 Key Secondary Study Hypothesis

The key secondary efficacy endpoint is a time-to-event endpoint. The statistical hypothesis is as follows:

- Null hypothesis (H_0): There is no difference in VOD-free survival by Day +100 post-HSCT between the DP and the BSC arms.

- Alternative hypothesis (H_1): There is a difference in VOD-free survival by Day +100 post-HSCT in favor of DP arm over BSC arm.

Superiority will be assessed using data from the ITT analysis set. To control the study-wise type I error, a sequential testing strategy will begin with the test on primary efficacy endpoint. If that test is significant, the test on the key secondary efficacy endpoint will be conducted at 1-sided alpha = 0.025. This gate-keeping approach will keep the family-wise error rate at 1-sided 0.025 for the comparisons of the 2 treatment arms in the primary and the key secondary efficacy endpoint analyses.

4.3.2.3 Other Secondary Endpoints

Other secondary efficacy endpoints will be tested without multiplicity adjustments, and nominal p-values will be reported. Other secondary efficacy endpoints include the following:

- Incidence of VOD by Day +30 post-HSCT
- VOD-free survival by Day +180 post-HSCT
- NRM by Days +100 and +180 post-HSCT

- Incidence of VOD-associated MOD (ie, severe VOD) by Days +30 and +100 post-HSCT (in those subjects who develop VOD)
- Proportion of subjects who have resolution of VOD by Day +180 post-HSCT and time to resolution of VOD
- Incidence of VOD after Day +30 post-HSCT up to Days +100 and +180 post-HSCT
- Health-related quality of life using EQ-5D-5L (adults only), EQ-5D-Y (proxy version 1; pediatric subjects 4 to 7 years of age), and EQ-5D-Y (self-report version 1; pediatric subjects 8 to <16 years of age)
- Pharmacokinetics of defibrotide
- Safety of defibrotide in addition to BSC vs BSC alone, including AE profile, SAE profile, laboratory abnormalities, and vital signs
- Incidence of Grades 2, 3, and 4 acute GvHD by Days +30, +100, and +180 post-HSCT, and the incidence of chronic GvHD by Day +180 post-HSCT
- Graft failure and time to neutrophil and platelet engraftment

4.3.3 Exploratory Endpoints

Exploratory endpoints include the following:

- Hospital resource utilization
- Evaluate plasma concentration of potential predictive or prognostic VOD biomarkers (which may include, but will not be limited to VCAM1, vWF, L-ficolin, PAI-1, thrombomodulin, CRP, ANG2) and/or GvHD biomarkers (which may include, but will not be limited to TNFR1, IL1RL1 (also known as ST2), and REG3α)
- Evaluate immunogenicity of defibrotide in subjects who receive defibrotide for treatment or prophylaxis

4.4 Study Treatments

For subjects randomized to the DP arm, defibrotide solution is administered intravenously by study site personnel at a dose of 25 mg/kg/day, divided into 4 equal doses of 6.25 mg/kg/dose given as 2-hour infusions every 6 hours. Defibrotide administration is recommended for a minimum of 21 days beginning within 24 hours prior to the start of the conditioning regimen (2-4 doses of defibrotide should be administered within 24 hours prior to conditioning regimen) and ending no later than Day +30 post-HSCT. Subjects in this arm of the study will also receive standard of care therapy based on local institutional guidelines and subject need.

Subjects randomized to the BSC arm should receive standard of care therapy according to institutional guidelines and subject need. Best supportive care is intended to serve as study control for comparison with those subjects randomized to receive DP. Administration of BSC will begin on the first day of conditioning and continue until Day +30 post-HSCT or hospital discharge, whichever is sooner, or diagnosis of VOD, if applicable.

4.5 Randomization Procedures and Blinding

After informed consent or assent has been obtained from subjects, or legal parent/guardians or representatives, as applicable, screening procedures will be performed within 14 days of the scheduled start of the subject's HSCT conditioning regimen. Eligible subjects will be randomly assigned to receive DP 25 mg/kg/day in addition to BSC (DP arm) or BSC alone (BSC arm) in a 1:1 ratio. Randomization will be stratified according to risk of developing VOD (high-risk or very high-risk), age (>16 years or ≤16 years), and country using an interactive web response system (IWRS). Enrollment of those subjects meeting high-risk criteria will be capped at 65% of the total enrollment using IWRS.

This is an open-label study. To minimize potential for bias, the following blinding measures will be employed:

- The central reviewer of imaging studies will be blinded to study treatment assignment and all non-radiologic subject data (see protocol Section 6.3.1.2).
- Members of the EPAC will be blinded to study treatment assignment, will not be employees of the Sponsor, and will not be otherwise involved in the study (see protocol Section 6.3.1.3 and Section 11.9.2).

4.6 Determination of the Sample Size

On the basis of literature and results from a previously conducted prevention study (Study 2004-000592-33) with defibrotide (Corbacioglu et al. 2012), the proposed sample size for this study is 200 subjects per treatment arm for a total sample size of 400 subjects. Through simulations, it is shown that this sample size provides a 90% power to detect a hazard ratio (HR) of 0.46 for VOD-free survival by Day +30 post-HSCT in DP arm as compared with BSC arm, with an average of 68 events total. The HR of 0.46 is based on 86% and 72% VOD-free survival rates by Day +30 post-HSCT for DP arm and BSC arm, respectively, which translate to 14% and 28% as the incidence of VOD or death by Day +30 post-HSCT for the 2 arms, respectively. The assumptions for the simulations to calculate the sample size also include: (1) a 2-look group sequential design at 1-sided significance level of 0.025 (overall) with 1 interim analysis for efficacy stopping (1-sided significance level of 0.0005) or nonbinding futility stopping at ≤10% conditional power; and (2) 10% dropout rate.

4.7 Planned Interim Analyses and Reviews

Due to uncertainties associated with the study design assumptions, specifically the background rate of events in the BSC treatment arm and the size of the treatment effect, an interim analysis to be overseen by the DMC is planned when 70% of subjects are evaluated for the primary efficacy endpoint (ie, VOD-free survival by Day +30 post-HSCT), with specific rules for efficacy stop (ie, 1-sided alpha of 0.0005), futility stop (ie, conditional power <10%), and possible sample size re-estimation up to a maximum of 600 subjects total when the conditional power is in the promising zone. Details on the content of the interim analysis and adaptive design decision rules are provided in the interim Statistical Analysis Plan (iSAP) and specified along with the responsibilities of the DMC as part of the DMC charter.

4.8 DMC Safety Reviews

The independent DMC will also oversee periodic safety analyses. The periodic safety analyses will begin after 50 subjects have been randomly assigned to study treatment and monitored for a minimum of 3 months, and will occur approximately every 6 months thereafter.

5 CHANGES IN THE CONDUCT OF PLANNED ANALYSES

Three TEAEs of special interest (pulmonary hemorrhage, gastrointestinal bleeding, and hypersensitivity reactions) will be summarized. This is not specified in the protocol.

Section 10.1 clarifies censoring rules for subjects who don't undergo HSCT. The protocol defines the timing variable for these subjects but does not describe how these subjects who are not at risk of post-HSCT events should be censored.

Section 10.1 also added censoring rules for subjects who develop VOD prior to HSCT. This scenario is a possible outcome, albeit rare, and was not addressed in the protocol.

Section 8.2.1 clarifies how baseline is defined. The protocol defines baseline as follows: "Baseline/Study Day 1 is defined as the day before conditioning begins for patients randomized to the DP arm and the day that conditioning begins for patients randomized to the BSC arm." As the first dose of defibrotide is administered within 24 hours prior to the first dose of conditioning for subjects randomized to DP arm, the two definitions should result into the same Study Day 1 if the subjects strictly follow the protocol. In practice, it is possible that the subjects receive the first dose of defibrotide and then do not start conditioning on the next day. Thus, the definition in the protocol could result in a baseline assessment that occurs after defibrotide administration begins. For safety analyses, the baseline value should be the last assessment taken prior to study drug administration. For this reason, the definitions of Baseline/ Study Day 1 and of baseline values were further clarified in the SAP and this is the default definition used in the analyses.

6 STUDY ANALYSIS SETS

6.1 Screened Analysis Set

The Screened Analysis Set consists of all subjects who provided written informed consent and who undergo study screening procedures.

6.2 Intent-to-Treat Analysis Set (ITT)

The ITT Analysis Set will include all randomized subjects. This will be the primary analysis set for the primary efficacy endpoint and all other efficacy endpoints. Subjects will be analyzed by the treatment they were randomized to receive.

6.3 Modified Intent-to-Treat Analysis Set (mITT)

The mITT Analysis Set will include all randomized subjects who proceed to HSCT. This will be used in some of the sensitivity analyses. Subjects will be analyzed by the treatment they were randomized to receive.

6.4 Safety Analysis Set

The overall safety population will include all subjects randomized to the DP arm who receive at least 1 dose of defibrotide and all subjects randomized to the BSC arm. Subjects will be analyzed by the treatment they actually receive.

6.5 PK Analysis Set

The PK Analysis Set will include all subjects who received at least one dose of defibrotide and had at least one evaluable defibrotide plasma concentration.

6.6 PK Evaluable Analysis Set

The PK Evaluable Analysis Set will include all subjects in the PK Analysis Set who have at least one evaluable defibrotide plasma PK parameter.

7 GENERAL CONSIDERATIONS

7.1 General Methods

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

Analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. SAS® version 9.3 (or higher) will be used to perform all data analyses and to generate tables, figures, and listings.

Summaries will order the treatment display from left to right as follows: DP (study treatment), BSC (control), and Total if a total column if applicable. Listings will include the randomized treatment arm, unique subject number, age, gender, and race. They will be sorted by treatment arm and then by subject number within treatment arm.

Unless otherwise specified, continuous data will be summarized using descriptive statistics comprising the number of subjects with data to be summarized (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). Categorical variables will be presented using counts and percentages. Every category will be kept in the summary even if it has 0 subjects. Summary statistics of central tendency will be reported to one more decimal place than the collected data. Summary statistics of variability will be reported to one more decimal place than the commensurate measure of central tendency. For example, the mean and median for age will be reported to one decimal place because it is collected in full years. The standard deviation

of age will then be reported to 2 decimal places. P-values > 0.9999 will be presented as '>0.9999' and p-value < 0.0001 will be presented as '< 0.0001'.

Subjects will be stratified at randomization according to country, risk of developing VOD (high risk or very high risk), and age (>16 years or ≤16 years). Analyses and summaries using the ITT and mITT analysis sets will be stratified using stratification data reported in the Interactive Response Technology (IRT) system at the time of randomization. Analyses and summaries using the Safety analysis set will be stratified using data reported in the Electronic Data Capture (EDC) system. If the number of subjects with discrepancies between IRT and EDC with regard to stratum assignment is greater than or equal to 5% of the randomized subjects, the primary and key secondary efficacy endpoint analyses will be repeated using the stratum assignment reported in EDC as sensitivity analyses. A listing of the discrepancies between IRT and EDC with regard to stratum assignment will be provided.

