STATISTICAL ANALYSIS PLAN

VERSION: 1.0
DATE: 12 JANUARY 2021

STUDY DRUG:

DEFIBROTIDE (DEFIBROTIDE SODIUM)

PROTOCOL/STUDY NUMBER:

JZP395-201 Protocol (09 February 2019)

STUDY TITLE:

Prospective, Multicenter, Open-Label, Single Arm, Phase 2 Study to Evaluate the Safety and Efficacy of Defibrotide in the Prevention of Chimeric Antigen Receptor-T-cell-associated Neurotoxicity in Subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma Receiving Axicabtagene Ciloleucel (Yescarta®)

SPONSOR:

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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

Table 1: List of Abbreviations

Abbreviation	Term
ASBMT	American Society for Blood and Marrow Transplantation
AE	Adverse event
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AUMC	Area under the first moment curve
CAR-T	Chimeric antigen receptor-T-cell
CI	Confidence interval
CRF	Case report form
CRS	Cytokine release syndrome
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
HLGT	High Level Group Term
ICE	Immune effector cell-associated encephalopathy
ICH	International Conference on Harmonisation
ICU	Intensive care unit
MedDRA	Medical Dictionary for Regulatory Activities
MLE	Maximum likelihood estimate
PK	Pharmacokinetics
PT	Preferred term
RP2D	Recommended phase 2 dose
SAC	Safety Assessment Committee
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SMQ	Standardised MedDRA Query
SOC	System organ class

TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

2. MODIFICATION HISTORY

Version History:

Version	**Date**	**Description**
Original	*12 January 2021*	

3. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical methodology and planned analyses for Protocol JZP395-201 for inclusion in the clinical study report (CSR). Mock tables, listings, and figure shells will be provided in a separate supporting document.

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

- Original Protocol, dated 09 February 2019
- Case report form (CRF), Version dated 05 December 2019

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

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

The primary objective of the study is to assess the efficacy of defibrotide for the prevention of chimeric antigen receptor-T-cell-associated (CAR-T-associated) neurotoxicity in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) receiving Yescarta.

4.1.2. Secondary Objectives

- To further assess the efficacy of defibrotide for the prevention of CAR-T-associated neurotoxicity in subjects with relapsed or refractory DLBCL receiving Yescarta
- To assess the safety of defibrotide for the prevention of CAR-T-associated neurotoxicity in subjects with relapsed or refractory DLBCL receiving Yescarta
- To assess the pharmacokinetics (PK) of defibrotide

4.1.3. Exploratory Objectives

- Biomarker analysis before and after defibrotide
- Biomarker analysis before and after Yescarta
- Duration of hospital stay and intensive care unit (ICU) stay

4.2. Study Endpoints

4.2.1. Primary Endpoints

The primary endpoint of the study is the incidence of CAR-T-associated neurotoxicity (any grade, defined by Common Terminology Criteria for Adverse Events [CTCAE] v5.0) by CAR-T Day +30.

4.2.2. Secondary Endpoints

- The secondary efficacy endpoints of the study are as follows:
  - Incidence of CAR-T-associated neurotoxicity of Grade 3 or greater defined by CTCAE v5.0 by CAR-T Day +30
  - Incidence of CAR-T-associated neurotoxicity (any grade and Grade 3 or greater) according to the ASBMT consensus grading system (Lee et al. 2019) by CAR-T Day +30
  - Incidence of cytokine release syndrome (CRS; any grade, according to the ASBMT consensus grading system [Lee et al. 2019]) by CAR-T Day +30
  - Use of high dose steroid by CAR-T Day +30
- The following safety endpoints will be evaluated as secondary endpoints of the study:
  - Incidence of TEAEs that occur up to 30 days after the last dose of defibrotide

  - Incidence of TESAEs that occur up to 30 days after the last dose of defibrotide
  - Lymphoma response evaluation by Cheson criteria (Cheson et al. 2016) up to CAR-T Day +60
- PK of defibrotide

4.2.3. Exploratory Endpoints

The following exploratory endpoints will be evaluated:

- Biomarker analysis before and after defibrotide
- Biomarker analysis before and after Yescarta
- Duration of hospital stay and ICU stay

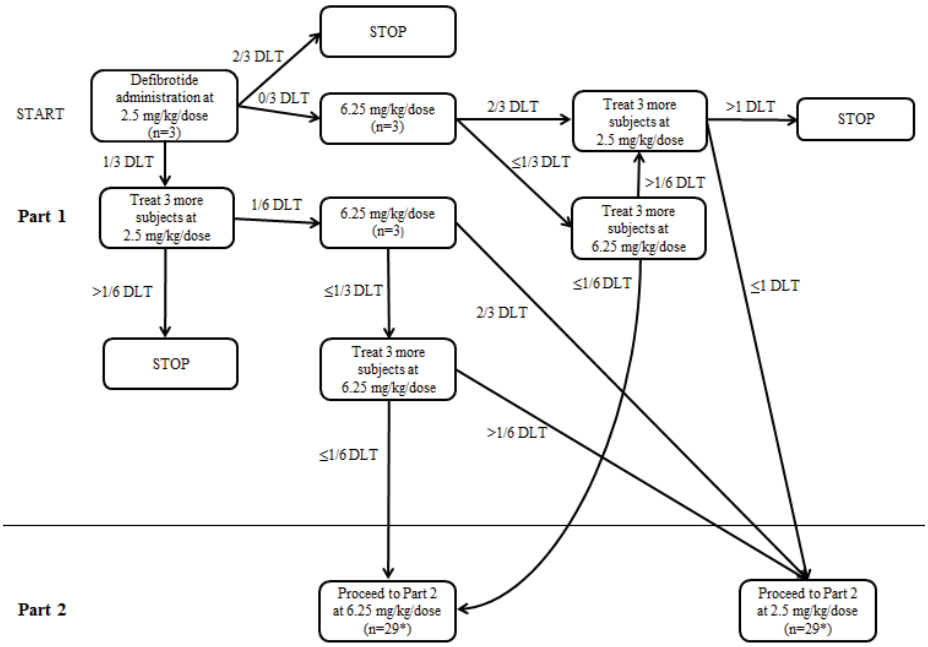
5. STUDY DESIGN

5.1. Summary of Study Design

This is a prospective, open-label, single-arm study evaluating the safety and efficacy of defibrotide for the prevention of CAR-T-associated neurotoxicity in subjects with relapsed or refractory DLBCL receiving Yescarta. The primary endpoint of the study is the incidence of CAR-T-associated neurotoxicity (any grade, defined by CTCAE v5.0) by CAR-T Day +30.

This is a 2-part study starting with a safety lead-in phase (Part 1) that will determine the recommended phase 2 dose (RP2D) to be used in all subsequent eligible subjects (Part 2). Part 1 of the study is based on a standard 3 + 3 design and will evaluate the safety of a 2.5 mg/kg/dose regimen of defibrotide in 3 to 6 eligible subjects before escalating to a 6.25 mg/kg/dose regimen in 3 to 6 eligible subjects, according to the algorithm shown in Figure 1. A Safety Assessment Committee (SAC) will be formed to determine the dose-limiting toxicities (DLTs) during Part 1 of the study. After the RP2D is established, Part 2 will enroll subjects to obtain a total of approximately 32 subjects treated at the RP2D, including those who were treated at the RP2D in Part 1. It is projected that 10% of enrolled subjects will not receive CAR-T treatment (Yescarta), and therefore, will not contribute to the primary efficacy analysis, ie, 29 of the 32 subjects treated at the RP2D will be efficacy evaluable (see definition of the Efficacy Evaluable Analysis Set in Section 6).

Figure 1: Dose Escalation Algorithm



*Efficacy evaluable; Subjects in Part 1 treated at the RP2D will be included in the efficacy and safety analyses.

An SAC will be formed for determination of any DLTs during Part 1 of the study. The SAC will continue monitoring safety in Part 2 of the study. The SAC will include the Sponsor's Study Medical Monitor, Study Biostatistician, Pharmacovigilance Physician, and Principal Investigators. The Sponsor's Study Medical Monitor will be the chair of the SAC. All roles and responsibilities of the SAC, as well as the timing of safety reviews, will be fully described in a SAC charter.

The significant toxicity from CAR-T treatment may not be distinguishable from TEAEs attributable to defibrotide, as the safety profile of defibrotide in this patient population has not been characterized. During Part 1 of the study, all TEAEs that occur from the start of the first dose of defibrotide up to 7 days after the last dose of defibrotide will be first screened for DLT by the principal investigator of the site where the event occurred and by the Sponsor. The final determination of DLT will then be made by the SAC from TEAEs considered to have a causal relationship to defibrotide. As an exception, all bleeding TEAEs, regardless of relationship to defibrotide, will be evaluated by the SAC as potential DLTs. Because all hemorrhagic events are considered adverse drug reactions of defibrotide, the SAC will focus on any grade of intracranial hemorrhage and any other hemorrhage of Grade 2 or greater, per CTCAE v5.0. Of note, CAR-T-associated neurotoxicity is not a DLT.

The study duration is expected to be approximately 21 months, with an estimated enrollment period of 18 months and participation for each subject of approximately 3 months. Each subject is considered to have completed the study once the CAR-T Day +37 visit is completed and lymphoma response data are available; if lymphoma response data are not available by CAR-T Day +60, the subject is considered to have completed the study on CAR-T Day +60. End of study for each subject is the time at which the subject completes the study, the time of death, lost to follow-up, or early termination from the study. The study is considered completed once all enrolled subjects have reached the end of study. The final analysis to support the CSR will take place after study completion.

