Clinical Study Protocol: JZP395-201

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®)
Study Number	JZP395-201
Study Phase:	Phase 2
Product Name:	Defibrotide (defibrotide sodium)
IND Number:	62,118
Indication:	Prevention of Chimeric Antigen Receptor-T-cell-associated Neurotoxicity
Investigators:	Multicenter
Sponsor:	Jazz Pharmaceuticals 3180 Porter Drive Palo Alto, CA 94304
Medical Director:	PI Jazz Pharmaceuticals 3180 Porter Drive Palo Alto, CA 94304 PI

Original Protocol:	09 February 2019

Confidentiality Statement

This study will be conducted under Good Clinical Practice guidelines.

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SYNOPSIS

SPONSOR	Jazz Pharmaceuticals
PRODUCT	Defibrotide (defibrotide sodium)
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®)
STUDY NUMBER	JZP395-201
STUDY PHASE	Phase 2
LOCATION	US multicenter
OBJECTIVES	To assess the safety and efficacy of defibrotide for the prevention of chimeric antigen receptor-T-cell (CAR-T)-associated neurotoxicity.
ENDPOINTS	Primary endpoint: • Incidence of CAR-T-associated neurotoxicity (any grade, defined by Common Terminology Criteria for Adverse Events [CTCAE] v5.0) by CAR-T Day +30 Secondary endpoints: Efficacy • 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 American Society for Blood and Marrow Transplantation (ASBMT) consensus grading system (Lee et al. 2018) by CAR-T Day +30 • Incidence of cytokine release syndrome (CRS; any grade, according to ASBMT consensus grading system [Lee et al. 2018]) by CAR-T Day +30 • Use of high dose steroid by CAR-T Day +30 Safety • Incidence of treatment-emergent adverse events (TEAEs) that occur up to 30 days after the last dose of defibrotide • Incidence of treatment-emergent serious adverse events (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 Pharmacokinetics (PK): • PK of defibrotide Exploratory endpoints: • Biomarker analysis before and after defibrotide • Biomarker analysis before and after Yescarta • Duration of hospital stay and intensive care unit (ICU) stay
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 diffuse large B-cell lymphoma (DLBCL) receiving Yescarta.

This is a 2-part study consisting of a low-dose safety lead-in phase (Part 1) that will determine the final treatment dose to be used in all subsequent eligible subjects (Part 2) to enroll a total of 32 subjects at the final treatment dose.

To ensure the safety of defibrotide administration in this subjects population, Part 1 (lead-in phase) of the study is based on a standard 3+3 design and will evaluate 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 in Figure 1. After the Safety Assessment Committee (SAC) establishes the recommended phase 2 dose (RP2D) based on dose-limiting toxicities (DLTs) during Part 1 of the study, Part 2 will enroll subjects at the RP2D to obtain a total of 29 efficacy evaluable subjects, including subjects in Part 1 who were treated at the RP2D. 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. The Efficacy Evaluable Analysis Set will include:

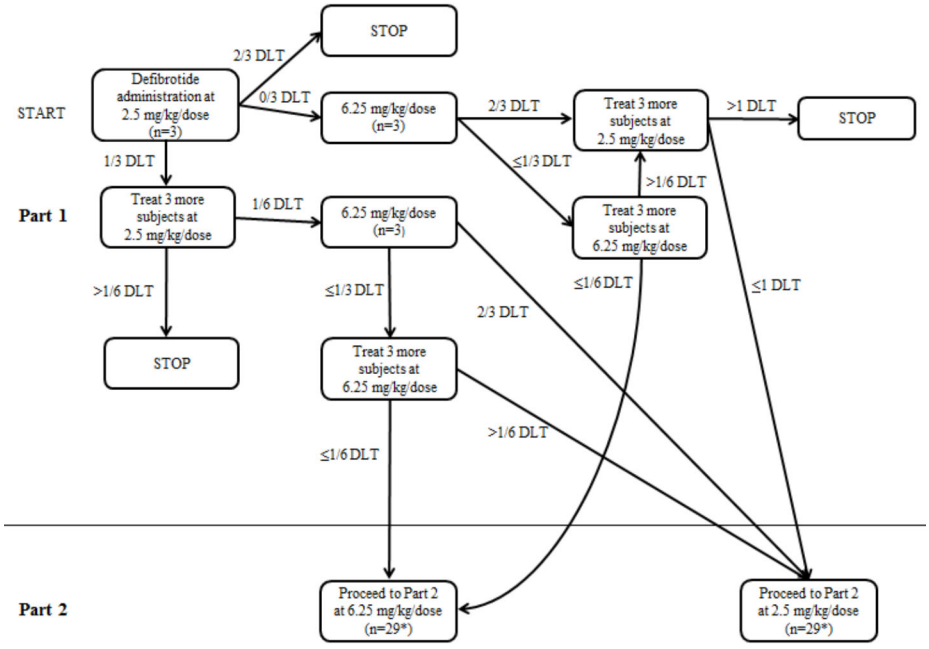
- All subjects who received at least 18 doses (of all 35) of defibrotide and either
  - developed CAR-T-associated neurotoxicity on or before CAR-T Day +30; OR
  - completed the CAR-T Day +30 neurological assessment

AND

- All subjects who discontinued treatment due to post-CAR-T-associated neurotoxicity before receiving 18 doses of defibrotide.