7.2 Multiple Comparisons and Multiplicity

The primary objective of the study is to compare the efficacy of DP in addition to BSC (DP arm) vs BSC alone (BSC arm) for the prevention of VOD as measured by VOD-free survival by Day +30 post-HSCT in subjects who are at high risk or very high risk for developing VOD. The study is designed with both an interim and a final analysis. To maintain an overall significance level at 1-sided alpha of 0.025, the incremental alpha is specified at 1-sided 0.0005 for interim analysis and 1-sided 0.0245 for final analysis (the corresponding nominal alpha is 1-sided 0.0005 for interim analysis and 1-sided 0.02498 for final analysis).

The key secondary objective of the study is to compare the efficacy of DP in addition to BSC (DP arm) vs BSC alone (BSC arm) for the prevention of VOD as measured by VOD-free survival by Day +100 post-HSCT in subjects who are at high risk or very high risk for developing VOD. To control the study-wise type I error, a sequential testing strategy will begin with the test on primary efficacy endpoint. If the test is significant, the test on the key secondary efficacy endpoint will be conducted at 1-sided alpha = 0.025. This gate-keeping approach will keep the family-wise error rate at 1-sided 0.025 for the comparisons of the 2 treatment arms in the primary and the key secondary efficacy endpoint analyses.

Other endpoints including secondary efficacy endpoints will be tested without multiplicity adjustments, and nominal p-values will be reported.

8 DATA HANDLING CONVENTIONS

8.1 Missing Data

8.1.1 Imputation of Non-Date 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.

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be "Yes". There will be no other imputation for missing data other than as described in Section 8.1.2 for partial dates and times.

8.1.2 Imputation of Partial Dates

8.1.2.1 Incomplete and Missing Adverse Event Start Date

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.

8.1.2.2 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*.

8.1.2.3 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 (e.g., 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*.

8.2 Baseline and Study Day Definitions

8.2.1 Baseline Date (Study Day 1)

Baseline is defined as the earliest date of the first dose of defibrotide or conditioning therapy.

8.2.2 Baseline Value

For assessments where time was collected for both the assessment and the first dose, the baseline value is defined as the last nonmissing value collected on or before the time of the first dose. For assessments where time was not collected, the baseline value is defined as the last nonmissing value collected on or before the date of the first dose. For subjects who do not have at least one dose of defibrotide or conditioning therapy, the baseline value is defined as the value that was collected where nominal Visit = Baseline. If this value is missing, then baseline value is defined as the value collected where Visit = Screening.

8.2.3 Day +0 Post-HSCT

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

8.2.4 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 do 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 follows:

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

8.2.5 Post-VOD Treatment Day

Day +0 post-VOD Treatment is defined as the VOD Treatment initiation date after VOD diagnosis. Post-VOD Treatment day is calculated relative to Day +0 post-VOD Treatment. For events that occurred after the VOD Treatment date (i.e. Day +X post-VOD Treatment), the day is calculated as follows:

X = [Date of the event] – [Date of Day +0 post-VOD Treatment]

8.3 Study Phase

In this study, the occurrence of VOD and the administration of rescue defibrotide represent a clinical landmark time point for safety. Therefore, for the safety analyses, 2 study phases are defined with respect to the administration of rescue defibrotide, as follows:

- **Prophylaxis Phase**:
    - If VOD occurs, the prophylaxis phase starts on the Baseline date and ends on the day before the start date of rescue defibrotide (ie, rescue treatment start date – 1).
    - If VOD does not occur, the prophylaxis phase starts on the Baseline date and ends on the date of study completion/early termination.
- **Rescue Treatment Phase**:
    - For the subset of subjects who developed VOD and received rescue defibrotide, the rescue treatment phase begins on the start date of rescue defibrotide and ends on the date of study completion/early termination.

The start date of rescue defibrotide will be derived as the date of the first administration of defibrotide on or after the investigator diagnosis of VOD.

Unless otherwise noted, safety summaries will be reported by study phase and by treatment received during the Prophylaxis Phase.

8.4 Visit Windows

Visit windows will be defined for the purpose of classifying assessments to be used in the analysis in the case that an assessment is obtained outside scheduled assessment times or if multiple assessments are collected. If multiple valid nonmissing 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 date of 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.

8.4.1 Laboratory Parameters

For the laboratory (hematology, coagulation and chemistry) parameters, Table 1 below provides the analysis windows for the purpose of identifying the assessments to be used in the analyses during the prophylaxis phase. Table 2 provides the analysis windows for the rescue phase.

Table 1 - Analysis Window for Laboratory Parameters During Prophylaxis Phase

Visit Identifier	Nominal Day	Lower Limit: HSCTSTDY	Upper Limit: HSCTSTDY
Baseline		The last nonmissing value collected on or before the first dose.	
Day +1 post-HSCT	HSCTSTDY=2	1	4
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 +30 post-HSCT	HSCTSTDY=31	26	34
Day +37 post-HSCT	HSCTSTDY=38	35	41
Day +44 post-HSCT	HSCTSTDY=45	42	48
Day +51 post-HSCT	HSCTSTDY=52	49	55
Day +60 post-HSCT	HSCTSTDY=61	56	66
Day +100 post-HSCT	HSCTSTDY=101	96	106
Day +180 post-HSCT	HSCTSTDY=181	171	191

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

Table 2 - Analysis Window for Laboratory Parameters During Rescue Phase

Visit Identifier	Nominal Day	Lower Limit: HSCTSTDY	Upper Limit: HSCTSTDY
Baseline		The last nonmissing value collected on or before the first dose.	
Day +1 post-VOD Treatment	HSCTSTDY=2	1	4
Day +7 post-VOD Treatment	HSCTSTDY=8	5	11

Day +14 post-VOD Treatment	HSCTSTDY=15	12	18
Day +21 post-VOD Treatment	HSCTSTDY=22	19	25
Day +30 post-VOD Treatment	HSCTSTDY=31	26	34
Day +37 post-VOD Treatment	HSCTSTDY=38	35	41
Day +44 post-VOD Treatment	HSCTSTDY=45	42	48
Day +51 post-VOD Treatment	HSCTSTDY=52	49	55
Day +60 post-VOD Treatment	HSCTSTDY=61	56	64
Day +67 post-VOD Treatment	HSCTSTDY=68	65	71
Day +30 post-HSCT[a]	HSCTSTDY=31	26	34
Day +100 post-HSCT[a]	HSCTSTDY=101	96	106
Day +180 post-HSCT[a]	HSCTSTDY=181	171	191

HSCTSTDY = DATE – (Date of Day +0 post-VOD Treatment) + 1, where DATE is the date of the lab assessment.
[a] HSCTSTDY = DATE – (Date of Day +0 post-HSCT) + 1, where DATE is the date of the lab assessment. If Day +30, +100 or +180 post-HSCT visit occurs during the Rescue Phase, the corresponding records will be summarized twice (once at post-VOD Treatment summary and once at post-HSCT summary).

8.4.2 Karnofsky and Lansky Performance Scores

For the Karnofsky and Lansky performance scores, Table 3 provides the analysis windows for the purpose of identifying the assessments to be used in the analyses.

Table 3 - Analysis Window for Karnofsky and Lansky Performance Scores

Visit Identifier	Nominal Day	Lower Limit: HSCTSTDY	Upper Limit: HSCTSTDY
Baseline		The last nonmissing value collected on or before the first dose.	
Day +0 post-VOD Treatment [a]	HSCTSTDY=1	1	4
Day +1 post-HSCT	HSCTSTDY=2	2	5
Day +7 post-HSCT	HSCTSTDY=8	6	12

Day +15 post-HSCT	HSCTSTDY=15	13	25
Day +30 post-HSCT	HSCTSTDY=31	26	51
Day +60 post-HSCT	HSCTSTDY=61	52	81
Day +100 post-HSCT	HSCTSTDY=101	82	141
Day +180 post-HSCT	HSCTSTDY=181	142	191

HSCTSTDY = DATE – (Date of Day +0 post-HSCT) + 1, where DATE is the date of the lab assessment.
[a] Rescue Phase only. HSCTSTDY = DATE – (Date of Day +0 post-VOD Treatment) + 1, where DATE is the date of the lab assessment.

8.4.3 Vital Signs

Intensive vital signs recorded during the first and second infusion of defibrotide on the first day of defibrotide dosing will be summarized at the nominal visit and time recorded in EDC. The analysis windows for all other visits will follow Table 1 and Table 2 in Section 8.4.1 for the prophylaxis and rescue phases, respectively.

9 STUDY POPULATION SUMMARIES

9.1 Enrollment

The number of subjects in each analysis set will be tabulated overall and by treatment group with the exception of screened subjects, who will only be tabulated in the Total column. The ITT Analysis Set will be further summarized by randomization strata. Counts and percentages will be presented for each stratification level separately (High Risk, Very High Risk, Adult, and Pediatric) and for the 4 combinations of strata for risk status and age group across all countries and centers and separately by center within country.

Additionally, summaries for public disclosure will tabulate subjects enrolled by country and site and by age category in the ITT Analysis Set.

The following summaries will be provided:

- Summary of analysis sets
- Summary of randomized subjects by risk status, age group, country, and center within country
- Number of subjects enrolled by country and site (for public disclosure)
- Number of subjects enrolled by age category (for public disclosure)

The following listings will be provided:

- Listing of analysis sets
    - This listing will include a column header for each Analysis Set. Subjects will be flagged as “Yes” or “No” depending on whether or not they are included in each Analysis Set.

- Listing of informed consent and eligibility
    - This listing will include the date of informed consent/assent, the protocol version for consent/assent, and inclusion and exclusion criteria that were not met for all enrolled subjects.
- Stratification at randomization
    - This listing will include each stratification factor of risk status, age group, and country collected in IRT at randomization.
- Discrepancies in risk status between IRT and EDC
    - This listing will include subjects who had a discrepant risk status between EDC and IRT. Stratification at randomization was based on data entered in IRT at the time of randomization. If this status was later found to be incorrect it was not changed in IRT but the correct status was entered into EDC.
- Reasons for Screen Failure
    - This listing will include the previous screening number (if applicable), screening date, and reason for screen failure for all subjects who failed screening and were not randomized.

9.2 Disposition

9.2.1 Subject Disposition

A summary and listing of subject disposition, including study completion, study withdrawal, and reasons for study withdrawal, will be provided overall and by treatment group. Additionally, a disposition summary by study period for public disclosure will be provided in the ITT Analysis Set.

The following summaries will be provided:
- Summary of subject disposition
- Study disposition by study period (for public disclosure)

The following listing will be provided:
- Subject disposition

9.2.2 Study Treatment Disposition during Prophylaxis Phase

A summary and listing of DP disposition including the number of subjects who received at least one dose of DP treatment, DP completion, DP discontinuation, and reasons for DP discontinuation will be provided for the DP arm using the ITT Analysis Set.

The following summaries will be provided:
- Summary of DP treatment disposition

The following listing will be provided:
- Listing of DP treatment disposition

9.2.3 Study Treatment Disposition during Rescue Phase

A summary and listing of defibrotide rescue treatment disposition including the number of subjects who received at least one dose of defibrotide rescue treatment, defibrotide rescue treatment completion, defibrotide rescue treatment discontinuation, and reasons for defibrotide rescue treatment discontinuation will be provided overall and by treatment group using the ITT Analysis Set.

The following summaries will be provided:

- Summary of defibrotide rescue treatment disposition

The following listing will be provided:

- Listing of defibrotide rescue treatment disposition

9.3 Protocol Deviations

Protocol deviations are classified as major or minor in accordance with the Protocol Deviation Management Plan. Major protocol deviations will be summarized overall and by treatment group for the ITT Analysis Set. Subjects with more than one major protocol deviations will be counted only once in the total number of subjects with major protocol deviations.