5.2. Study Treatment

Subjects will receive defibrotide at 2.5 mg/kg/dose or 6.25 mg/kg/dose, lymphodepletion chemotherapy (per the investigator's standard of care), and Yescarta (per labeled use).

Defibrotide solution is administered intravenously by study site personnel at 2.5 mg/kg/dose or 6.25 mg/kg/dose. Each defibrotide dose should be infused over 2 hours ± 15 minutes. Individual doses of defibrotide are determined for individual subjects based on body weight at baseline, which in this study is defined as the date of the first defibrotide infusion, prior to initiation of infusion. To facilitate efficient drug administration, each dose will be rounded to the nearest 10 mg for subjects weighing > 35 kg and the nearest 5 mg for subjects weighing ≤ 35 kg.

To minimize the endothelial damage from lymphodepletion chemotherapy, defibrotide is to start on the first day (CAR-T Day -5 [Study Day 1]; see definition of Study Day in Section 7.2.2) of lymphodepletion chemotherapy (with 1 administration of defibrotide per day) and continue for 3 days (with administration of defibrotide on each day occurring immediately prior to lymphodepletion chemotherapy). The window between the end of defibrotide infusion and start of lymphodepletion chemotherapy should not exceed 2 hours. On CAR-T Day -2 (Study Day 4) and CAR-T Day -1 (Study Day 5), defibrotide will not be administered. Starting on CAR-T Day 0 (Study Day 6), defibrotide will be administered every 6 hours (4 times a day) until CAR-T Day +7 (Study Day 13). A minimum of 2 doses of defibrotide must be administered prior to Yescarta infusion on CAR-T Day 0. Yescarta may be delayed for up to 2 days, in which case CAR-T Day 0 will correspond to Study Day 7 (1-day delay) or Study Day 8 (2-day delay).

Each defibrotide dose (infused over an infusion period of 2 hours ± 15 minutes) may be administered within ± 1 hour of the scheduled dosing time, provided that there is at least a 2-hour window between the end of an infusion and the start of the next infusion.

This dosing schedule is summarized in the table below:

Schedule of Defibrotide Dosing

	Outpatient					Inpatient required			
CAR-T Day	-5	-4	-3	-2	-1	0 (+2 days)[a]	+1 to +7 (+2 days)[a]	+8 to +37 (+2 days)[a]	+60 (+2 days)[a]
Study Day	1	2	3	4	5	6	7-13	14-43	66
Lymphodepletion chemotherapy	X[b]	X[b]	X[b]						
Yescarta						X[c]			
Defibrotide[d]	QD[e]	QD[e]	QD[e]			QID[f]	QID[f]		

Abbreviations: CAR-T = chimeric antigen receptor T-cell; QD = once daily; QID = 4 times a day.

[a] Yescarta may be delayed for up to 2 days, in which case CAR-T Day 0 will correspond to Study Day 7 (1-day delay) or Study Day 8 (2-day delay).

[b] Per the investigator's standard of care.

[c] Per the labeled use.

[d] Defibrotide should be administered within ±1 hour of the scheduled dose, provided that there is at least a 2-hour window between the end of an infusion and the start of the next infusion.

[e] Defibrotide must be administered immediately prior to lymphodepletion chemotherapy. The window between the end of defibrotide infusion and start of lymphodepletion chemotherapy should not exceed 2 hours.

[f] At least 2 doses of defibrotide must be administered on CAR-T Day 0 (Study Day 6) prior to administration of Yescarta.

If a subject develops any grade intracranial hemorrhage or any other hemorrhage of Grade 2 or greater, defibrotide must be discontinued. In addition, discontinuation of defibrotide is recommended for subjects that need to undergo surgery or invasive procedures. If a subject experiences Grade 3 or greater CAR-T-associated neurotoxicity, the treatment must discontinue, as such an event is considered failure to prevent CAR-T-associated neurotoxicity. Subjects who discontinue defibrotide due to toxicity must not resume defibrotide treatment on this study but should still continue protocol defined evaluations as long as the subject remains on the study.

5.3. Power and Sample Size Considerations

Part 1 of the study will determine the RP2D by evaluating the safety of defibrotide in subjects receiving CAR-T-cell therapy (Yescarta). Two cohorts (2.5 mg/kg/dose and 6.25 mg/kg/dose) will be evaluated in a standard 3 + 3 design. If DLTs are observed in greater than 1 out of 3 or greater than 1 out of 6 subjects under the same dose level, then the dose is considered not safe. The highest dose that is determined to be safe (ie, the RP2D) will be given to subjects enrolled in Part 2 of the study and will be evaluated for the safety and efficacy of defibrotide for prevention of CAR-T-associated neurotoxicity. Subjects treated at the RP2D in Part 1 will be included in the efficacy and safety analyses of the study.

The primary objective of the study is to assess the efficacy of defibrotide for the prevention of CAR-T-associated neurotoxicity. Simon's optimal 2-stage design (Simon 1989) is employed to test the incidence rate of CAR-T-associated neurotoxicity by CAR-T Day +30 in the target patient population, in order to avoid unnecessarily exposing subjects to a non-efficacious therapy. The historical rate of CAR-T-associated neurotoxicity is 64% (Neelapu et al. 2017); it is hypothesized that administration with defibrotide will reduce this by half, to a CAR-T-associated neurotoxicity

rate of 32% (ie, a no CAR-T-associated neurotoxicity rate of 68%). The sample size calculation is based on testing the null and alternative hypotheses (see details in Section 7.3) with an overall 1-sided Type I error rate of 0.05 and a statistical power of at least 92% when the rate of no CAR-T-associated neurotoxicity rate is ≥ 68%. In the first stage, 10 efficacy evaluable subjects will be accrued. If there are 4 or fewer subjects without CAR-T-associated neurotoxicity post-CAR-T-cell therapy in these 10 subjects, the study will be stopped. Otherwise, 19 additional efficacy evaluable subjects will be accrued for a total of 29. The null hypothesis will be rejected if 15 or more subjects without CAR-T-associated neurotoxicity post-CAR-T-cell therapy are observed in these 29 subjects.

The total sample size of the study comprises the sum of subjects from Part 1 of the study, and those from Part 2 of the study. Subjects treated at the RP2D in Part 1 will be included in the efficacy and safety analyses. Under the assumption that defibrotide is safe at one of the 2 dose levels tested, the maximum number of subjects in Part 1 is 12, with 6 treated at the RP2D; the minimum is 9, with 6 treated at the RP2D. Allowing for 10% of enrolled subjects to be non-eligible for the efficacy evaluation (ie, not in the Efficacy Evaluable Analysis Set), a planned maximum total of 38 subjects and a planned minimum total of 35 will be required. Additional subjects may be enrolled to provide 29 efficacy evaluable subjects.

5.4. Randomization and Blinding

Randomization is not applicable, as this is a single-arm study.

Blinding is not applicable in this open-label study.

5.5. Interim Analysis

No formal interim analysis is planned for this study.

6. ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Analysis Set	Description
Enrolled	All subjects who signed the informed consent form and met all eligibility criteria for the study
Safety	The Safety Analysis Set will include all enrolled subjects who received at least 1 dose of defibrotide.
Enrolled (RP2D)	The Enrolled (RP2D) Analysis Set will include all enrolled subjects treated with at least 1 dose of defibrotide at the RP2D and having Yescarta infusion.
Efficacy Evaluable	The Efficacy Evaluable Analysis Set will consist of all subjects in the Enrolled (RP2D) Analysis Set: • who received at least 18 doses (of all 35) of defibrotide and either - developed CAR-T-associated neurotoxicity on or before CAR-T Day +30; OR - completed the CAR-T Day +30 neurological assessment; AND • who discontinued defibrotide due to CAR-T-associated neurotoxicity before receiving 18 doses of defibrotide. In addition, subjects must NOT have their Yescarta infusion delayed by more than 2 days from the original schedule.
PK	The PK Analysis Set will include all subjects who received at least 1 dose of defibrotide and had at least 1 evaluable PK concentration.
PK Evaluable	The PK Evaluable Analysis Set will include all subjects in the PK Analysis Set whose key PK parameters such as area under the curve (AUC), CL, and $t_{1/2}$ can be determined for the CAR-T Day -5 visit (see Section 11.3 for the definitions of CL and $t_{1/2}$).

7. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

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

7.1. General Methods

All study data will be summarized using descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for continuous variables (eg, age, weight) and using the number and percentage of subjects for categorical variables (eg, sex, race), unless otherwise specified. Data listings will be organized by study part (by cohort within Part 1) and then by subject within each cohort in Part 1 and Part 2.

All summaries, statistical analyses, and data listings described below will be completed using Version 9.4 or later of the Statistical Analysis System (SAS Institute, Inc., Cary, NC).

7.2. Baseline and Study Day Definitions

7.2.1. Baseline

For procedures and assessments, baseline is defined as the date of the first defibrotide infusion (ie, Study Day 1 or CAR-T Day -5 as defined in Section 7.2.2), prior to initiation of infusion.

For safety analyses, baseline is defined as the same as above.