In addition, subjects whose Yescarta infusion is delayed by more than 2 days from the original schedule are considered not evaluable for efficacy

Figure 1: Dose Escalation Algorithm



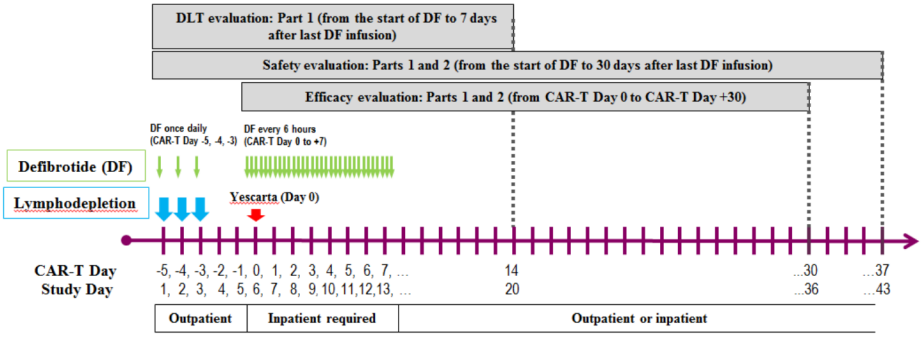
*Efficacy evaluable; subjects in Part 1 treated at the RP2D will be included in the efficacy and safety analyses.
Abbreviations: DLT = dose-limiting toxicity; RP2D = recommended Phase 2 dose.

Safety Assessment Committee

A SAC will be formed for determination of any DLTs during Part 1 of the study. After determination of the RP2D, 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. Definition of Dose-Limiting Toxicity The significant toxicity from CAR-T treatment may not be distinguishable from TEAEs attributable to defibrotide, as the safety profile of defibrotide in this subject 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. **Dose Evaluation and Treatment** Part 1: Lead-in Phase and Determination of RP2D Part 1 of this study is to evaluate the safety of 2.5 mg/kg/dose and 6.25 mg/kg/dose based on a standard 3+3 design. The Sponsor does not plan to evaluate a higher dose. The SAC will determine the RP2D based on DLT determination in Part 1 of the study. Part 2: Evaluating Safety and Efficacy of Defibrotide at the RP2D for Prevention of CAR-T-associated Neurotoxicity A total of 32 subjects (anticipated 29 efficacy evaluable) are to be treated at the RP2D. Subjects treated at the RP2D in Part 1 will be included in the efficacy and safety analyses. The SAC will continue to monitor safety data, including serious and Grade 3 or greater TEAEs throughout Part 2 of the study.
ESTIMATED DURATION OF STUDY	The study is expected to be approximately 21 months in duration, with an estimated enrollment period of 18 months and participation for each subject of approximately 3 months. End of study for each subject is the time at which the subject completes the study or the time of death, lost to follow-up, or early termination from the study, whichever comes first. 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 will be considered to have completed the study on CAR-T Day +60. The study will be considered completed once all enrolled subjects have reached the end of study.
STUDY POPULATION	Approximately 35 to 38 adult subjects are planned for enrollment. Part 1 of the study has the potential to enroll 12 subjects. The 6 subjects in Part 1 treated at the RP2D will be included in the efficacy and safety analyses.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	**Inclusion Criteria** Subjects must meet the following criteria to be enrolled in this study: 1. Subject must be ≥ 18 years of age at signing of informed consent. 2. Subject must be diagnosed with relapsed or refractory DLBCL (including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma) and scheduled to receive treatment with Yescarta. 3. Female subjects of childbearing potential who are sexually active and male