The following summaries will be provided:

- Summary of major protocol deviations

The following listing of all protocol deviations will be provided:

- Listing of all protocol deviations
    - This listing will include deviation type, deviation category, date of deviation, a description, and whether it was major or minor.

9.4 Demographics and Baseline Characteristics

9.4.1 Demographics and Baseline Characteristics

Subject demographics (gender, race, ethnicity, and age at screening) and baseline characteristics (weight, height, and body mass index [BMI]) will be summarized overall and by treatment group for the ITT Analysis Set and the Safety Analysis Set. Additionally, information pertaining to the underlying disease will be presented including primary disease, time since initial diagnosis, number of recurrences for the primary disease, whether it is a malignant disease, and prior treatment for the primary diagnosis (eg, surgery, radiation, chemotherapy, other). This summary will be repeated for the pediatric and adult subgroups. It will also be repeated by risk status (high risk and very high risk). Summaries by risk subgroups in the ITT Analysis Set will use the randomized risk status recorded in IRT, whereas summaries by risk status in the Safety Analysis Set will use the actual risk status recorded in EDC.

The following summaries will be provided:

- Demographic and baseline characteristics in the ITT Analysis Set
- Demographic and baseline characteristics in the Safety Analysis Set

- Demographic and baseline characteristics for the pediatric subgroup in the ITT Analysis Set
- Demographic and baseline characteristics for the pediatric subgroup in the Safety Analysis Set
- Demographic and baseline characteristics for the adult subgroup in the ITT Analysis Set
- Demographic and baseline characteristics for the adult subgroup in the Safety Analysis Set
- Demographic and baseline characteristics for the high risk subgroup in the ITT Analysis Set
- Demographic and baseline characteristics for the high risk subgroup in the Safety Analysis Set
- Demographic and baseline characteristics for the very high risk subgroup in the ITT Analysis Set
- Demographic and baseline characteristics for the very high risk subgroup in the Safety Analysis Set

The following listing will be provided:

- Demographic and baseline characteristics
    - This listing will include the demographic and baseline characteristics noted above.
- Childbearing potential and pregnancy test results
    - This listing will contain childbearing potential status, the type of pregnancy test, and the results of the pregnancy test.
- Disease history
    - This listing will include the information pertaining to underlying disease noted above.
- Listing of risk factors for VOD
    - This listing will present high risk and very high risk factors for VOD collected on the eCRF. These are risk factors reported in EDC and were used in determining the risk category for safety analyses.
- Liver history
    - This listing will present liver history information including history of active hepatitis, liver metastasis, and test data and result.

9.4.2 Transplant Characteristics

Transplant characteristics and information pertaining to HSCT including type of graft, source of graft, degree of human leukocyte antigen (HLA) matching, and type of conditioning regimen will be summarized overall and by treatment group using the ITT Analysis Set. These data will also be listed. The type of conditioning regimen will be derived as follows:

- Myeloablative
    - The type of conditioning regimen will be categorized as ‘Myeloablative’ if at least 2 alkylating agents are reported on the conditioning regimen eCRF from this list:
        - Busulfan, cyclophosphamide, melphalan, bendamustine, carmustine, cisplatin, chlorambucil, carboplatin, oxaliplatin, thiotepa, lomustine, treosulfan

OR

- if Total Body Irradiation (TBI) is reported on the conditioning regimen eCRF plus at least 1 alkylating agent from this list:
  - Busulfan, cyclophosphamide, melphalan, bendamustine, carmustine, cisplatin, chlorambucil, carboplatin, oxaliplatin, thiotepa, lomustine, treosulfan

- Non-Myeloablative
  - If the conditioning regimen has not been categorized 'Myeloablative' as specified above, and if the type of conditioning regimen is recorded as 'Non-myeloablative' on the conditioning regimen eCRF, then the type will be categorized as 'Non-myeloablative'.

- Reduced Intensity Chemistry (RIC)
  - If the conditioning regimen has not been categorized 'Myeloablative' or 'Non-myeloablative' as specified above, and if the type of conditioning regimen is recorded as 'Reduced Intensity Chemistry (RIC)' on the conditioning regimen eCRF, then the type will be categorized as 'Reduced Intensity Chemistry (RIC)'.

- Other
  - If none of the above criteria are met, the type of conditioning regimen will be categorized as "Other."

The following summary will be provided:
- Summary of transplant characteristics

The following listing will be provided:
- Listing of transplant characteristics

9.4.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. A summary of medical conditions and surgical events by treatment group, system organ class (SOC), and preferred term (PT) will be provided for the ITT Analysis Set. SOC and PT within SOC will be sorted by frequency in the DP arm and then alphabetically for those with the same frequency.

The following summary will be provided:
- Summary of medical history

The following listing of medical conditions and surgical events will be provided along with the start date, ongoing (Yes or No), and the end date, if not ongoing:
- Listing of medical history

9.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and will be summarized by treatment group for the ITT Analysis Set. Summaries will show the number and percentage of subjects taking medications. Each subject is counted once within each unique term. Summaries will be sorted by descending frequency in the DP arm.

Prior medications are defined as those medications taken prior to the Baseline date. Concomitant medications are defined as medications taken at any time on or after Baseline. If any medications were taken prior to Baseline and continued to be taken after Baseline, they will be counted as both prior and concomitant medications. The prior and concomitant categorization of medications will be derived after taking into consideration any partial or missing start and end dates as described in Sections 8.1.2.2 and 8.1.2.3.

Information on conditioning regimen for HSCT is collected on the Conditioning Regimen eCRF and will be presented as a separate subset of concomitant medications. A summary of conditioning regimen for HSCT will be provided by treatment group for the ITT Analysis Set.

The following summaries will be provided:

- Summary of prior medications
- Summary of concomitant medications
- Summary of conditioning regimen for HSCT

The following listings of medication will be provided along with the start date, ongoing (Yes or No), the end date if not ongoing, dose, unit, indication, frequency, and route:

- Listing of prior medications
- Listing of concomitant medications
- Listing of conditioning regimen for HSCT

Additionally, the following listing will be provided to include the date and reason for donor lymphocyte infusion:

- Listing of donor lymphocyte infusion

10 EFFICACY

Although randomization is stratified by 3 variables, only 2 stratification variables (very high risk or high risk and pediatric [≤16 years] or adults [>16 years]) recorded in IRT will be used in the stratified tests described in this section (ie, the stratified log-rank test, the stratified Cox proportional hazards regression model and Cochran-Mantel-Haenszel [CMH] test) for the primary efficacy endpoint and the secondary efficacy endpoints, as appropriate. These 2 stratification variables yield 4 distinct strata corresponding to unique levels of randomization strata. If there are fewer than 20 subjects in at least 1 of the 4 distinct strata, only the very high risk/high risk strata will be used in the stratified tests. Although the randomization will be stratified by country as well to ensure balance of treatment, due to the expected low enrollment within some countries, the stratified efficacy analyses will not be stratified by country.

Analyses and summaries using the ITT and mITT analysis sets will be stratified using data reported in the IRT system at the time of randomization. If the number of subjects with discrepancies between IRT and EDC with regard to stratum assignment is greater than or equal to 5% of the randomized subjects, the primary and key secondary efficacy endpoint analyses will be repeated using the stratum assignment reported in EDC as sensitivity analyses.

10.1 Analysis of Primary Endpoint

The primary efficacy endpoint is VOD free survival by Day +30 post-HSCT. An event for the primary efficacy endpoint is defined as VOD diagnosis (as assessed by EPAC) or death, whichever is earlier, up to Day +30 post-HSCT.

The time to event for the primary efficacy endpoint will be measured in days and will be calculated as described in Section 8.2.4 with the event date equal to the date of VOD diagnosis by EPAC, the date of death up to Day +30 post-HSCT, or the censoring date if no VOD or death occurred.

Subjects will be censored under the following conditions:

- No event by Day +30 post-HSCT:
  - If EPAC makes an assessment of 'No VOD' and the subject is still alive at Day +30 post-HSCT, the censoring date will be defined as earliest date of the last assessments available for the modified Seattle criteria components (total bilirubin, weight gain or ascites evaluation, hepatomegaly evaluation) or the last biopsy assessment, whichever is later. Only assessment dates occurring on or before Day+30 post-HSCT will be taken into consideration when censoring.
  - If the subject is still alive at Day +30 post-HSCT and has EPAC-assessed VOD after Day +30 post-HSCT, the censoring date will be Day +30 post-HSCT.
- Not evaluable by Day +30 post-HSCT:
  - If the EPAC makes an assessment of 'Not Evaluable' and the subject has not died by Day +30 post-HSCT, the censoring date will be defined as the last date at which VOD could be evaluated (as specified by the EPAC).
  - If the EPAC indicates the last date at which VOD could be evaluated is prior to HSCT, the censoring date will be Day +1 post-HSCT.
- Event occurs prior to HSCT:
  - If the EPAC indicates the date of VOD onset is prior to Day +0 post-HSCT or if the subject dies prior to Day +0 post-HSCT, the censoring date will be Day +1 post-HSCT because the subject was not at risk at the start of the observation period.
- Subject does not undergo HSCT:
  - The date of randomization will be used as Day +0 post-HSCT. The censoring date will be Day +1 post-HSCT.
- Rescue treatment:
  - If a subject in the BSC arm receives rescue treatment with defibrotide but VOD (as assessed by investigator) is not confirmed by EPAC (either EPAC made an assessment of 'No VOD' or 'Not Evaluable' by Day +30 post-HSCT or the EPAC

made an assessment of VOD but the VOD date is more than 3 days later than the rescue initiation date), the subject will be censored at the date of rescue initiation.

Subjects assessed for the primary efficacy endpoint before the interim analysis make up the stage 1 sample and those subjects assessed after the interim analysis make up the stage 2 sample. At the interim analysis, a stratified log rank test will be performed where the strata are defined by risk status (high risk versus very high risk) and age group (pediatric vs. adult). If there are fewer than 20 subjects within a stratum, the stratified log rank test will be performed considering high risk versus very high risk strata only. The strata used in the stage 1 analysis will also be used to calculate the stratified log rank statistic for stage 2, regardless of the sizes of the strata observed in the stage 2 sample. For the final analysis, the method of Cui, Hung, and Wang (CHW) (Cui, Hung, & Wang, 1999) will be used to combine the independent increments of the stratified log rank statistics from stage 1 and stage 2.

Let Z_1 and Z_2 denote the independent stratified log rank statistics (see, eg, Collett 2003) calculated based on the samples from stage 1 and stage 2, respectively. The stratified log rank statistics will be calculated with respect to events in the control group so that they have positive expectation under the alternative hypothesis. The final test statistic is

$$Z_{CHW} = \sqrt{w}\, Z_1 + \sqrt{1-w}\, Z_2$$

where $w = 0.7 = 252/360$, the planned information fraction at the time of the interim analysis.

The stage 1 stratified log rank statistic $Z_1 = U_1/\sqrt{V_1}$ is calculated based on log rank score U_1 with variance V_1.