For efficacy analyses, baseline is defined as the date of CAR-T-cell therapy (Yescarta) infusion (ie, CAR-T Day 0 as defined in Section 7.2.2).

7.2.2. Study Day

Study Day 1 is defined as the date of the first defibrotide infusion. For this study, the schedule of procedures and assessments will also reference the day relative to CAR-T Day 0, which is defined as the date of CAR-T-cell therapy (Yescarta) infusion. For example, Study Day 1 of this study will also be referred to as CAR-T Day -5, whereas the date of Yescarta infusion, CAR-T Day 0 will also be referred to as Study Day 6. Yescarta infusion may be delayed for up to 2 days, in which case CAR-T Day 0 will correspond to Study Day 7 (1-day delay) or Study Day 8 (2-day delay). Refer to the defibrotide dosing schedule table in Section 5.2.

7.2.3. Visit Windows

7.2.3.1. Neurotoxicity Evaluation and CRS Grading at the Primary Efficacy Evaluation Visit

For the neurotoxicity evaluation and CRS grading at the primary efficacy evaluation visit scheduled on CAR-T Day +30, an analysis window of + 3 days will be used to identify the last assessments to be used for the analyses of the secondary efficacy endpoints according to the ASBMT consensus grading system. The upper limit of the analysis window is CAR-T Day +33. All valid non-missing assessments from CAR-T Day 0 up to CAR-T Day +33 will be used in the analyses.

7.2.3.2. Adverse Events

For the adverse event (AE) evaluations at the primary efficacy evaluation visit scheduled on CAR-T Day +30 and at the final safety follow-up visit scheduled on CAR-T Day +37, the table below provides the upper limits of the analysis windows for the purpose of identifying the last assessments to be used in the analyses.

Visit Identifier	Upper Limit
CAR-T Day +30	CAR-T Day +33
CAR-T Day +37	CAR-T Day +43

All valid non-missing assessments from CAR-T Day 0 to CAR-T Day +33 will be used for the analyses of the primary and secondary efficacy endpoints based on CTCAE v5. All valid non-missing assessments from the date of the first defibrotide infusion to CAR-T Day +43 will be used for the safety analyses.

7.2.4. Missing Data

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

7.2.4.1. Incomplete and Missing AE Start Date

For this study, the first dose date is defined the same as baseline for the safety analysis (ie, the date of the first defibrotide infusion). 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 31;
  - if *year* > year of first dose, set *month* and *day* to January 1.
- If year and month are present, and day is missing,
  - if *year* = year of first dose, and
    - if *month* = month of first dose, set *day* to day of first dose;
    - if *month* < month of first dose, set *day* to the last day of *month*;
    - if *month* > month of first dose, set *day* to the first day of *month*;

- if *year* < year of first dose, set *day* to the last day of *month*;
- if *year* > year of first dose, set *day* to the first day of *month*.

For all other cases that are not covered above, set the date to the first dose date.

7.2.4.2. 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 1.
- If year and month are present, and day is missing, set day to the first day of month.

7.2.4.3. Incomplete and Missing Prior and Concomitant Medication End Date

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

- If it is indicated that the concomitant 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 concomitant 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 31.
- If year and month are present, and day is missing, set day to the last day of month.

7.2.4.4. Missing Treatment Relationship for AEs and SAEs

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

7.2.4.5. Missing Lymphoma Response

For the analysis of lymphoma response up to CAR-T Day +60, missing data on lymphoma response will be handled using a "Missing = Failure" approach.

7.3. Hypotheses Testing

The primary endpoint of the study will be evaluated by the proportion of the study subjects treated at the RP2D who did not develop any CAR-T-associated neurotoxicity by CAR-T Day +30 using the Efficacy Evaluable Analysis Set. The rate of no CAR-T-associated neurotoxicity, denoted by p, will be tested against a pre-defined threshold, 36%, using the rejection rule based on Simon's optimal 2-stage design.

Symbolically, this is expressed as follows,

H_0: $p \leq 36\%$ (ie, the rate of CAR-T-associated neurotoxicity is more than 64%)

versus

H_a: $p > 68\%$ (ie, the rate of CAR-T-associated neurotoxicity is no more than 32%).

The null hypothesis will be tested using a 1-sided test with a Type I error rate of 0.05.

7.4. Level of Significance & Multiplicity Adjustment

The Type I error rate for testing the null hypothesis for the analysis of the primary endpoint is 0.05, 1-sided (Section 7.3). There will be no adjustments for multiple testing in the analyses for this study.

7.5. Subgroups and Subgroup Analyses

Not applicable.

7.6. Changes to Planned Analyses

Study objectives are not clearly defined in the protocol. Study objectives are defined in this document corresponding to the study endpoints (see Sections 4.1 and 4.2).

In the protocol, the All Enrolled Analysis Set is defined as all enrolled subjects treated at the RP2D. In this document, this analysis set is renamed and redefined for clarity as the following: The Enrolled (RP2D) Analysis Set is defined as all enrolled subjects treated at the RP2D with at least 1 dose of defibrotide and having Yescarta infusion (see Section 6). Two sensitivity analyses are defined, with one based on the Enrolled (RP2D) Analysis Set and the other based on all subjects enrolled at RP2D and having Yescarta infusion. The latter includes all subjects in the Enrolled (RP2D) Analysis Set and subjects who did not receive any defibrotide.

As the study goes on, the duration of CAR-T-associated neurotoxicity has been identified as of clinical importance. The following analyses have been added accordingly (see Section 9.3.2):

- Analysis of Duration of CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 for All Efficacy Evaluable Subjects
- Analysis of Duration of CAR-T-associated Neurotoxicity of Grade or Greater Defined by CTCAE v5.0 for All Efficacy Evaluable Subjects

8. STUDY POPULATION SUMMARIES

Summaries will be produced by dose level for Part 1, for the phase 2 part of the study and overall, using the Safety Analysis Set unless otherwise specified. For Part 1, there will be no statistical comparison between the 2 dose levels for any of the measures in this section. For the phase 2 part, summaries will be provided for all subjects treated at the RP2D. Note that since subjects treated at the RP2D in Part 1 will also be included in the phase 2 part under the 2-stage design, those subjects will be included in the summaries for both Part 1 and the phase 2 part.

8.1. Analysis Sets

All analysis sets will be summarized. The Enrolled Analysis Set will be summarized overall only. The Enrolled (RP2D) and Efficacy Evaluable Analysis Sets will be summarized for the phase 2 part and overall only. The number of subjects screened and enrolled by center and reasons for screen failures will be summarized separately overall only. The following summaries will be provided:

- Analysis Sets by Study Phase and Overall
- Screened and Enrolled Subjects by Center
- Reasons for Screen Failures

Additionally, summaries for public disclosure will tabulate subjects enrolled by country and site and by age category using the Enrolled Analysis Set. The following summaries will be provided:

- Number of Subjects Enrolled by Country and Site
- Number of Subjects Enrolled by Age Category

The following listing will be provided:

- Reasons for Screen Failures

8.2. Disposition

8.2.1. Subject Disposition

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

- Subject Disposition by Study Phase and Overall

Every category will be kept in the summary even if it has 0 subjects. Additionally, a disposition summary will be provided using the Enrolled Analysis Set:

- Study Disposition (for Public Disclosure)

The following listing of subject disposition will be provided with date of screening/Study Day, date of enrollment/Study Day, study part, study completion (Yes or No), the last on-study date/Study Day/CAR-T Day and primary reason for study withdrawal (if No to study completion):

- Subject Disposition

If a subject completes the study per protocol, the last on-study date is the last visit date for this subject; if a subject terminates the study early, the date entered in the early termination folder in EDC is the last on-study date for this subject.

8.2.2. Defibrotide Disposition

A summary of defibrotide disposition, including defibrotide completion, defibrotide premature discontinuation, and primary reason for defibrotide premature discontinuation, will be provided:

- Defibrotide Disposition by Study Phase and Overall

Every category will be kept in the summary even if it has 0 subjects. The following listing of defibrotide disposition will be provided with the first dose date/Study Day/CAR-T Day, the start date of Yescarta administration/Study Day, the last dose date/Study Day/CAR-T Day, defibrotide completion (Yes or No), and primary reason for defibrotide premature discontinuation (if No to defibrotide completion):

- Defibrotide Disposition

8.3. Demographic and Baseline Disease Characteristics

A summary of demographic and baseline disease characteristics will be provided:

- Demographic and Baseline Disease Characteristics by Study Phase and Overall

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

- Age in years at baseline (as a continuous variable)
- Age group at baseline (18-64 or ≥ 65 years)
- Sex at birth (Female or Male)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Declined to state, or Mutiple)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, or Declined to state)
- Weight in kg at baseline
- Eastern Cooperative Oncology Group performance status at baseline (0, 1, 2, 3, or 4)
- Neurotoxicity evaluation at baseline
  - Immune effector cell-associated encephalopathy (ICE) score (Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4)
  - Depressed level of consciousness (Grade 0, Grade 1, Grade 2, Grade 3, or Grade 4)
  - Seizure (Grade 0, Grade 3, or Grade 4)
  - Motor findings (Grade 0, or Grade 4)
  - Raised intracranial pressure/cerebral edema (Grade 0, Grade 3, or Grade 4)
- CRS at baseline
  - Hypotension (Grade 1, Grade 2, Grade 3, or Grade 4)

- Hypoxia (Grade 1, Grade 2, Grade 3, or Grade 4)

o Disease history

- Time in days between the date of initial diagnosis and baseline
- Number of previous treatment regimens
- Primary refractory disease (Yes or No)
- Refractory to the previous treatment (less than partial response after last treatment; Yes or No)
- Previous autologous stem cell transplant (Yes or No)
- Number of recurrences (defined as number of previous treatment regimens - 1)

For race, if multiple options are checked, the subject will be categorized under "Multiple". For the ICE score, Grade 0 in a specific category is defined as no toxicity. The following listing of all demographic and baseline disease characteristics specified above will be provided:

- Demographic and Baseline Disease Characteristics

8.4. Medical History

Medical history includes diseases and conditions by standard body systems, and information on resolved conditions, intermittent conditions, concurrent illnesses, and previous surgeries. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 21.1. A summary of medical history by system organ class (SOC) and preferred term (PT) will be provided:

- Medical History by Study Phase and Overall

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

- Medical History

8.5. Yescarta Administration

Information pertaining to Yescarta administration, including the start date of Yescarta infusion in terms of Study Day (Study Day 6, Study Day 7 or Study Day 8) and infused cell count, will be summarized:

- Yescarta Administration by Study Phase and Overall

The numbers of subjects who did not receive Yescarta and whose Yescarta administration got delayed for more than 2 days will also be included in the summary. Note that for the phase 2 part of the study, subjects who did not receive Yescarta and whose Yescarta administration got delayed for more than 2 days are not efficacy evaluable. The following listing of Yescarta administration will be provided with the start date/Study Day and time, the end date/Study Day and time, and infused cell count (unit):

- Yescarta Administration

8.6. Prior and Concomitant Medications

Prior medications are defined as all medications and therapies received between the date of the first screening procedure and baseline (but not during treatment with defibrotide), and all prior therapies for the primary disease taken within 90 days prior to signing of the initial informed consent form, inclusive. Concomitant medications are defined as all medications and therapies taken between baseline (for safety analyses) and 30 days after the last dose of defibrotide, inclusive, including lymphodepletion chemotherapy, and medications and therapies started before treatment with defibrotide and continuing on or after the first dose of defibrotide. For reporting purpose, the following approach will be used to determine prior or concomitant medications, after the imputation rules for all incomplete and missing start and end dates (Sections 7.2.4.2 and 7.2.4.3) are applied:

Start Date	End Date	Decision
Before baseline	Before baseline	Prior medication
Missing	Before baseline	Prior medication
Before baseline	On or after baseline	Prior and concomitant medication
Baseline to 30 days after the last dose of defibrotide	On or after baseline	Concomitant medication
Baseline to 30 days after the last dose of defibrotide	Missing	Concomitant medication
Before baseline	Missing, but Ongoing = No at or before baseline	Prior medication
Before baseline	Missing, but Ongoing = No after baseline	Prior and concomitant medication
Before baseline	Missing, but Ongoing = Yes	Prior and concomitant medication
Before baseline	Missing, and Ongoing (Yes or No) not answered	Prior and concomitant medication
Missing	On or after baseline	Prior and concomitant medication
Missing	Missing, but Ongoing = No at or before baseline	Prior medication
Missing	Missing, but Ongoing = No after baseline	Prior and concomitant medication
Missing	Missing, but Ongoing = Yes	Prior and concomitant medication

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

Prior and concomitant medications will be coded using the World Health Organization drug dictionary (WHODRUG C3 Global 2019Q1), and summarized separately by the generic name. Medications that are not coded will only be listed.

8.6.1. Prior Medications

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

- Prior Medications by Study Phase and Overall

The summary of prior medications will be provided by anatomical therapeutic chemical (ATC) 4th level and PT, and ATCs will be ordered alphabetically, with PTs within an ATC sorted in descending order of incidence in overall. Subjects reporting more than 1 prior medication will be counted only once in the total number of subjects taking a prior medication. Prior medications will be sorted in descending order of incidence in overall. The following listing of prior medications will be provided with ATC 4th level classification, PT, indication, the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route:

- Prior Medications

8.6.2. Concomitant Medications

Information regarding concomitant medications is collected on the Prior and Concomitant Medications page of the CRF. Concomitant medications will be summarized separately for lymphodepletion chemotherapy (Section 8.6.2.1) and other concomitant medications (Section 8.6.2.2). For each summary, subjects reporting medications with the same generic name 2 or more times will be counted only once for that generic name, and subjects reporting more than 1 concomitant medication will be counted only once in the total number of subjects taking a concomitant medication.

8.6.2.1. Lymphodepletion Chemotherapy

Lymphodepletion chemotherapy includes cyclophosphamide and fludarabine. A summary of lymphodepletion chemotherapy will be provided:

- Concomitant Medications: Lymphodepletion Chemotherapy by Study Phase and Overall

The summary of lymphodepletion chemotherapy will be provided by ATC 4th level and PT, and ATCs will be ordered alphabetically, with PTs within an ATC sorted in descending order of incidence in overall. The following listing of lymphodepletion chemotherapy will be provided with ATC 4th level classification, PT, indication, the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route:

- Concomitant Medications: Lymphodepletion Chemotherapy

8.6.2.2. Other Concomitant Medications

Other concomitant medications include concomitant medications other than lymphodepletion chemotherapy. A summary of other concomitant medications will be provided:

- Concomitant Medications: Other (Lymphodepletion Chemotherapy Excluded) by Study Phase and Overall

The summary of other concomitant medications will be provided by ATC 4th level and PT, and ATCs will be ordered alphabetically, with PTs within an ATC sorted in descending order of incidence in overall. The following listing of other concomitant medications will be provided with ATC 4th level classification, PT, indication, the start date, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route:

- Concomitant Medications: Other (Lymphodepletion Chemotherapy Excluded)

8.7. Protocol Deviations

Major protocol deviations will be summarized:

- Major Protocol Deviations by Study Phase and Overall

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

- Inclusion/exclusion criteria
- Informed consent procedure
- Concomitant medication/therapy
- Laboratory assessments/procedures
- Study procedures
- Serious adverse event reporting
- Study drug dosing
- Visit schedule/interval
- Other

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

- All Protocol Deviations

9. EFFICACY

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

9.1. Primary Efficacy Endpoint and Analysis

9.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the incidence of CAR-T-associated neurotoxicity of any grade defined by CTCAE v5.0 by CAR-T Day +30. See Section 7.2.3.2 for the identification of the AE evaluations at the primary efficacy evaluation visit scheduled on CAR-T Day +30 to be used in the analysis. The actual number of efficacy evaluable subjects and the number of efficacy evaluable subjects who did not experience CAR-T-associated neurotoxicity of any grade by CAR-T Day +30 will be provided. The rate of no CAR-T-associated neurotoxicity of any grade will be estimated using the method of Koyama and Chen (2008), which incorporates the 2-stage design. The corresponding confidence interval (CI) and p-value will also be calculated using the method of Koyama and Chen (2008). If the actual Stage 2 sample size is the planned sample size, the null hypothesis will be rejected if 15 or more subjects with no CAR-T-associated neurotoxicity of any grade post-CAR-T-cell therapy by CAR-T Day +30 are observed in these 29 subjects. If the actual Stage 2 sample size is not the planned sample size, the method that takes both the planned and actual sample sizes into account for the 2-stage design will be used to calculate the rate of no CAR-T-associated neurotoxicity, the corresponding CI, and p-value (Koyama and Chen 2008); rejection of the null hypothesis after Stage 2 will be based on the p-value. The following summary will be provided:

- Analysis of the Incidence of CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 for All Efficacy Evaluable Subjects

The following listing of all CAR-T-associated neurotoxicity of any grade defined by CTCAE v5.0 by CAR-T Day +30 will be provided for all subjects enrolled at RP2D and having Yescarta infusion, with the start date of Yescarta administration/Study Day, the start date of the CAR-T-associated neurotoxicity/Study Day/CAR-T Day, the MedDRA High Level Group Term (HLGT) of the neurotoxicity, the grade of the neurotoxicity, a flag for being in the Efficacy Evaluable Analysis Set, and a flag for being in the Enrolled (RP2D) Analysis Set:

- All CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30

For each subject who experienced CAR-T-associated neurotoxicity of any grade by CAR-T Day +30, all reported CAR-T-associated neurotoxicity events by CAR-T Day +30 will be included in this listing.

9.1.2. CTCAE v5.0 Grading of Neurotoxicity

The MedDRA HLGTs that are indicative of neurotoxicity are shown in Appendix 1. Each of these HLGTs is in the MedDRA SOC of either Nervous System Disorders or Psychiatric Disorders. The CTCAE v5.0 grading for AEs in the Nervous System Disorder and Psychiatric Disorder SOCs is shown in Appendix 2, and this will be used to grade events of neurotoxicity.

9.1.3. Analysis of the Primary Efficacy Endpoint

A Simon's design is usually indexed by 4 numbers that represent Stage 1 sample size (n_1), Stage 1 critical value (R_1), final sample size (n_t), and final critical value (R_t). Let X_1 be the number of successes in Stage 1, X_2 be the number of successes in Stage 2, and X_t be the total number of successes (ie, $X_t = X_1 + X_2$), so X_1 follows a binomial distribution with parameters n_1 and p, and X_2 follows a binomial distribution with parameters n_2 and p, where $n_2 = n_t - n_1$ is the Stage 2 sample size. The rules for using the critical values, R_1 and R_t are:

- If $X_1 < R_1$, the trial will be stopped for futility; otherwise, an additional sample will be taken until a total number of n_t subjects are obtained.
- Out of the n_t subjects, if $X_t \geq R_t$, efficacy is concluded by rejecting H_0; otherwise, futility is concluded.