Let $t_{(1)} < \cdots < t_{(J)}$ be the ordered event times across the two treatment groups within stratum s. At time $t_{(j)}$ there are d_{sj} events in stratum s and just before time $t_{(j)}$ there are a total of $r_{sj} = r_{Csj} + r_{Esj}$ subjects at risk in stratum s, with r_{Csj} subjects at risk in the control group (BSC) and r_{Esj} subjects at risk in the experimental group (DP) (Collett, 2003).

In the stratified case, the log rank score is given as the sum of the scores calculated separately within each stratum:

$$U_1 = \sum_{s=1}^{S} O_s - E_s$$

where $O_s = \sum_{j=1}^{J} O_{sj}$ is the total number of events in the control group in stratum s, and $E_s = \sum_{j=1}^{J} E_{sj} = \sum_{j=1}^{J} \left(\frac{r_{Csj}}{r_{sj}}\right) d_{sj}$ is the total number of expected events in the control group in stratum s.

Similarly, the variance of the score is given by the sum of the variances calculated separately within each stratum:

$$V_1 = \sum_{s=1}^{S} V_s$$

where $V_s = \sum_{j=1}^{J} \frac{r_{Csj}\, r_{Esj}\, d_{sj}\, (r_{sj} - d_{sj})}{r_{sj}^2 (r_{sj} - 1)}$

The stage 2 stratified log rank statistic $Z_2 = U_2/\sqrt{V_2}$ is calculated based on log rank score U_2 with variance V_2.

Under the null hypothesis of no difference in survival curves within each stratum, Z_1 and Z_2 have standard normal asymptotic distribution. Thus, at the interim analysis the p-value is calculated as follows:

$$p_1 = 1 - \Phi(Z_1)$$

Let c_1 and c_2 be the efficacy boundaries at the interim and final analysis times such that

$$1 - \Phi(c_1) = 0.0005$$

or equivalently,

$$c_1 = \Phi^{-1}(0.9995) = 3.2905$$

And

$$P_0(Z_1 \leq c_1 \; and \; Z_{CHW} > c_2) = 0.0245$$

Using numerical integration one can solve this equation to get $c_2 = 1.9603$.

Let

$$\alpha_2 = 1 - \Phi(c_2) = 0.02498$$

The decision rule for declaring efficacy at the interim analysis is as follows:

If $p_1 < 0.0005, \; or \; equivalently \; Z_1 > c_1$, then reject H_0 at the interim analysis and recommend stopping the trial early for overwhelming efficacy.

The p-value at the final analysis is defined by

$$p_{CHW} = 1 - \Phi(Z_{CHW})$$

The decision rule for declaring efficacy at the final analysis is:

If $p_{CHW} < \alpha_2 \; \; or \; equivalently \; \; Z_{CHW} > c_2$, then reject H_0 and declare efficacy.

Cui, Hung, and Wang have shown that the type-1 error will be preserved at the specified α level despite the possibility of a data dependent increase in the sample size.

The primary analysis will be performed on the ITT Analysis Set as described above. The independent stratified log rank statistics from stage 1 (Z_1) and stage 2 (Z_2) will be presented along with Z_{CHW} and the p-value (P_{CHW}). In addition, the following descriptive statistics will be presented to support the analysis of the primary efficacy endpoint:

- The number of subjects by treatment group who had an event and who were censored (either due to not having an event or for other reasons as described above).
- The Kaplan-Meier (KM) estimates of the VOD-free survival rate (%) by Day +30 post-HSCT (95% CI).
- the KM estimate of median time to VOD or death in days (95% CI).
- The HR (95% CI) from a Cox proportional hazards regression model stratified by risk status and age group.
- A KM plot will be presented up to Day +180 post-HSCT for each treatment arm. The number of subjects at risk will be displayed at 10-day intervals. A vertical line will be included to indicate Day +30 post-HSCT.

The following summary will be provided:

- Analysis of VOD-free survival by Day +30 post-HSCT

The following figure will be provided:

- VOD-free survival by Day +30 post-HSCT (primary efficacy endpoint): KM Plot with number of subjects at risk

The following listing will be provided and will include the EPAC diagnosis, rationale, VOD onset date, criteria met for diagnosis, and the last date VOD could be evaluated if the case was nonevaluable:

- Listing of EPAC assessment of VOD

10.1.1 Sensitivity Analyses of Primary Endpoint

This section describes alternative analysis approaches to address missing data, as well as to explore modifications to the definition of the primary endpoint and analysis population. The additional analyses described in this section will serve as sensitivity analyses, to be used for qualitative evaluation of the robustness of the primary analysis methodology. The sensitivity analyses will be conducted using the same methods as the primary efficacy endpoint analysis described in Section 10.1 unless otherwise noted.

10.1.1.1 Sensitivity Analysis I: Early Termination before Day +30 post-HSCT

If a subject is terminated early (prior to the Day +180 post-HSCT visit as recorded on the end of study eCRF), lost to follow-up, or assessed as ‘Not Evaluable’ by EPAC before Day +30 post-HSCT with the last assessment for evaluation of VOD less than Day +23 post-HSCT and this subject does not have VOD or death by Day +30 post-HSCT, a worst-case comparison will be

performed as a sensitivity analysis. If in the DP arm, these subjects will be analyzed with an event on the day after the date of the last available assessment for the evaluation of VOD; if in the BSC arm, these subjects will be censored on the date of the last available assessment for the evaluation of VOD. The last available assessment for the evaluation of VOD is defined as the latter of the following 2 dates: 1) the last biopsy assessment date if a biopsy is done 2) the earliest date of the last assessments of the modified Seattle criteria components: bilirubin, weight gain or ascites evaluation, hepatomegaly evaluation. This worst-case comparison is a conservative method to evaluate the impact of missing data on the primary efficacy endpoint.

The following summary will be provided:

- Sensitivity analysis I: Analysis of VOD-free survival by Day +30 post-HSCT

The following figure will be provided:

- VOD-free survival by Day +30 post-HSCT (sensitivity analysis I): KM plot with number of subjects at risk

10.1.1.2 Sensitivity Analysis II: CMH Test on the Composite Event Rate

A composite event defined as a binary outcome where subjects who had either VOD (assessed by EPAC) or death by Day +30 post-HSCT will be considered to have an event. These events will be analyzed using a CMH test, stratified by the risk status (high risk vs very high risk) and age group (pediatric vs adult). If there are fewer than 20 subjects within a stratum, the CMH test will be performed considering high risk versus very high risk strata only.

The following summary will be provided:

- Sensitivity analysis II: Analysis of VOD-free survival by Day +30 post-HSCT

10.1.1.3 Sensitivity Analysis III: Unstratified Log Rank Test

The primary endpoint of VOD-free survival by Day +30 post-HSCT will be analyzed using a log rank test, without consideration of the stratification factors. This analysis is a simple comparison to the stratified analysis specified as the main analysis, and is expected to be less powerful.

The following summary and figure will be provided:

- Sensitivity analysis III: Analysis of VOD-free survival by Day +30 post-HSCT

The following figure will be provided:

- VOD-free survival by Day +30 post-HSCT (sensitivity analysis III): KM plot with number of subjects at risk

10.1.1.4 Sensitivity Analysis IV: Stratified Log Rank Test in the mITT Analysis Set

The primary efficacy analysis of VOD-free survival by Day +30 post-HSCT will be repeated for the mITT Analysis Set.

The following summary will be provided:

- Sensitivity analysis IV: Analysis of VOD-free survival by Day +30 post-HSCT

The following figure will be provided:

- VOD-free survival by Day +30 post-HSCT (sensitivity analysis IV): KM plot with number of subjects at risk

10.1.1.5 Sensitivity Analysis V: Log Rank Test on VOD-free Survival by Day +30 post-HSCT (with EPAC Assessment Only)

In all of the previously described analyses, if a subject in the BSC arm is rescued but VOD (assessed by investigator) is not confirmed by the EPAC (either the EPAC made an assessment of No VOD by Day +30 post-HSCT, or the EPAC made an assessment of VOD but the VOD date is more than 3 days later than the rescue initiation date), the subject will be censored at the time of rescue initiation. In this sensitivity analysis, such a consideration is dismissed. A subject's VOD diagnosis by Day +30 post-HSCT status on will be based on the EPAC assessment only, without consideration of the administration of rescue defibrotide.

The following summary will be provided:

- Sensitivity analysis V: Analysis of VOD-free survival by Day +30 post-HSCT

The following figure will be provided:

- VOD-free survival by Day +30 post-HSCT (sensitivity analysis V): KM plot with number of subjects at risk

10.1.2 Subgroup Analyses of Primary Endpoint

The primary efficacy endpoint will be analyzed for each combination of the subgroups from the 2 stratification variables (very high risk/high risk and pediatric [≤16 years]/adults [>16 years]). For each of the subgroups, the analysis will be conducted using the same methods as the primary efficacy endpoint analysis described in Section 10.1, except that the log rank test will be un-stratified and no hypothesis testing will be performed.

An additional subgroup analysis will be performed by prior liver disease status. Subjects are considered to have prior liver disease if they have at least one of the following criteria checked off on the 'Risk Factors for VOD' eCRF:

- Transaminase level >2.5 times the upper limit of normal (ULN) during screening period
- Serum total bilirubin level >1.5 times the ULN during screening period
- Cirrhosis (with biopsy evidence)
- Hepatic fibrosis (by histology)
- Known history of active viral hepatitis within 1 year prior to the start of study treatment
- Any prior hepatic irradiation, including abdominal irradiation covering the hepatic area

- Documented diagnosis of iron overload (serum ferritin > 2000 ng/mL within 3 months prior to start of study treatment)

The following summaries will be provided:

- Analysis of VOD-free survival by Day +30 post-HSCT by age group
- Analysis of VOD-free survival by Day +30 post-HSCT by risk status
- Analysis of VOD-free survival by Day +30 post-HSCT by age group and risk status
- Analysis of VOD-free survival by Day +30 post-HSCT by prior liver disease status

The following figures will be provided:

- Figure of VOD-free survival by Day +30 post-HSCT by age group
- Figure of VOD-free survival by Day +30 post-HSCT by risk status
- Figure of VOD-free survival by Day +30 post-HSCT by age group and risk status
- Figure of VOD-free survival by Day +30 post-HSCT by prior liver disease status

10.1.3 Concordance between Investigator and EPAC Assessed VOD by Day +30 post-HSCT

The investigator-assessed VOD by Day +30 post-HSCT will be derived from the clinical database, whereas the EPAC assessed VOD by Day +30 post-HSCT will be extracted from the EPAC assessment forms. Investigator assessments will be binary (‘yes’ or ‘no’). The EPAC can assess a case as ‘yes’, ‘no’, or ‘not evaluable’. All combinations of investigator and EPAC assessments will be tabulated for the mITT Population by treatment group and by site and treatment group (ie, ‘yes/yes’, ‘yes/no’, ‘no/no’, ‘no/yes’, ‘yes/not evaluable’, ‘no/not evaluable’). A concordant assessment is defined as the following: the outcome of VOD by Day +30 post-HSCT matches between investigator and EPAC assessments (ie, ‘yes/yes’ or ‘no/no’).

For cases where both the investigator and EPAC assessed VOD by Day +30 post-HSCT (ie, ‘yes’, ‘yes’), the dates of VOD diagnosis will be compared to determine if they match between the two assessments. A case will be considered concordant if the dates of diagnosis match. The number of concordant and discordant cases will be tabulated by treatment group and by site and treatment group.

A descriptive analysis of investigator-assessed VOD-free survival by Day +30 post-HSCT will be conducted using the same methods as the primary efficacy endpoint analysis described in Section 10.1. No hypothesis testing will be performed.

The following summaries will be provided:

- Concordance between PI and EPAC assessed VOD by Day +30 post-HSCT
- Concordance between PI and EPAC assessed VOD by Day +30 post-HSCT by site
- Analysis of investigator-assessed VOD-free Survival by Day +30 post-HSCT

The following listing will be provided and will include VOD diagnosis, date of diagnosis, criteria met, and biopsy results:

- Listing of investigator-assessed VOD

The following figure will be provided:

- Investigator-assessed VOD-free survival by Day +30 post-HSCT: KM plot with number of subjects at risk

10.2 Analysis of Secondary Endpoints

10.2.1 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is VOD-free survival by Day +100 post-HSCT and will be analyzed using the same methods described in Section 10.1 for the primary efficacy endpoint in the ITT Analysis Set.

The following summary will be provided:

- Analysis of VOD-free survival by Day +100 post-HSCT

The following figure will be provided:

- Figure of VOD-free survival by Day +100 post-HSCT

10.2.2 Other Secondary Efficacy Endpoints

These other secondary efficacy endpoints will be tested without multiplicity adjustments, and nominal p-values will be reported. The ITT Analysis Set will be used for these analyses.

10.2.2.1 Incidence of VOD by Day +30 post-HSCT

The incidence of EPAC-assessed VOD by Day +30 post-HSCT will be compared between treatment arms using the CMH test stratified by 2 stratification variables for randomization (very high risk/high risk and pediatric/adults).

The following summary will be provided:

- Incidence of VOD by Day +30 post-HSCT

10.2.2.2 VOD-Free Survival by Day +180 post-HSCT

The secondary efficacy endpoint of VOD-free survival by Day +180 post-HSCT will be analyzed using the methods described in Section 10.1 in the ITT Analysis Set. For monitoring of VOD-free survival by Day +180 post-HSCT, the diagnosis of VOD through Day +100 post-HSCT will be made by EPAC, and the diagnosis of VOD after Day +100 post-HSCT will be based on investigator assessments.

The following summary will be provided:

- Analysis of VOD-free survival by Day +180 post-HSCT

The following figure will be provided:

- Figure of VOD-free survival by Day +180 post-HSCT

10.2.2.3 Non-Relapse Mortality by Days +100 and +180 post-HSCT

The incidence of NRM by Day +100 post-HSCT will be compared between the treatment arms. NRM is defined as death that occurs after HSCT in subjects who were noted as having malignant primary disease on the disease history eCRF and who do not have primary disease relapse post-HSCT. Only subjects with malignant primary disease at baseline will be included in the analysis. The time to NRM is the number of days from the date of Day +0 post-HSCT to the date of NRM. If the subject has disease relapse, they will be censored on the date of relapse. If they do not have disease relapse and do not die by Day +100 post-HSCT then will be censored on the date of the Day +100 post-HSCT disease relapse assessment. If the Day +100 post-HSCT disease relapse assessment is missing, they will be censored on the date of the last disease relapse assessment performed. If a subject does not undergo HSCT, the subject will be censored at the date of Day +1 post-HSCT.

This analysis will be repeated for NRM by Day +180 post-HSCT. The following will be presented for NRM by Day +100 post-HSCT and by Day +180 post-HSCT:

- The number of subjects by treatment group who had an event and who were censored (either due to not having an event or for other reasons as described above).
- The p-value from a log rank test stratified by risk status and age group.
- The KM estimates of the NRM rate (%) with 95% CI.
- the KM estimate of median time to NRM in days (95% CI).
- The hazard ratio (95% CI) from a Cox proportional hazards regression model stratified by risk status and age group.
- A KM plot will be presented up to Day +180 post-HSCT for each treatment arm. The number of subjects at risk will be displayed at 10-day intervals.

The following summary will be provided:

- Analysis of non-relapse mortality post-HSCT

The following figure will be provided:

- Figure of non-relapse mortality post-HSCT

The following listing will be provided and will include the relapse status at each visit and the date of relapse if applicable:

- Listing of primary disease relapse

10.2.2.4 Incidence of VOD-associated MOD by Days +30 and +100 post-HSCT

VOD-associated MOD is defined for subjects as occurring if the investigator answers “Yes” to the question “Has the subject been diagnosed with VOD associated MOD?” in the eCRF. The number and proportion of subjects who develop VOD-associated MOD by Days +30 and +100 post-HSCT will be summarized and compared between the 2 treatment arms using a chi-square test.

The following summary will be provided:

- Summary of VOD-associated MOD

The following listing will be provided and will include the date of MOD and type of renal and pulmonary dysfunction:

- Listing of VOD-associated MOD

10.2.2.5 Resolution of VOD by Day +180 post-HSCT and Time to Resolution of VOD

Of those subjects who were diagnosed with VOD by Day +30 post-HSCT by the investigator, the proportion of subjects who have resolution of VOD by Day +180 post-HSCT will be summarized by treatment arm.

Time to resolution of VOD will be calculated as follows:

> **Time to resolution of VOD** = [Date of VOD resolution] – [Date of VOD diagnosis by investigator]

If VOD does not resolve by Day +180 post-HSCT, the subject will be censored on the date of the Day +180 post-HSCT VOD resolution assessment. If the Day +180 post-HSCT VOD resolution assessment is missing, they will be censored on the date of the last VOD resolution assessment performed.

The following will be presented for VOD resolution by Day +180 post-HSCT:

- The number of subjects by treatment group who had an event and who were censored (either due to not having an event or for other reasons as described above).
- The p-value from a log rank test stratified by risk status and age group.
- The KM estimates of the NRM rate (%) with 95% CI.
- the KM estimate of median time to NRM in days (95% CI).
- The HR (95% CI) from a Cox proportional hazards regression model stratified by risk status and age group.
- A KM plot will be presented up to Day +180 post-HSCT for each treatment arm. The number of subjects at risk will be displayed at 10-day intervals.

The following summary will be provided:

- Analysis of VOD resolution by Day +180 post-HSCT

The following figure will be provided:

- Figure of VOD resolution by Day +180 post-HSCT

The following listing will be provided and will include whether or not VOD was resolved, the criteria met for resolution, and the date of resolution:

- Listing of VOD resolution

10.2.2.6 Incidence of VOD by Day +100 post-HSCT and Day +180 post-HSCT

The number and proportion of subjects who develop VOD after Day +30 post-HSCT but by Day +100 post-HSCT and by Day +180 post-HSCT will be summarized and compared between the treatment arms using a chi-square test at each timepoint. The diagnosis of VOD through Day +100 post-HSCT will be made by EPAC, and the diagnosis of VOD after Day +100 post-HSCT will be based on investigator assessments.

The following summary will be provided:

- Incidence of VOD by Day +100 post-HSCT and Day +180 post-HSCT in subjects who develop VOD after Day +30

11 SAFETY

Safety summaries will be provided by treatment arm and study phase based on the Safety Analysis Set.

11.1 Extent of Exposure

Defibrotide administration will be summarized for the Prophylaxis and Rescue Treatment phases. The following will be summarized and listed:

- Days of study drug treatment: The number of days the subject received at least one dose of study drug treatment.
- Duration of study drug treatment in days: (date of last dose – date of first dose) +1
- The total number of doses received
- The number of doses per day: Total number of doses received divided by the duration of study drug treatment.
- Total exposure (mg): Total amount of study drug received by the subject in mg.
- The daily dose in mg/day: Total exposure divided by the duration of treatment.
- The daily dose in mg/kg/day: Total exposure divided by the duration of study drug treatment in days, and then divided by Baseline weight in kg.

The following summary will be provided:

- Summary of defibrotide administration

The following listing will be provided:

- Listing of defibrotide administration
- List of subjects receiving test drug from specific batches

11.2 Adverse Events

Adverse events recorded in the case report form will be coded to SOC and PT using the MedDRA 19.1. The investigator will assess the relatedness of each AE to study drug. The severity of AEs will be recorded using the Common Terminology Criteria for Adverse Events (CTCAE 4.03).

At a minimum, for subjects in either the DP or BSC arm, the investigator must record all AEs and SAEs that occur from the time written informed consent is obtained until screen failure if applicable, or Day +60 post-HSCT, regardless of their relationship to study drug or procedure. Even if the minimum of Day +60 post-HSCT is met, the investigator must continue to record all AEs and SAEs that occur within 30 days after the last dose of defibrotide, regardless of their relationship to study drug or procedure. For subjects who do not receive HSCT, AEs must be collected for 70 days after Baseline or early termination, whichever occurs first. For subjects randomized but not treated, AEs will be collected for 70 days after randomization or early termination, whichever is earlier. Any SAE assessed as related to defibrotide or study procedures by the investigator should be reported regardless of time after study termination.
Related SAEs reported after study termination will be collected in the Safety database only.

A treatment-emergent adverse event (TEAE) is defined as any event with onset date on or after the first dose of study treatment (either DP or conditioning regimen) or any ongoing event that worsens in severity after the date of the first dose of study treatment through the protocol-specific reporting period. Only TEAEs with the onset date on or before the end of the protocol-specific AE reporting period noted above will be included in summary tables unless otherwise specified. All AEs will be listed. For the purpose of calculating treatment emergence, incomplete onset dates will be imputed as detailed in Section 8.1.2.1.

AEs 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 investigator did not record severity will be categorized as “missing” for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

Treatment-related AEs are those for which the investigator answers “Yes” to the question “Was this adverse event related to study treatment?” in the eCRF. Events for which the investigator did not record relationship to study treatment will be considered related to study treatment in summaries if the subject received defibrotide. They will be considered not related if the subject did not receive defibrotide. Data listings will show treatment relationship as missing.

Serious AEs are those for which the investigator answers “Yes” to the question “Was the adverse event serious?” in the eCRF. The clinical database will be reconciled with the serious AE database before database finalization.

For all AE summaries, if a subject has more than 1 AE within a PT, the subject is counted only once at the maximum severity and with the closest relationship to study drug. If a subject has more than 1 AE within a SOC, the subject is similarly counted once when reporting results for that SOC. SOC and PT will be sorted by frequency in the DP arm and then alphabetically for those with the same frequency.

The following summaries will be provided (all summaries except the overall summary will be presented by SOC and PT within SOC):

- Overall summary of TEAE

- Summary of TEAE by SOC and PT
- Summary of TEAE by PT
- Summary of TEAE by age group
- Summary of serious TEAE
- Summary of treatment-related TEAE
- Summary of serious treatment-related TEAE
- Summary of Grade 3 or 4 TEAE
- Summary of treatment-related Grade 3 or 4 TEAE
- Summary of TEAE leading to study drug discontinuation
- Summary of treatment-related TEAE leading to study drug discontinuation
- Summary of TEAE by maximum toxicity grade
- Summary of treatment-related TEAE by maximum toxicity grade
- Summary of TEAE leading to death
- Summary of treatment-related TEAE leading to death
- Summary of TEAE by SOC and PT including events recorded outside of the protocol-specific AE reporting period
    - Some sites continued to record AEs beyond the protocol-defined reporting period. This table will summarize all AEs with onset date on or after the first dose of study treatment (either DP or conditioning regimen) through the end of the study.