Therefore, for this study, $n_1 = 10$, $R_1 = 5$, $n_t = 29$, and $R_t = 15$ (see Section 5.3).

If $X_1 < R_1$ and futility is concluded in Stage 1, the p-value can be calculated as

$$P(X_1 \geq x_1 | p = p_0),$$

where x_1 is the observed number of successes in Stage 1, and p_0 is the probability of success under H_0. For this study, the probability of success is the rate of no CAR-T-associated neurotoxicity and $p_0 = 36\%$ (see Section 7.3). If the study continues to Stage 2, the p-value can be calculated as

$$\sum_{x_1 = R_1}^{n_1} P(X_1 = x_1 | p = p_0) cp(x_1, x_2, n_2, p_0), \quad (1)$$

where $cp(x_1, x_2, n_2, p_0) = P(X_2 \geq x_2 | X_1 = x_1, p = p_0)$, x_2 is the observed number of successes in Stage 2 (ie, $x_2 = x_t - x_1$), and x_t is the observed total number of successes. The term $cp(x_1, x_2, n_2, p_0)$ can be called as the conditional p-value, which is the p-value of Stage 2 given the result of Stage 1. Under the situation that the actual Stage 2 is not the planned sample size, $cp(x_1, x_2, n_2, p_0)$ in (1) will be replaced by $A(x_1, n_2, p^*)$, in order to be extended to the potential values of X_1; therefore, the p-value can be calculated as

$$\sum_{x_1 = R_1}^{n_1} P(X_1 = x_1 | p = p_0) A(x_1, n_2, p^*), \quad (2)$$

where $A(x_1, n_2, p)$, called the conditional power of Stage 2 given the results of Stage 1, can be calculated as

$$A(x_1, n_2, p) = \sum_{x_2 = R_2(x_1)}^{n_2} \binom{n_2}{x_2} p^{x_2} (1-p)^{(n_2 - x_2)}, \quad (3)$$

p^* is the solution of $A(x_1, n_2, p^*) = cp(x_1, x_2, n_2, p_0)$, and $R_2(x_1) = R_t - x_1$ for $R_1 \leq x_1 < R_t$, and 0 for $R_t \leq x_1$.

To maintain consistency between hypothesis testing and CI, since Simon's design is used in the setting of 1-sided hypothesis testing, a 1-sided CI of the form $(p_L, 1]$ will be calculated. With a type I error rate of 0.05, a 2-sided 90% CI will be calculated to obtain the lower bound for the 1-sided CI (p_L). Using formula (1), a p-value can be calculated to test H_0: $p \leq p_0'$ for any p_0'. A 2-sided 90% CI is a collection of p_0' such that the corresponding p-value is within the interval of [0.05, 0.95]. If the Stage 2 sample size is not the planned sample size, formula (2) will be used instead to calculate of the CI.

The maximum likelihood estimator of p, denoted by $\hat{p}$, can be calculated as $\hat{p} = x_t/n_t$, if $x_1 \geq R_1$ or $\hat{p} = x_1/n_1$, if $x_1 < R_1$, and has been shown to underestimate the true success probability in Simon's designs (Koyama and Chen 2008). Formula (1) with $p = p_0'$ can be used to calculate the p-value to test H_0: $p \leq p_0'$ for any p_0', as mentioned above. The value of p_0' that makes the p-value = 0.5 can be used as a reasonable estimate of p. If the Stage 2 sample size is not the planned sample size, formula (2) will be used instead to calculate of the point estimate of p.

The R functions that compute the p-value, point estimate and CI using the methods described above can be found using the following link:

http://biostat.mc.vanderbilt.edu/wiki/pub/Main/TatsukiRcode/twostage2018Web.R.

9.1.4. Sensitivity Analyses

9.1.4.1. Sensitivity Analysis: Analysis of CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 for All Enrolled Subjects Treated at RP2D and Having Yescarta Infusion

The primary efficacy endpoint will be analyzed based on the Enrolled (RP2D) Analysis Set for this sensitivity analysis. The maximum likelihood estimate (MLE) for the rate of no CAR-T-associated neurotoxicity of any grade defined by CTCAE v5.0 by CAR-T Day +30 (ie, the sample proportion for subjects with no CAR-T-associated neurotoxicity of any grade defined by CTCAE v5.0 by CAR-T Day +30) will be calculated. The following summary will be provided:

- Analysis of the Incidence of CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 for All Enrolled Subjects Treated at RP2D and Having Yescarta Infusion

For the listing of all CAR-T-associated neurotoxicity of any grade corresponding to this sensitivity analysis, refer to the listing of All CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 specified in Section 9.1.1.

9.1.4.2. Sensitivity Analysis: Analysis of CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 for All Subjects Enrolled at RP2D and Having Yescarta Infusion

For this sensitivity analysis, subjects enrolled at RP2D who had Yescarta infusion but did not receive any defibrotide will be included, in addition to the subjects in the Enrolled (RP2D) Analysis Set. This analysis will be conducted using the same methods as the sensitivity analysis described in Section 9.1.4.1. The following summary will be provided:

- Analysis of the Incidence of CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 for All Subjects Enrolled at RP2D and Having Yescarta Infusion

For the listing of all CAR-T-associated neurotoxicity of any grade corresponding to this sensitivity analysis, refer to the listing of All CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 specified in Section 9.1.1.

If all subjects enrolled at RP2D are treated with at least 1 dose of defibrotide, this sensitivity analysis is the same as the sensitivity analysis specified in Section 9.1.4.1, and therefore will not be performed.

9.1.5. Subgroup Analyses

Not applicable.

9.2. Secondary Endpoints and Analyses

9.2.1. Secondary Efficacy Endpoint

9.2.1.1. Incidence of CAR-T-associated Neurotoxicity of Grade 3 or Greater Defined by CTCAE v5.0 by CAR-T Day +30

The MLE for the rate of no CAR-T-associated neurotoxicity of Grade 3 or greater defined by CTCAE v5.0 by CAR-T Day +30 (ie, the sample proportion for subjects with no CAR-T-associated neurotoxicity of Grade 3 or greater defined by CTCAE v5.0 by CAR-T Day +30) will be calculated. The following summary will be provided:

- Analysis of the Incidence of CAR-T-associated Neurotoxicity of Grade 3 or Greater Defined by CTCAE v5.0 by CAR-T Day +30 for All Efficacy Evaluable Subjects

For the listing of all CAR-T-associated neurotoxicity of Grade 3 or greater corresponding to this analysis, refer to the listing of All CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 by CAR-T Day +30 specified in Section 9.1.1.

9.2.1.2. Incidence of CAR-T-associated Neurotoxicity (Any Grade and Grade 3 or Greater) according to the ASBMT Consensus Grading System by CAR-T Day +30

The MLE for the rate of no CAR-T-associated neurotoxicity of any grade (Grades 1, 2, 3 or 4) according to the ASBMT consensus grading system by CAR-T Day +30 (ie, the sample proportion for subjects with no CAR-T-associated neurotoxicity of any grade according to the ASBMT consensus grading system by CAR-T Day +30) will be calculated. The MLE for the rate of no CAR-T-associated neurotoxicity of Grade 3 or greater according to the ASBMT consensus grading system by CAR-T Day +30 (ie, the sample proportion for subjects with no CAR-T-associated neurotoxicity of Grade 3 or greater according to the ASBMT consensus grading system by CAR-T Day +30) will be calculated. See Section 7.2.3.1 for identification of the neurotoxicity evaluations at the primary efficacy evaluation visit scheduled on CAR-T Day +30 to be used in the analyses. There will be no hypothesis testing for the analysis of either of these secondary endpoints. The ASBMT consensus grading of CAR-T-associated neurotoxicity is provided in Appendix 3. The following summary will be provided:

- Analysis of the Incidence of CAR-T-associated Neurotoxicity according to the ASBMT Consensus Grading System by CAR-T Day +30 for All Efficacy Evaluable Subjects

including the following two sections:

- Analysis of the incidence of CAR-T-associated neurotoxicity of any grade
- Analysis of the incidence of CAR-T-associated neurotoxicity of Grade 3 or greater

The following listing of all CAR-T-associated neurotoxicity of any grade according to the ASBMT consensus grading system by CAR-T Day +30 will be provided for all efficacy evaluable subjects, with the start date of Yescarta administration/Study Day, the start date of the CAR-T-associated neurotoxicity/Study Day/CAR-T Day, the grades of ICE score, depressed level of consciousness, seizure, motor finding, and raised intracranial pressure/cerebral edema, and the grade of the neurotoxicity:

- All CAR-T-associated Neurotoxicity of Any Grade according to the ASBMT Consensus Grading System by CAR-T Day +30

For each subject who experienced CAR-T-associated neurotoxicity of any grade by CAR-T Day +30, all reported CAR-T-associated neurotoxicity events by CAR-T Day +30 will be included in this listing.