Additionally, the following TEAE summaries for public disclosure will be provided:

- Summary of treatment-emergent serious AEs (for public disclosure)
- Summary of treatment-emergent non-serious AEs occurring in greater than 5% of subjects (for public disclosure)

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

- Listing of all AEs
- Listing of SAEs
- Listing of Grade 3 and 4 AEs
- Listing of AEs leading to study drug discontinuation
- Listing of AEs leading to death

11.2.1 Adverse Events of Special Interest

AEs of special interest include pulmonary hemorrhage, gastrointestinal bleeding, and hypersensitivity reactions. The list of PTs used to search for AEs of special interest is provided in Appendix I and was reviewed by Jazz Drug Safety & Pharmacovigilance and an independent DMC.

The following summaries will be provided:

- Summary of TEAEs of special interest: Pulmonary hemorrhage

- Summary of TEAEs of special interest: Pulmonary hemorrhage by age group
- Summary of TEAEs of special interest: Gastrointestinal bleeding
- Summary of TEAEs of special interest: Gastrointestinal bleeding by age group
- Summary of TEAEs of special interest: Gastrointestinal bleeding likely pre-existing neurological or neonatal conditions
- Summary of TEAEs of special interest: Gastrointestinal bleeding likely pre-existing neurological or neonatal conditions by age group
- Summary of TEAEs of special interest: Hypersensitivity reactions
- Summary of TEAEs of special interest: Hypersensitivity reactions by age group

The following listings will be provided:

- Listing of AEs of special interest: Pulmonary hemorrhage
- Listing of AEs of special interest: Gastrointestinal bleeding
- Listing of AEs of special interest: Gastrointestinal bleeding likely pre-existing neurological or neonatal conditions
- Listing of AEs of special interest: Hypersensitivity reactions

11.3 Laboratory Assessments

For all hematology, coagulation, and chemistry parameters, the lab values at baseline and each of the postbaseline assessments will be summarized and presented using descriptive statistics. See Section 8.4.1 for the identification of the assessments used in the analyses. For each of the postbaseline assessments, change between baseline and that assessment in a specific lab value will be calculated as follows,

Change from baseline = [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 missing at either baseline or a specific post-baseline assessment for a subject, change from baseline will be missing.

- Summary of clinical laboratory results: Hematology
- Summary of clinical laboratory results: Chemistry
- Summary of clinical laboratory results: Coagulation

For each of the following select laboratory parameters: total bilirubin, serum creatinine, absolute neutrophil count, and platelet count, a shift table from baseline grade to the highest postbaseline grade will be provided:

- Shift table of selected postbaseline laboratory results from baseline

All laboratory results will be listed. In addition, a listing of subjects who have abnormal postbaseline lab values for select lab parameters (total bilirubin, serum creatinine, absolute neutrophil count, and platelet count) will be provided with corresponding normal ranges. The following listings will be provided:

- Listing of clinical laboratory results: Hematology
- Listing of clinical laboratory results: Chemistry
- Listing of clinical laboratory results: Coagulation

- Listing of subjects with abnormal post-baseline laboratory values

11.4 Vital Signs

Systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature at baseline and each of the post-baseline assessments will be summarized and presented using descriptive statistics. See Section 8.4.3 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 from baseline = [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 missing at either baseline or a specific post-baseline assessment for a subject, change from baseline will be missing.

Maximum decrease and increase from baseline in systolic and diastolic blood pressure will be summarized separately using descriptive statistics, to assess the potential for defibrotide to cause peri-infusional hypotension.

Baseline and post-baseline values for each visit in Section 8.4.3 will be categorized as low, normal, or high and presented on a shift table based on the criteria listed in Table 4.

Table 4 – Vital Signs Normal Ranges

Parameter	Low	Normal	High
Systolic blood pressure	< 60 mmHg	≥60 and ≤160 mmHg	>160 mmHg
Diastolic blood pressure	<50 mmHg	≥50 and ≤100 mmHg	>100 mmHg
Pulse rate	<40 beats per min.	≥40 and ≤120 beats per min.	>120 beats per min.
Respiratory rate	<10 breaths per min.	≥10 and ≤40 breaths per min.	>40 breaths per min.
Temperature	<36 degrees Centigrade	≥36 and ≤39 degrees Centigrade	>39 degrees Centigrade

The following summaries will be provided:

- Summary of vital signs
- Summary of maximum decrease and increase from baseline in systolic and diastolic blood pressure
- Shift table of vital signs results from baseline

The following listings will be provided:

- Listing of vital signs

11.5 Graft-versus-Host Disease

The proportion of subjects who develop chronic GvHD by Day +180 post-HSCT will be summarized.

The proportion of subjects with Grade 1, 2, 3, 4, 2-4, and 1-4 acute GvHD by Days +30, +100 and +180 post-HSCT will be summarized. Acute GvHD (defined separately for subjects ≥ 45 kg or < 45 kg) is defined using stages and grades according to Jacobsohn and Vogelsang (Jacobsohn and Vogelsang 2007), as shown in Table 5.

The following summary will be provided:

- Summary of GvHD

The following listings will be provided:

- Listing of acute GvHD
- Listing of chronic GvHD

Table 5. Staging and Grading of Acute Graft versus Host Disease

	Skin	Liver	Gut
		Total bilirubin (mg/dL)	**Stool output (mL/day)**
Stage			
0	No GvHD rash	<2	<500 or persistent nausea
1	Maculopapular rash <25% BSA	2-3	500-999 or 10-20 mL/kg/day for subjects <45 kg
2	Maculopapular rash 25%-50% BSA	3.1-6	1000-1500 or >20-35 mL/kg/day for subjects <45 kg
3	Maculopapular rash >50% BSA	6.1-15	>1500 or >35 mL/kg/day for subjects <45 kg
4	Generalized erythroderma plus bullous formation	>15	Severe abdominal pain with or without ileus
Grade	**Skin**	**Liver**	**Gut**
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	—	Stage 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	—

GvHD: Graft-versus-host disease; BSA: Body surface area.
Source: Jacobsohn & Vogelsang 2007

11.6 Graft Failure and Time to Neutrophil and Platelet Engraftment

The incidence of neutrophil engraftment will be compared between the treatment arms. The date of neutrophil engraftment will be recorded on the eCRF and is defined as the first date after HSCT of an absolute neutrophil count > 0.5×10^9/L that is maintained for 3 consecutive days.

The definition of "absolute neutrophil count" includes both segmented neutrophils and "bands," immature neutrophils.

The time to neutrophil engraftment is the number of days from the date of Day +0 post-HSCT to the date of neutrophil engraftment. Subjects with engraftment failure will be censored at the date of last contact or the Day+180 post-HSCT assessment date whichever is earlier. Subjects with 'Never Below' status will be censored at Day+1 post-HSCT. The remainder of the subjects who have not been considered as Engraftment/Failure/Never Below will be considered as 'Undetermined' and censored at the last neutrophil engraftment assessment date. For these undetermined subjects who have no assessment date or if the assessment date is prior to or on the HSCT date, they will be censored at Day+1 post-HSCT. If a subject does not undergo HSCT, the subject will be censored at the date of Day +1 post-HSCT.

This analysis will be repeated for platelet engraftment. The date of platelet engraftment will be recorded on the eCRF and is defined as the first date after HSCT of a platelet count > 20×10^9/L without a platelet transfusion in the preceding 7 days.

The following will be presented for neutrophil engraftment and platelet engraftment:

- The number of subjects by treatment group who achieved engraftment by Day +30 post-HSCT, Day +100 post-HSCT, and Day +180 post-HSCT.
- The number of subjects who were censored.
- The number of subjects who were 'Never Below'.
- The number of subjects who did not have HSCT.
- The KM estimates of the engraftment rate (%) at Day +100 post-HSCT (95% CI).
- The KM estimate of median time to engraftment in days (95% CI).
- A KM plot will be presented up to Day +180 post-HSCT for each treatment arm. The number of subjects at risk will be displayed at 10-day intervals.

The following summaries will be provided:

- Analysis of time to neutrophil engraftment
- Analysis of time to platelet engraftment
- Summary of graft failure

The following figures will be provided:

- Figure of neutrophil engraftment
- Figure of platelet engraftment

The following listings will be provided displaying the dates for engraftment or graft failure:

- Listing of neutrophil and platelet engraftment
- Listing of engraftment status

11.7 Karnofsky and Lansky Performance Scores

For Karnofsky and Lansky performance scores, descriptive statistics as well as changes from baseline will be summarized and listed for each visit in Section 8.4.2. For each of the postbaseline assessments, change between baseline and that assessment will be calculated as follows:

Change from baseline = [post-baseline assessment date] – [baseline assessment date]

and will be summarized and presented using descriptive statistics. If the performance score is missing at either baseline or a specific postbaseline assessment for a subject, change from baseline will be missing.

The following summary will be provided:

- Summary of Karnofsky and Lansky performance scores

The following listing will be provided:

- Listing of Karnofsky and Lansky performance scores

11.8 Abdominal Ultrasound

Abdominal ultrasound assessments will be presented in the following listing and will include the date, liver size, presence of hepatomegaly, presence of ascites, and reversal of portal venous flow:

- Listing of abdominal ultrasound

12 HOSPITAL RESOURCE UTILIZATION

Hospital resource utilization will be summarized by treatment arm for the Safety Analysis Set.

The duration of hospital stay in days will be calculated as follows:

Days in hospital = [Date of hospital discharge] – [Date of hospital admission] + 1

If hospital re-admission occurs during the study, the duration of each re-admission will be calculated as noted above and the number of days in the hospital across all admissions will be summed to obtain the total duration of the hospital stay for each subject. If the date of hospital admission is prior to the date of informed consent, the informed consent date will be used as the date of admission. If the subject is still in the hospital at the time of study completion, death, or early termination, the discharge date will be recorded as "Not Applicable" on the eCRF and the date of study completion/early termination/death will be used as the discharge date. The total duration of the hospital stay will be summarized. The number of subjects who were hospitalized prior to informed consent and the number who were still hospitalized at the end of study participation will be tabulated.

The total number of days in Intensive Care Unit (ICU) will be calculated using the same method noted above and summarized.

Inpatient resource use and/or use of diagnostic tests during the initial hospital stay or during any re-admissions will be summarized and listed including the following:

- Number of blood transfusions

- Total number of units for all transfusions received
- Total number of days of ventilator use
- Type of dialysis
- Total number of days on dialysis
- Number of liver biopsies
- Number of bone marrow biopsies
- Number of other biopsies

The following summary will be provided:

- Summary of hospital stay and resource utilization

The following listings will be provided:

- Listing of hospital and ICU stay
- Listing of inpatient resource utilization

13 HEALTH-RELATED QUALITY OF LIFE

Health-related quality of life results will be summarized by treatment arm for the Safety Analysis Set.

13.1 EQ-5D-5L

13.1.1 EQ-5D-5L Dimension

For each of the 5 dimensions of mobility, self-care, activity, pain, and anxiety based on the descriptive system of the EQ-5D-5L, the numbers and percentages of subjects for all categories (the five levels of reported problems and question not completed) 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 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:

- Summary of EQ-5D-5L dimensions for adult subjects (age ≥16 years) by assessment
- Summary of change in EQ-5D-5L dimensions from baseline for adult subjects (age ≥16 years) by assessment

The following listing will be provided including results for each of the 5 dimensions and the visual analogue scale (VAS) score:

- Listing of EQ-5D-5L

13.1.2 EQ VAS Score

The EQ VAS score at baseline and each of the post-HSCT assessments will be summarized and presented using descriptive statistics. 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 and will be summarized and presented using descriptive statistics.

Change in the EQ VAS = [EQ VAS at the post-HSCT assessment] – [EQ VAS at baseline]

The following summary will be provided:

- Summary of EQ-5D-5L VAS score for adult subjects (age ≥16 years)

13.2 EQ-5D-Y

13.2.1 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) 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 five dimensions in EQ-5D-5L (Section 13.1.1). 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:

- Summary of EQ-5D-Y dimensions for pediatric subjects (age ≥8 and ≤15 years) by assessment
- Summary of change in EQ-5D-Y dimensions from baseline for pediatric subjects (age ≥8 and ≤15 years) by assessment
-

The following listing will be provided and will include results for each of the 5 dimensions and the VAS score:

- Listing of EQ-5D-Y

13.2.2 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 13.1.2 for a specified subject, and will be summarized and presented using descriptive statistics.

The following summary will be provided:

- Summary of EQ VAS score for pediatric subjects (age ≥8 and ≤15 years)

13.3 EQ-5D-Y Proxy Version 1

13.3.1 EQ-5D-Y Proxy Version 1 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 three levels of reported problems and question not completed) 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 (Section 13.1.1). 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:

- Summary of EQ-5D-Y dimensions for pediatric subjects (age ≥4 and ≤7 years) by assessment
- Summary of change in EQ-5D-Y dimensions from baseline for pediatric subjects (age ≥4 and ≤7 years) by assessment

The following listing will be provided and will include results for each of the 5 dimensions and the VAS score:

- Listing of EQ-5D-Y Proxy Version 1

13.3.2 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 13.1.2 for a specified subject, and will be summarized and presented using descriptive statistics.

The following summary will be provided:

- Summary of EQ VAS score for pediatric subjects (age ≥4 and ≤7 years)

14 BIOMARKERS

Biomarker analysis is not within the scope of this SAP and a separate report will be provided for the analysis of biomarkers.

15 IMMUNOGENICITY

Immunogenicity analysis is not within the scope of this SAP and a separate report will be provided for the analysis.

16 PHARMACOKINETIC ANALYSES

16.1 General Considerations

Pharmacokinetic (PK) analysis for this study will be conducted in 2 separate efforts. For those subjects with intensive PK sampling scheme and those who developed VOD and received defibrotide rescue treatment, a noncompartmental analysis will be conducted and reported in this CSR. The PK sample collection schedule in subjects who developed VOD and received defibrotide rescue treatment underwent several changes across protocol amendments. The results of this analysis will be produced and summarized by day and time points as covered by the protocol version which was current at the time of PK sample collection, and as outlined in Sections 16.2 and 16.3. For those subjects with sparse PK sampling scheme, a population-based PK analysis will be conducted together with PK data from other studies. The population PK will be reported separately from the CSR.

Quantitative variables will be summarized using descriptive statistics (sample size, arithmetic mean, SD, coefficient of variation, median, min, and max). Geometric statistics (mean and SD) will be included for PK concentrations and parameters, where applicable.

All defibrotide concentration data will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in listings. The rounded derived PK parameters will be considered the source data for the calculation of descriptive statistics and other statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (eg, maximum defibrotide concentration [C_{max}]) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (eg, time to maximum activity [T_{max}]) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the arithmetic and geometric means and SDs will be presented with precision of 1 digit more than the source data. The minimum, median, and maximum will be presented with the same precision as the source data. Coefficients of variation will always be reported with 1 decimal place.

16.2 Defibrotide Plasma Concentrations

The defibrotide plasma concentrations will be summarized by nominal time point using descriptive statistics as described in Section 16.1. Concentrations that are below the limit of quantitation (BLQ) will be treated as a numeric value of 0, and the associated geometric statistics will be designated and reported as not done.

The following summaries will be provided:

- Summary of defibrotide plasma concentrations in subjects consented for intensive PK collection

  - On Day +1 and Day +7 post-HSCT: prior to defibrotide infusion, and 2, 2.25, 2.5, 2.75, 3, 3.5, 4 and 5 hours after start of defibrotide infusion;
  - On Day +15 and Day +30 post-HSCT: 2 hours post start of defibrotide infusion;
- Summary of defibrotide plasma concentrations in subjects with sparse PK sampling
  - On Day +7 post-HSCT: 2 hours post start of defibrotide infusion, 2 to 4 hours after the end of defibrotide infusion;
  - On Day +15 and Day +30 post-HSCT: 2 hours post start of defibrotide infusion;
- Summary of defibrotide plasma concentrations in subjects who developed VOD and received defibrotide rescue treatment by treatment arm (BSC or DP)
  - On Day 1 after the start of rescue treatment: prior to defibrotide infusion, and 2, 3, 4 and 5 hours after start of defibrotide infusion (Protocol Amendment 3);
  - On Day 7 after the start of rescue treatment: 2 hours post start of defibrotide infusion (Protocol Amendment 3);
  - On Day 14 after the start of rescue treatment: prior to defibrotide infusion, at 2 hours post start of defibrotide infusion, and at 1, 2 and 3 hours after end of defibrotide infusion (Original Protocol), or prior to defibrotide infusion, and 2, 3, 4 and 5 hours after start of defibrotide infusion (Protocol Amendments 1&2)
  - On Day 30 after the start of rescue treatment: 2 hours post start of defibrotide infusion (Original Protocol, and Protocol Amendments 1&2);

Figures of individual and arithmetic mean defibrotide concentration-time profiles (± SD, as appropriate) using nominal time points in patients consented to intensive PK collection on Day +1 and Day +7 post-HSCT and in patients receiving defibrotide rescue treatment on Day 1 and Day 14 after the start of recue treatment, will be presented on linear and semi-logarithmic scales. For graphing purposes, the BLQ values will be considered as missing and, if applicable, 2 neighboring values will be connected.

The following figures will be provided:

- Mean Defibrotide Plasma Concentration-time Profile on Linear and Semi-logarithmic Scales following Defibrotide Infusion at 6.25 mg/kg on Day +1 post-HSCT
- Mean Defibrotide Plasma Concentration-time Profile on Linear and Semi-logarithmic Scales following Defibrotide Infusion at 6.25 mg/kg on Day +7 post-HSCT
- Mean Defibrotide Plasma Concentration-time Profile on Linear and Semi-logarithmic Scales following Defibrotide Infusion at 6.25 mg/kg after the start of rescue treatment in Patients from DP Arm by Visit
- Mean Defibrotide Plasma Concentration-time Profile on Linear and Semi-logarithmic Scales following Defibrotide Infusion at 6.25 mg/kg after the start of rescue treatment in Patients from BSC Arm by Visit

A listing of all defibrotide plasma concentrations by subject, with visit (day), study arm, PK blood sample collection date/time, calculated actual collection times relative to the previous dose, and derived sampling time deviations will be provided:

- Listing of defibrotide plasma concentrations

16.3 Defibrotide Pharmacokinetic Parameters

Subjects with partial defibrotide concentrations data, protocol violations or events with the potential to affect PK will be evaluated on a case-by-case basis to determine if sufficient data are available for reliable estimation of PK parameters.

PK parameters will be calculated for he patients consented for intensive PK collection on Day +1 and Day +7 post-HSCT; and for patients who developed VOD and received defibrotide for rescue treatment on Day 1 (Protocol Amendment 3) and on Day 14 (Original Protocol, and Protocol Amendments 1&2) after the start of rescue treatment, as data permit.

The defibrotide plasma PK parameters will be calculated using the standard noncompartmental analysis methods according to current working practices and Phoenix WinNonlin (Certara USA, Inc., v6.3 or higher).

All calculations of noncompartmental parameters will be based on actual sampling times for the analysis, but all predose times will be assigned a numerical value of 0 to prevent overestimation of the AUC.

Defibrotide plasma concentrations that are BLQ or missing will be handled the following way:

- Predose samples concentrations that are BLQ or missing will be assigned a numerical value of 0.
- Any other BLQ value will be assigned a value of 0 if they precede quantifiable samples in the initial portion of the profile.
- A BLQ value that occurs between quantifiable data points, especially prior to C_{max}, will be evaluated to determine if an assigned value of 0 makes sense, or if exclusion of the data (flagged in the data and identified to be treated as missing) is warranted.
- Following C_{max}, the BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters.
- If a BLQ value occurs at the end of the collection interval (after the last quantifiable activity), it will be set to 0.
- If consecutive BLQ values are followed by quantifiable values in the terminal portion of the concentration curve, these quantifiable values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile.

Where possible the following PK parameters listed in Table 6 will be determined from defibrotide plasma concentrations.

Table 6. PK Parameters to be Summarized

C_{max}	Maximum defibrotide plasma concentration, obtained directly from the observed data
T_{max}	Time of maximum defibrotide concentration (in hours), obtained directly from the observed data
C_{last}	The last quantifiable defibrotide concentration, obtained directly from observed data
T_{last}	Time of the last quantifiable defibrotide concentration (in hours), obtained directly from the observed data
AUC_{0-t}	Area under the defibrotide concentration-time curve in the sampled matrix from 0 (predose) to time of last quantifiable defibrotide concentration at time "t"
AUC_{tau}	Area under the defibrotide plasma concentration-time curve from 0 (predose) to the end of the dosing period (Day +7 post-HSCT and Days 1 and 14 after the start of rescue treatment in patients from DP arm)
AUC_{0-inf}	Area under the defibrotide plasma concentration-time curve from 0 (predose), extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant to AUC_{0-t}: $AUC_{0-t} + C_{last} / \lambda_z$ (Day +1 post-HSCT and Day 1 after the start of recue treatment in patients from BSC arm)
λ_z (k_{el})	Apparent terminal elimination rate constant (in 1/hour), determined by linear regression of the terminal points of the log-linear defibrotide concentration-time curve Visual assessment will be used to identify the terminal linear phase of the defibrotide concentration-time profile. A minimum of 3 data points will be used for the determination.
$t_{1/2}$	Terminal elimination half-life (in hours): $\ln(2) / \lambda_z$
CL	Systemic clearance after intravenous dosing, calculated as • $Dose/AUC_{0-inf}$ (Day +1 post-HSCT and Day 1 after the start of rescue treatment in patients from BSC arm) • $Dose/AUC_{tau}$ (Day +7 post-HSCT and Days 1 and 14 after the start of rescue treatment in patients from DP arm)
V_{ss}	Estimate of the volume of distribution at steady state following intravenous dosing: $MRT_{0-inf} \times CL$, where MRT_{0-inf} is mean residence time extrapolated to infinity

All AUC parameters will be calculated using Linear trapezoidal / Linear Interpolation trapezoidal summation. The minimum requirement for the calculation of AUC will be the

inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification, with at least 1 of these concentrations following C_{max}.

The PK parameters listed in Table 7 will be calculated for diagnostic or parameter derivation purposes and listed, but will not be summarized.