9.2.1.3. Incidence of CRS (Any Grade according to the ASBMT Consensus Grading System) by CAR-T Day +30

The MLE for the rate of no CRS of any grade (Grades 1, 2, 3 or 4) according to the ASBMT consensus grading system by CAR-T Day +30 (ie, the sample proportion for subjects with no CRS of any grade according to the ASBMT consensus grading system by CAR-T Day +30) will be calculated. See Section 7.2.3.1 for the identification of the CRS grading at the primary efficacy evaluation visit scheduled on CAR-T Day +30 to be used in the analysis. The grading of CRS by ASBMT criteria is provided in Appendix 4. The following summary will be provided:

- Analysis of the Incidence of CRS of Any Grade according to the ASBMT Consensus Grading System by CAR-T Day +30 for All Efficacy Evaluable Subjects

The following listing of all CRS of any grade according to the ASBMT consensus grading system by CAR-T Day +30 will be provided for all subjects enrolled at RP2D and having Yescarta infusion, with the start date of Yescarta administration/Study Day, the date of CRS assessment/Study Day/CAR-T Day, the grades of hypotension and hypoxia, a flag for being in the Efficacy Evaluable Analysis Set, and a flag for being in the Enrolled (RP2D) Analysis Set:

- All CRS of Any Grade according to the ASBMT Consensus Grading System by CAR-T Day +30

For each subject who experienced CRS of any grade by CAR-T Day +30, all reported CRS events by CAR-T Day +30 will be included in this listing.

9.2.1.4. Use of High Dose Steroid by CAR-T Day +30

The information regarding use of high dose steroid will be flagged on the Prior and Concomitant Medications page of the CRF. For the analyses of this secondary efficacy endpoint, use of high

dose steroid to treat CAR-T-associated neurotoxicity is the event of interest. The number of subjects who used high dose steroids by CAR-T Day +30 to treat CAR-T-associated neurotoxicity will be reported. The MLE for the proportion of subjects who use high dose steroids by CAR-T Day +30 to treat CAR-T-associated neurotoxicity (ie, the sample proportion for subjects who used high dose steroids by CAR-T Day +30 to treat CAR-T-associated neurotoxicity) will be calculated. For the subjects who used high dose steroids by CAR-T Day +30 to treat CAR-T-associated neurotoxicity, the time in days from the start of Yescarta administration to the start of high dose steroids, and the duration of use will be summarized separately using descriptive statistics. If use of high dose steroids is ongoing at the time of study completion, study withdrawal, or death, the date of study completion, study withdrawal, or death will be used to calculate the duration of use for the summary. The following summary will be provided:

- Analysis of Use Of High Dose Steroid by CAR-T Day +30 to Treat CAR-T-associated Neurotoxicity for All Efficacy Evaluable Subjects

The following listing of all incidence of high dose steroid use to treat CAR-T-associated neurotoxicity by CAR-T Day +30 will be provided for all efficacy evaluable subjects with the start date of Yescarta administration/Study Day, the start date/Study Day/CAR-T Day, ongoing (Yes or No), the end date, if not ongoing, dose (unit), frequency, and route:

- Use of High Dose Steroid by CAR-T Day +30 to Treat CAR-T-associated Neurotoxicity

All incidence of high dose steroid use to treat CAR-T-associated neurotoxicity by CAR-T Day +30 will be included in this listing.

9.2.2. Sensitivity Analyses

A sensitivity analysis will be performed for the following secondary efficacy endpoint: the incidence of CRS (any grade according to the ASBMT consensus grading system) by CAR-T Day +30 using the Enrolled (RP2D) Analysis Set. The analysis will be conducted using the same methods as described in Section 9.2.1.3. The following summary will be provided:

- Analysis of the Incidence of CRS of Any Grade according to the ASBMT Consensus Grading System by CAR-T Day +30 for All Enrolled Subjects at RP2D

For the listing of all CRS of any grade corresponding to this sensitivity analysis, refer to the listing of All CRS of Any Grade according to the ASBMT Consensus Grading System by CAR-T Day +30 specified in Section 9.2.1.3.

9.2.3. Subgroup Analyses

Not applicable.

9.3. Exploratory Endpoints

9.3.1. Duration of Hospital Stay and ICU Stay

For the analyses of these endpoints, the following rules will be used to determine the hospitalization admission and discharge dates, and ICU admission and discharge dates under certain situations specified below:

- If the hospitalization admission date or ICU admission date is prior to the date of informed consent, use the date of informed consent as the hospitalization admission date or ICU admission date.
- If a subject is hospitalized or in the ICU at the time of study completion, study withdrawal, or death, use the date of study completion, study withdrawal, or death as the hospitalization discharge date or ICU discharge date.

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

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

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

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

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

- Analysis of Duration of Hospital Stay and ICU Stay for All Efficacy Evaluable Subjects

and the following sections will be included in the summary:

- Hospital stay
- ICU stay

The following listing of all hospital stays will be provided with hospitalization admission date, hospitalization discharge date, was the subject admitted to the ICU (Yes or No), ICU admission date, and ICU discharge date:

- Duration of Hospital Stay and ICU Stay

For each subject, if there are multiple hospital stays, each hospital stage will be listed separately. For each hospital stay, if there is no ICU stay, ICU admission date and ICU discharge date will be left blank in the listing. If there is an ICU stay with no hospital stay, hospitalization admission date and hospitalization discharge date will be left blank in the listing. For one hospital stay, if there are multiple ICU stays, the information will be listed in the following format:

Subject Identifier/ Age/ Race	Hospitalization Admission Date	Hospitalization Discharge Date	Was the subject admitted to the ICU?	ICU Admission Date	ICU Discharge Date
10011001/ 17/ White	*Hospitalization Admission Date*	*Hospitalization Discharge Date*	*Yes*	*ICU Admission Date 1*	*ICU Discharge Date 1*
				ICU Admission Date 2	*ICU Discharge Date 2*

9.3.2. Duration of CAR-T-associated Neurotoxicity by CTCAE v5.0

The following summaries will be provided:

- Analysis of Duration of CAR-T-associated Neurotoxicity of Any Grade Defined by CTCAE v5.0 for All Efficacy Evaluable Subjects
- Analysis of Duration of CAR-T-associated Neurotoxicity of Grade or Greater Defined by CTCAE v5.0 for All Efficacy Evaluable Subjects

For each of these analyses, the duration of CAR-T-associated neurotoxicity for each subject will be calculated in the following 2 ways:

- Method 1: duration is defined as the number of days between the start date of the first observed event and the end date of the last observed event.
- Method 2: duration is defined as the number of days between the start date of the first observed event and the end date of the last observed event, excluding the number of days in between on which no event was observed.

For the CAR-T-associated neurotoxicity that is ongoing at study completion, study withdrawal, or death, the date of study completion, study withdrawal or death will be used as the end date of that event.

10. SAFETY

Safety analyses will be performed by dose level for Part 1 and for the phase 2 part of the study, using the Safety Analysis Set, unless otherwise specified. Note that since subjects treated at the RP2D in Part 1 will also be included in the phase 2 part under the 2-stage design, those subjects will be included in the summaries for both Part 1 and the phase 2 part of the study.

10.1. Exposure

10.1.1. Extent of Exposure

A summary of defibrotide exposure will be provided using descriptive statistics:

- Defibrotide Exposure by Study Phase

The following information will be included in the summary:

- Days of defibrotide exposure: number of days on which a subject received at least 1 dose of defibrotide
- Total number of doses received
- Total number of doses received before date of Yescarta
- Total number of doses received on and after date of Yescarta
- Number of doses per day before date of Yescarta:

  [Total number of doses received before date of Yescarta] ÷ [Days of defibrotide exposure before date of Yescarta]

- Number of doses per day on and after date of Yescarta:

  [Total number of doses received on and after date of Yescarta] ÷ [Days of defibrotide exposure on and after date of Yescarta]

- Number of doses per day:

  [Total number of doses received] ÷ [Days of defibrotide exposure]

- Total exposure in mg: total amount of defibrotide received by a subject
- Daily dose in mg/day:

  [Total exposure in mg] ÷ [Days of defibrotide exposure]

- Daily dose in mg/kg/day:

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

The following listing of defibrotide administration will be provided, including the information regarding dose number per 24 hours, was dose given (Yes or No), start date/time, end date/time, dose per administration (unit), was defibrotide given as protocol specified time frame (Yes or No), and reason for delay:

- Defibrotide Administration

For the administration of defibrotide given with lymphodepletion chemotherapy, dose number per 24 hours is not applicable and will be specified as such in this listing.

10.1.2. Treatment Compliance

Not applicable.

10.2. Adverse Events

Adverse events recorded in the CRF will be coded to SOC and PT using MedDRA 21.1. Investigators will assess the relatedness of each AE to defibrotide and to study procedures. The severity of AEs will be recorded using CTCAE, version 5.0.

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

Treatment-related AEs for defibrotide are those for which investigators answer "Yes" to the question "Is this event related to study drug (Defibrotide)?" in the CRF. Events for which investigators do not record relationship to defibrotide will be considered as related to defibrotide for summary purpose (see Section 7.2.4.4). Listings will show treatment-relationship as missing. AEs for which "Yes" is marked for the question "Is this event related to study procedure?" in the CRF will be identified and included in AE listings.