Table 7. PK Parameters for Diagnostic or Parameter Derivation Purposes

Span	The time spanned by λz (upper λz – lower λz) divided by the estimated $t_{1/2}$. The $t_{1/2}$ will be estimated over a time period of at least 2 half-lives, where possible. Where a $t_{1/2}$ is estimated over a time period of less than 2 half-lives, it may be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value will be discussed in the CSR.
$t_{1/2}$, N	Number of data points included in the log-linear regression analysis to determine λ_z A minimum of 3 data points will be used for determination.
Rsq, adjusted	Goodness of fit statistic for calculation of λ_z A value of ≥ 0.8 for the adjusted R-squared value will be used as the criterion for the reliable estimation of λ_z and reporting of the $t_{1/2}$. If the adjusted R-squared value does not meet this criterion for a given subject the $t_{1/2}$, $AUC_{0\text{-inf}}$, CL, and V_{ss} will be listed but not included in the descriptive statistics.
$\%AUC_{extr}$	Percentage of $AUC_{0\text{-inf}}$ obtained by extrapolation: $[(C_{last} / \lambda_z) / AUC_{0\text{-inf}} \times 100]$ If $\%AUC_{extr}$ is greater than 20% of $AUC_{0\text{-inf}}$, then $AUC_{0\text{-inf}}$, CL, and V_{ss} will be listed but not included in summary statistics.
$AUMC_{last}$	Area under the first moment curve (AUMC) from 0 (pre-dose) to time of last quantifiable defibrotide concentration at time "t"
$AUMC_{0\text{-inf}}$	Area under the first moment curve (AUMC) extrapolated to infinity, based on the last observed concentration, calculated as $AUMC_{last} + (T_{last} \times C_{last}) / \lambda_z + C_{last} / \lambda_z$
$MRT_{0\text{-inf}}$	Mean residence time extrapolated to infinity, calculated for infusion models as $(AUMC_{0\text{-inf}} / AUC_{0\text{-inf}} – TI / 2$, where TI is infusion time

All PK parameters will be summarized by visit and study arm using descriptive statistics as described in Section 16.1. Geometric mean will not be calculated for T_{max} and T_{last}.

The following summaries will be provided:

- Defibrotide plasma pharmacokinetic parameters following defibrotide infusion at 6.25 mg/kg on Day +1 post-HSCT

- Defibrotide plasma pharmacokinetic parameters following defibrotide infusion at 6.25 mg/kg on Day +7 post-HSCT
- Defibrotide plasma pharmacokinetic parameters following defibrotide infusion at 6.25 mg/kg after the start of rescue treatment by Visit.

The following listing will be provided and will include all generated individual PK parameters by subject, visit (day), and treatment arm:

- Listing of PK parameters

17 PHARMACODYNAMIC ANALYSES

Not applicable.

18 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:

- Listing of subjects impacted by the COVID-19 pandemic

19 REFERENCES

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20 APPENDIX I: PREFFERRED TERMS FOR ADVERSE EVENTS OF SPECIAL INTEREST

20.1 PTs for Pulmonary Hemorrhage

Bronchial haemorrhage
Bronchial varices haemorrhage
Epistaxis
Haemoptysis
Pulmonary alveolar haemorrhage
Pulmonary haemorrhage
Pulmonary haematoma
Respiratory tract haemorrhage
Respiratory tract haemorrhage neonatal
Tracheal haemorrhage

20.2 PTs for Gastrointestinal Bleeding

Chronic gastrointestinal bleeding
Colonic haematoma
Diarrhoea haemorrhagic
Duodenal ulcer haemorrhage
Duodenitis haemorrhagic
Enterocolitis haemorrhagic
Gastric haemorrhage
Gastric occult blood positive
Gastric ulcer haemorrhage
Gastric ulcer haemorrhage, obstructive
Gastritis haemorrhagic
Gastroduodenal haemorrhage
Gastroduodenitis haemorrhagic
Gastrointestinal haemorrhage
Haematemesis
Haematochezia
Haemorrhagic erosive gastritis
Intestinal hematomashaematoma
Intestinal haemorrhage
Intestinal varices haemorrhage
Intra-abdominal haematoma
Large intestinal haemorrhage
Large intestinal ulcer haemorrhage
Lower gastrointestinal haemorrhage
Melaena

Mesenteric haemorrhage
Occult blood positive
Oesophageal haemorrhage
Oesophageal intramural haematoma
Oesophageal ulcer haemorrhage
Oesophagitis haemorrhagic
Peptic ulcer haemorrhage
Proctitis haemorrhagic
Rectal haemorrhage
Rectal ulcer haemorrhage
Small intestinal haemorrhage
Small intestinal ulcer haemorrhage
Ulcer haemorrhage
Upper gastrointestinal haemorrhage

20.3 PTs for Gastrointestinal Bleeding likely pre-existing neurological or neonatal conditions

Anal haemorrhage
Anal ulcer haemorrhage
Anastomotic haemorrhage
Anastomotic ulcer haemorrhage
Anorectal varices haemorrhage
Diverticulitis intestinal haemorrhagic
Diverticulum intestinal haemorrhagic
Duodenal operation
Duodenal vascular ectasia
Gastric antral vascular ectasia
Gastric haemangioma
Gastric varices haemorrhage
Gastritis alcoholic haemorrhagic
Gastrointestinal anastomotic leak
Gastrointestinal angiectasia
Gastrointestinal angiodysplasia haemorrhagic
Gastrointestinal polyp haemorrhage
Haemorrhoidal haemorrhage
Mallory-Weiss syndrome
Melaena neonatal
Neonatal gastrointestinal haemorrhage
Oesophageal varices haemorrhage
White nipple sign

20.4 PTs for Hypersensitivity Reactions

Acute generalised exanthematous pustulosis
Administration site dermatitis
Administration site eczema
Administration site hypersensitivity
Administration site rash
Administration site recall reaction
Administration site urticaria
Administration site vasculitis
Allergic bronchitis
Allergic colitis
Allergic cough
Allergic cystitis
Allergic eosinophilia
Allergic gastroenteritis
Allergic hepatitis
Allergic keratitis
Allergic myocarditis
Allergic oedema
Allergic otitis externa
Allergic otitis media
Allergic pharyngitis
Allergic respiratory disease
Allergic respiratory symptom
Allergic sinusitis
Allergic transfusion reaction
Allergy alert test positive
Allergy test positive
Allergy to immunoglobulin therapy
Allergy to surgical sutures
Allergy to vaccine
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Anaphylaxis treatment
Angioedema
Anti-neutrophil cytoplasmic antibody positive vasculitis
Antiallergic therapy
Antiendomysial antibody positive

Application site dermatitis
Application site eczema
Application site hypersensitivity
Application site rash
Application site recall reaction
Application site urticaria
Application site vasculitis
Arthritis allergic
Aspirin-exacerbated respiratory disease
Atopy
Blepharitis allergic
Blood immunoglobulin E abnormal
Blood immunoglobulin E increased
Bromoderma
Bronchospasm
Catheter site dermatitis
Catheter site eczema
Catheter site hypersensitivity
Catheter site rash
Catheter site urticaria
Catheter site vasculitis
Chronic eosinophilic rhinosinusitis
Chronic hyperplastic eosinophilic sinusitis
Circulatory collapse
Circumoral oedema
Conjunctival oedema
Conjunctivitis allergic
Contact stomatitis
Contrast media allergy
Contrast media reaction
Corneal oedema
Cutaneous vasculitis
Dennie-Morgan fold
Dermatitis
Dermatitis acneiform
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis contact
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis herpetiformis
Dermatitis infected

Dermatitis psoriasiform
Device allergy
Dialysis membrane reaction
Distributive shock
Documented hypersensitivity to administered product
Drug cross-reactivity
Drug eruption
Drug hypersensitivity
Drug provocation test
Drug reaction with eosinophilia and systemic symptoms
Eczema
Eczema infantile
Eczema nummular
Eczema vaccinatum
Eczema vesicular
Eczema weeping
Encephalitis allergic
Encephalopathy allergic
Eosinophilic granulomatosis with polyangiitis
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Epiglottic oedema
Erythema multiforme
Erythema nodosum
Exfoliative rash
Eye allergy
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
Fixed drug eruption
Giant papillary conjunctivitis
Gingival oedema
Gingival swelling
Gleich's syndrome
Haemorrhagic urticaria
Hand dermatitis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Heparin-induced thrombocytopenia
Hereditary angioedema
Hypersensitivity

Hypersensitivity vasculitis
Idiopathic urticaria
Immediate post-injection reaction
Immune thrombocytopenic purpura
Immune tolerance induction
Immune-mediated adverse reaction
Implant site dermatitis
Implant site hypersensitivity
Implant site rash
Implant site urticaria
Incision site dermatitis
Incision site rash
Infusion site dermatitis
Infusion site eczema
Infusion site hypersensitivity
Infusion site rash
Infusion site recall reaction
Infusion site urticaria
Infusion site vasculitis
Injection site dermatitis
Injection site eczema
Injection site hypersensitivity
Injection site rash
Injection site recall reaction
Injection site urticaria
Injection site vasculitis
Instillation site hypersensitivity
Instillation site rash
Instillation site urticaria
Interstitial granulomatous dermatitis
Intestinal angioedema
Iodine allergy
Kaposi's varicelliform eruption
Kounis syndrome
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Mast cell degranulation present
Medical device site dermatitis

Medical device site eczema
Medical device site hypersensitivity
Medical device site rash
Medical device site recall reaction
Medical device site urticaria
Mouth swelling
Mucocutaneous rash
Multiple allergies
Nephritis allergic
Nikolsky's sign
Nodular rash
Oculomucocutaneous syndrome
Oculorespiratory syndrome
Oedema mouth
Oral allergy syndrome
Oropharyngeal blistering
Oropharyngeal spasm
Oropharyngeal swelling
Palatal oedema
Palatal swelling
Palisaded neutrophilic granulomatous dermatitis
Palpable purpura
Pathergy reaction
Periorbital oedema
Pharyngeal oedema
Pruritus allergic
Radioallergosorbent test positive
Rash
Rash erythematous
Rash follicular
Rash generalised
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash neonatal
Rash papulosquamous
Rash pruritic
Rash pustular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Reaction to azo-dyes

Reaction to colouring
Reaction to drug excipients
Reaction to preservatives
Red man syndrome
Rhinitis allergic
Scleral oedema
Scleritis allergic
Scrotal oedema
Serum sickness
Serum sickness-like reaction
Shock
Shock symptom
Skin necrosis
Skin reaction
Skin test positive
Solar urticaria
Solvent sensitivity
Stevens-Johnson syndrome
Stoma site hypersensitivity
Stoma site rash
Swelling face
Swollen tongue
Symmetrical drug-related intertriginous and flexural exanthema
Tongue oedema
Toxic epidermal necrolysis
Toxic skin eruption
Tracheal oedema
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction
Type IV hypersensitivity reaction
Urticaria
Urticaria cholinergic
Urticaria chronic
Urticaria contact
Urticaria papular
Urticaria physical
Urticaria pigmentosa
Urticaria vesiculosa
Urticarial vasculitis
Vaccination site dermatitis
Vaccination site eczema

Vaccination site exfoliation
Vaccination site hypersensitivity
Vaccination site rash
Vaccination site recall reaction
Vaccination site urticaria
Vaccination site vasculitis
Vaccination site vesicles
Vaginal exfoliation
Vaginal ulceration
Vasculitic rash
Vessel puncture site rash
Vessel puncture site vesicles
Vulval ulceration
Vulvovaginal rash
Vulvovaginal ulceration