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

A TEAE is defined as any event with a start date on or after the first dose date and up to 30 days after the last dose of defibrotide, or any ongoing event that worsens in severity after the first dose date and up to 30 days after the last dose of defibrotide. Only TEAEs with the onset date through the end of the AE reporting period (30 days after the last dose of defibrotide) will be included in the summaries unless otherwise specified. For the purpose of determining treatment-emergent, incomplete and missing AE start dates will be imputed as specified in Section 7.2.4.1.

See Section 7.2.3.2 for the identification of the AE evaluations at the final safety follow-up visit scheduled on CAR-T Day +37 to be included in the analyses.

10.2.1. Dose-limiting Toxicities

During Part 1 of the study, all TEAEs that occur from the start of the first dose of defibrotide up to 7 days after the last dose of defibrotide will be screened for DLT. The final determination of DLTs will then be made by the SAC from TEAEs considered to have a causal relationship to defibrotide. As an exception, all bleeding TEAEs, regardless of relationship to defibrotide will be evaluated by the SAC as potential DLTs. Because all hemorrhagic events are considered adverse drug reactions of defibrotide, the SAC will review any grade (per CTCAE v5.0) of intracranial hemorrhage and any other hemorrhage of Grade 2 or greater. The SAC will also review all nonhemorrhagic TEAEs of Grade 3 or greater as possible DLTs. Of note, CAR-T-associated neurotoxicity is not a DLT. The number of subjects with DLTs for each cohort in Part 1 will be summarized by cohort using the Safety Analysis Set. The following summary will be provided:

- DLTs by Cohort for Part 1

The following listing of all DLTs for Part 1 will be provided with subject identifier, dose level, SOC, PT, start date, end date, severity grade, seriousness, relationship to defibrotide, relationship to a study procedure, action taken, and outcome of the AE:

- All DLTs for Part 1

10.2.2. Adverse Events

The following summaries of AEs will be provided for all subjects in the Safety Analysis Set:

- TEAEs by PT and by Study Phase
- Serious TEAEs by SOC and PT and by Study Phase
- Treatment-related TEAEs by SOC and PT and by Study Phase
- Serious Treatment-related TEAEs by SOC and PT and by Study Phase
- TEAEs Leading to Defibrotide Discontinuation by SOC and PT and by Study Phase
- Treatment-related TEAEs Leading to Defibrotide Discontinuation by SOC and PT and by Study Phase
- TEAEs Leading to Death by SOC and PT and by Study Phase
- Treatment-related TEAEs Leading to Death by SOC and PT and by Study Phase
- TEAEs by SOC and PT, by Maximum Severity and by Study Phase
- Treatment-related TEAEs by SOC and PT, by Maximum Severity and by Study Phase

Treatment-emergent AEs will be summarized by PT, sorted in descending order of incidence for the phase 2 part of the study. The other AE summaries will be provided by SOC and PT, and SOCs will be ordered alphabetically, with PTs within an SOC sorted in descending order of incidence for the phase 2 part of the study. If a subject has more than 1 AE within a PT, the subject is counted only once at the maximum severity; if a subject has more than 1 AE within an SOC, the subject is counted once at the maximum severity when reporting results for that SOC.

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

- Summary of Treatment-emergent Serious Adverse Events (for Public Disclosure)
- Summary of Treatment-emergent Non-serious Adverse Events Occurring in Greater Than 5% of Subjects

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

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

10.2.3. Adverse Events of Special Interest

As TEAEs of special interest, bleeding events will be summarized by SOC and PT. The MedDRA 21.1 Standardised MedDRA Query (SMQ) Haemorrhage terms (excluding laboratory terms) will be used to search for bleeding events and is provided in Appendix 5. The following summary will be provided:

- TEAEs of Special Interest: Bleeding by SOC and PT and by Study Phase

System organ classes will be ordered alphabetically, with PTs within an SOC sorted in descending order of incidence in the defibrotide prophylaxis arm. If a subject has more than 1 TEAE of special interest within a PT, the subject is counted only once at the maximum severity; if a subject has more than 1 TEAE of special interest within an SOC, the subject is counted once at the maximum severity when reporting results for that SOC.

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

- TEAEs of Special Interest: Bleeding

10.2.4. Summary of Adverse Events

The following summary of AEs will be provided:

- Summary of Adverse Events by Study Phase and Overall

The following information will be included in the summary: the numbers of subjects with at least 1 TEAE, the numbers of subjects with at least 1 serious TEAE, the numbers of subjects with at least 1 treatment-related TEAE, the numbers of subjects with at least 1 serious treatment-related TEAE, the numbers of subjects with at least 1 TEAE of Grade 3 or greater, the numbers of subjects with at least 1 treatment-related TEAE of Grade 3 or greater, the numbers of subjects with TEAEs leading to defibrotide discontinuation, the numbers of subjects with treatment-related TEAEs leading to defibrotide discontinuation, the numbers of subjects with TEAEs leading to death, the numbers of subjects with treatment-related TEAEs leading to death, and the numbers of subjects with at least 1 TEAE of special interest: bleeding.

10.3. Laboratory Assessments

For the following laboratory tests:

- chemistry: blood urea nitrogen, calcium, chloride, direct bilirubin, indirect bilirubin, magnesium, potassium, phosphorus, sodium, total bilirubin, and total protein
- hematology: hematocrit, mean corpuscular volume, basophils (absolute and relative), eosinophils (absolute and relative), relative lymphocyte count, monocytes (absolute and relative), relative neutrophil count, bands (absolute and relative), and blast (absolute and relative)
- coagulation: activated partial thromboplastin time, and international normalized ratio

a shift table of post-baseline results (with respect to the normal range value) from baseline will be provided for each type of laboratory tests:

- Shift Table from Baseline of Selected Laboratory Results with Respect to the Normal Range by Study Phase: Chemistry
- Shift Table from Baseline of Selected Laboratory Results with Respect to the Normal Range by Study Phase: Hematology
- Shift Table from Baseline of Selected Laboratory Results with Respect to the Normal Range by Study Phase: Coagulation

For each laboratory test, the shift table will include change in normal range value from baseline for the worst post-baseline case. Lab values at unscheduled visits, if any, will also be considered, and subjects with both abnormal low and high post-baseline values will be counted twice.

For the following laboratory tests:

- chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, calcium, creatinine, glucose, magnesium, potassium, sodium, and total bilirubin
- hematology: hemoglobin, platelet count, white blood cell count, absolute lymphocyte count, and absolute neutrophil count

a shift table of post-baseline results (in CTCAE v5.0 grade) from baseline will be provided for each type of laboratory tests:

- Shift Table in CTCAE v5.0 Grade from Baseline of Selected Laboratory Results by Study Phase: Chemistry
- Shift Table in CTCAE v5.0 Grade from Baseline of Selected Laboratory Results by Study Phase: Hematology

For each laboratory test, the shift table will include change in CTCAE v5.0 grade from baseline for the worst post-baseline case. Lab values at unscheduled visits, if any, will also be considered.

A listing of abnormal post-baseline lab values for each type of laboratory tests will be provided with specimen collection date/Study Day, test name, result (unit), corresponding normal ranges, and reference range flag:

- Abnormal Post-baseline Laboratory Values: Chemistry
- Abnormal Post-baseline Laboratory Values: Hematology
- Abnormal Post-baseline Laboratory Values: Urinalysis
- Abnormal Post-baseline Laboratory Values: Coagulation

10.4. Vital Signs

For systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature, a shift table of post-baseline results (with respect to the normal range value) from baseline will be provided:

- Shift Table from Baseline of Selected Vital Signs with Respect to the Normal Range by Study Phase

For each vital sign listed above, the shift table will include change in normal range value from baseline for the worst post-baseline case. Vital signs at unscheduled visits, if any, will also be considered, and subjects with both abnormal low and high post-baseline values will be counted twice.

A listing abnormal post-baseline vital sign values will be provided with date of measurement/Study Day, test name, body temperature measurement method (for body temperature only), and result (unit):

- Abnormal Post-baseline Vital Signs

In order to create the shift table and the listing, the following values are considered to represent abnormal vital signs:

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

10.5. Lymphoma Response

Investigator assessed outcome of Yescarta response will be summarized with the following categories: complete response, partial response, stable disease, progressive disease, and not evaluable. For the purpose of the summary, if lymphoma response information is missing for a subject, the subject will be considered to have had progressive disease (Section 7.2.4.5). The following summary will be provided:

- Lymphoma Response by Study Phase

The following listing of lymphoma response will be provided with subject identifier, study part, date of overall response/Study Day/CAR-T Day, overall response, was a PET/CT scan performed (Yes or No), date of PET/CT scan and result (if Yes to was a PET/CT scan performed), was a bone marrow evaluation performed (Yes or No), date of bone marrow evaluation, bone marrow type and was the bone marrow involved with lymphoma (if Yes to was a bone marrow evaluation performed):

- Lymphoma Response

11. PHARMACOKINETIC ANALYSES

11.1. General Considerations

Some minor modifications may be necessary to the planned design of tables, figures, and listings to accommodate data collected during the actual study conduct.

Quantitative variables will be summarized using descriptive statistics (sample size, arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum). Geometric statistics (mean and standard deviation) 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 bio-analytical 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 standard deviations 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.

11.2. Defibrotide Plasma Concentrations

Analyses specified in this section will be performed using the PK Analysis Set.

For each dose level, the defibrotide plasma concentrations will be reported by Nominal Time Point (prior to defibrotide infusion, and 1, 2, 4, 6 and 24 hours post start of defibrotide infusion on CAR-T Day -5; prior to defibrotide infusion, and 2 and 4 hours post start of defibrotide infusion on CAR-T Day 0 and CAR-T Day +7), using descriptive statistics as described in Section 11.1. 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 summary will be provided:

- Defibrotide Plasma Concentrations by Dose Level and Nominal Time Point on CAR-T Day -5, CAR-T Day 0 and CAR-T Day +7

Figures of individual and arithmetic mean defibrotide concentration-time profiles (± standard deviation, as appropriate) using Nominal Time Points (prior to defibrotide infusion, and 1, 2, 4, 6 and 24 hours post start of defibrotide infusion on CAR-T Day -5) will be presented on linear and semi-logarithmic scales by dose level for the CAR-T Day -5 visit. 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 Scale following Defibrotide Infusion on CAR-T Day -5
- Mean Defibrotide Plasma Concentration-time Profile on Semi-logarithmic Scale following Defibrotide Infusion on CAR-T Day -5

A listing of all defibrotide plasma concentrations will be provided:

- Defibrotide Plasma Concentrations

11.3. Defibrotide Pharmacokinetic Parameters

Analyses specified in this section will be performed using the PK Evaluable Analysis Set.

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 the CAR-T Day -5 visit as data permit.

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

All calculations of non-compartmental parameters will be based on actual sampling times for the analysis, but all pre-dose 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:

- Pre-dose sample 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 will be determined from defibrotide plasma concentrations for the CAR-T Day -5 visit:

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 (pre-dose) to time of last quantifiable defibrotide concentration at time "t"
AUC_{0-inf}	Area under the defibrotide plasma concentration-time curve from 0 (pre-dose), extrapolated to infinity by addition of the last quantifiable concentration divided by the elimination rate constant to AUC_{0-t}: $AUC_{0-t} + C_{last} / \lambda_z$
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 divided by AUC_{0-inf}
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 following PK parameters will be calculated for diagnostic or parameter derivation purposes and listed, but will not be summarized.

$t_{1/2}$, Interval	The time interval (in hours) of the log-linear regression to determine λ_z. 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 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 dose level for the CAR-T Day -5 visit using descriptive statistics as described in Section 11.1. Geometric mean will not be calculated for T_{max} and T_{last}. The following summaries will be provided:

- Defibrotide Plasma Pharmacokinetic Parameters by Dose Level on CAR-T Day -5

A listing of all generated individual PK parameters will be provided:

- Defibrotide Plasma Pharmacokinetic Parameters on CAR-T Day -5

12. PHARMACODYNAMIC ANALYSES

Not applicable.

13. COVID-19

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

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

- Subjects Impacted by the COVID-19 Pandemic

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Topp MS, Gökbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapses or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015; 16(1): 57-66.

APPENDIX 1. MEDDRA HIGH LEVEL GROUP TERMS INDICATIVE OF NEUROTOXICITY

The high-level group terms that are indicative of neurotoxicity include (Topp et al. 2015):

Cranial nerve disorders

Deliria, including confusion

Disturbances in thinking and perception

Encephalopathies

Mental impairment disorders

Movement disorders, including Parkinsonism

Neurologic disorders not elsewhere classified (NEC)

Neuromuscular disorders

Personality disorders and disturbances in behavior

Psychiatric disorders NEC

Seizures, including subtypes

APPENDIX 2. CTCAE VERSION 5.0 GRADING FOR NERVOUS SYSTEM DISORDERS AND PSYCHIATRIC DISORDERS

The severity of neurotoxicity events (defined in Appendix 1) should be based on CTCAE v5.0.

Nervous system disorders					
	Grade				
CTCAE Term	1	2	3	4	5
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the abducens nerve (sixth cranial nerve).					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the accessory nerve (eleventh cranial nerve).					
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the acoustic nerve (eighth cranial nerve).					
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Anosmia	Present	-	-	-	-
Definition: A disorder characterized by a change in the sense of smell.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.					
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.					
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.					

Nervous system disorders					
	Grade				
CTCAE Term	1	2	3	4	5
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function.					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent ntervention indicated	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond.					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.					
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (eg, oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.					
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Definition: A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the facial muscles.					
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the facial nerve (seventh cranial nerve).					

Nervous system disorders					
	Grade				
CTCAE Term	1	2	3	4	5
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the glossopharyngeal nerve (ninth cranial nerve).					
Guillain-Barre syndrome	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgen intervention indicated; intubation	Death
Definition: A disorder characterized by the body's immune system attacking the peripheral nervous system causing ascending paralysis.					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.					
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized by excessive sleepiness during the daytime.					
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the hypoglossal nerve (twelfth cranial nerve).					
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.					
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe	Death
Definition: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-

Nervous system disorders					
	Grade				
CTCAE Term	1	2	3	4	5
Definition: A disorder characterized by uncontrolled and purposeless movements.					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evidence on physical exam	Symptomatic; evidence on physical exam; limiting instrumental	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body.					
Muscle weakness right-sided	Symptomatic; perceived by patient but not evidence on physical exam	Symptomatic; evidence on physical exam; limiting instrumental	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body.					
Myasthenia gravis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by weakness and rapid fatigue of any of the skeletal muscles.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the olfactory nerve (first cranial nerve).					
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth.					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by damage or dysfunctionof the peripheral motor nerves.					
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by damage or dysfunction of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (eg, near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
Radiculitis	Mild symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					

Nervous system disorders					
	Grade				
CTCAE Term	1	2	3	4	5
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (eg, thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by paralysis of the recurrent laryngeal nerve.					
Reversible posterior leukoencephalopathy syndrome	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization	Life-threatening consequences	Death
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and/or seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition. Also known as posterior reversible encephalopathy syndrome (PRES).					
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences; prolonged repetitive seizures	Death
Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive sleepiness and drowsiness.					
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening consequences; unable to move active or passive range of motion	Death
Definition: A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
Spinal cord compression	-	-	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by pressure on the spinal cord.					
Stroke	Incidental radiographic findings only	Mild to moderate neurologic deficit; limiting instrumental ADL	Severe neurologic deficit; limiting self care ADL; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					
Tendon reflux decreased	Ankle reflex reduced	Ankle reflex absent; other reflexes reduced	Absence of all reflexes	-	-
Definition: A disorder characterized by less than normal deep tendon reflexes.					
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.					
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trigeminal nerve (fifth cranial nerve).					
Trochlear nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trochlear nerve (fourth cranial nerve).					

Nervous system disorders					
	Grade				
CTCAE Term	1	2	3	4	5
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; FLAIR = fluid-attenuated inversion recovery; ICP = intracranial pressure; PRES = posterior reversible encephalopathy syndrome; SAS = subarachnoid space.

Psychiatric disorders					
	Grade				
CTCAE Term	1	2	3	4	5
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; urgent intervention indicated; new onset	Life-threatening consequences, threats of harm to self or others; urgent intervention indicated	Death
Definition: A disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					

Psychiatric disorders					
	Grade				
CTCAE Term	**1**	**2**	**3**	**4**	**5**
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (eg, hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-being which is disproportionate to events and stimuli.					
Hallucinations	Mild hallucinations (eg, perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by a false sensory perception in the absence of an external stimulus.					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characterized by difficulty in falling asleep and/or remaining asleep.					
Irritability	Mild/ easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable; medical or psychiatric intervention indicated	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized by a decrease in sexual desire.					
Libido increased	Present	-	-	-	-
Definition: A disorder characterized by an increase in sexual desire.					
Mania	Mild manic symptoms (eg, elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (eg, relationship and work difficulties; poor hygiene)	Severe manic symptoms (eg, hypomania; major sexual or financial indiscretions); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behavior and elevation of mood.					
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	-
Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking.					
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (eg, disorganized speech; impaired reality testing)	Severe psychotic symptoms (eg, paranoid; extreme disorganization); hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be still.					
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own life.					

Psychiatric disorders					
	Grade				
CTCAE Term	**1**	**2**	**3**	**4**	**5**
Suicide attempt	-	-	Suicide attempt or gesture without intent to die	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own life.					
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events.

APPENDIX 3. ASBMT CONSENSUS GRADING SYSTEM OF IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) FOR ADULTS

Neurotoxicity	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	Not applicable	Not applicable	Any clinical seizure, focal or generalized that resolves rapidly; or nonconvulsive seizures on electroencephalogram that resolve with intervention	Life-threatening prolonged seizure (> 5 minutes); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	Not applicable	Not applicable	Not applicable	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure/cerebral edema	Not applicable	Not applicable	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema or Cushing's triad

Note: ICANS grade is determined by the most severe event not attributable to any other cause. For example, a patient with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

[a] A patient with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy.

Source: Lee et al. 2019

APPENDIX 4. GRADING OF CRS BY ASBMT CRITERIA

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopression	Requiring multiple vasopressors (excluding vasopressin)
And/or[b]				
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Note: Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading.

[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy, such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with termperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS.

[c] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.

Abbreviations: ASBMT = American Society of Blood and Marrow Transplant; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events.

Source: Lee et al. 2019

APPENDIX 5. MEDDRA 21.1 SMQ HAEMORRHAGE TERMS (EXCL LABORATORY TERMS)

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

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

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

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

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

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

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