	subjects who are sexually active and have female partners of childbearing potential must agree to use a highly effective method of contraception with their partners during exposure to defibrotide and for 30 days after the last dose of defibrotide. Highly effective methods of contraception include abstinence (when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence, eg, calendar, postovulation, symptothermal methods, and withdrawal are not acceptable methods]), combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (ie, birth control pills, patches, vaginal ring), progestogen-only hormonal contraception associated with inhibition of ovulation (ie, progestin implant or injection), intrauterine device, intrauterine hormone-releasing system, surgical sterilization, and vasectomy (> 6 months before CAR-T Day -5 [Study Day 1]). Surgically sterile women and men and postmenopausal women (ie, women with > 2 years of amenorrhea) do not need to use contraception. 4. Subject must be able to understand and sign written informed consent. **Exclusion Criteria** Subjects who meet any of the following criteria will be excluded from the study: 1. Subject is currently receiving dialysis or expected to receive dialysis. 2. Subject has used any investigational anticancer agent within 3 weeks prior to the first dose of defibrotide, or is using or plans to use any investigational agent during the study. 3. Subject has previously been treated with CAR-T therapy. 4. Hemodynamic instability requiring vasopressors or uncontrolled hypertension with persistent systolic blood pressure > 180. 5. Subject has clinically significant active bleeding, history of intracranial bleeding, or is at risk for intracranial bleeding as determined by the Investigator. 6. Subject plans to use any medication that increases the risk of bleeding, including, but not limited to, systemic heparin, low molecular weight heparin, heparin analogs, alteplase, streptokinase, urokinase, antithrombin III (ATIII), oral anticoagulants including warfarin, and factor Xa inhibitors. Subjects may receive heparin (up to 100 U/kg/day) or other anticoagulants for routine central venous line management and/or intermittent dialysis or ultrafiltration. 7. Subject, in the opinion of the Investigator, may not be able to comply with the study protocol, including appropriate supportive care, follow-up, research tests, and safety monitoring requirements. 8. Subject has a serious active disease or comorbid medical condition, as judged by the Investigator, that is likely to interfere with the conduct of this study. 9. Subject is pregnant or lactating and does not agree to stop breastfeeding. 10. Subject has a known history of hypersensitivity to defibrotide or any of the excipients. 11. Subject has primary central nervous system lymphoma.
TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION	**Test Product:** Defibrotide (Defitelio®) Intravenous solution 200 mg/2.5 mL (80 mg/mL) vial. Note: Study Day 1 is defined as the day of the first defibrotide infusion. In this protocol, the schedule of procedures and assessments will also reference the day relative to the day of CAR-T-cell therapy (Yescarta) infusion (CAR-T Day 0). For example, Study Day 1 of this study will also be referred to as CAR-T Day -5, whereas the day of Yescarta infusion (CAR-T Day 0) will be referred to as Study Day 6. 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).

	Dose and Mode of Administration: Eligible subjects will receive defibrotide (2.5 mg/kg/dose or 6.25 mg/kg/dose) infused intravenously over 2 hours (±15 min). To minimize the endothelial damage from lymphodepletion chemotherapy, defibrotide is to start on the first day (CAR-T Day -5 [Study Day 1]) 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). 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) prior to Yescarta infusion, 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. Each defibrotide dose (infused over a 2 hour ±15 min infusion period) 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 Figure 2. **Figure 2: Defibrotide Dosing**  Abbreviations: CAR-T = chimeric antigen receptor T-cell; DF = defibrotide; DLT = dose-limiting toxicity.
REFERENCE THERAPY	Not applicable
DURATION OF TREATMENT	Defibrotide will be administered for a total of 11 days, as described below: • Once a day for 3 days on CAR-T Days -5, -4, -3 (Study Days 1, 2, 3) during lymphodepletion chemotherapy; • No defibrotide administration on CAR-T Day -2 (Study Day 4) and CAR-T Day -1 (Study Day 5); and • 4 times a day for 8 days on CAR-T Days 0 to +7 (Study Days 6 to 13).
EFFICACY ASSESSMENTS	Efficacy will be assessed through monitoring of subject symptoms, physical examinations, laboratory testing, imaging studies, and electroencephalography to assess neurotoxicity as needed per local standard of care and by recording survival status. Assessment of neurotoxicity will be performed by the local Investigator using the following grading systems: • CTCAE v5.0 • ASBMT consensus grading system (Lee et al. 2018) Steroid use will be assessed by recording all concomitant medications used. Hospital resource use will be assessed by recording hospital and ICU stay days.

PHARMACOKINETICS ASSESSMENTS	Serial blood samples will be obtained from all subjects on CAR-T Day -5 (Study Day 1), CAR-T Day 0 (Study Day 6), and CAR-T Day +7 (Study Day 13). Plasma defibrotide concentrations will be measured using a validated bioanalytical method, and PK of plasma defibrotide will be assessed.
BIOMARKER ASSESSMENTS	Serum cytokines, including markers of endothelial damage, will be analyzed from serial blood samples, which will be collected once daily on CAR-T Days -5 and -3 (Study Days 1 and 3) and once every other day starting from CAR-T Day 0 (Study Day 6) to discharge but not beyond CAR-T Day +14. In addition, blood collection will be performed once on CAR-T Day +14 (±3 days) and on CAR-T Day +30 (±3 days), which may be performed either in the hospital or as an outpatient.
SAFETY ASSESSMENTS	The DLT assessment period is from the start of the first dose of defibrotide to 7 days after the last dose of defibrotide during Part 1 of the study. In addition, through Part 1 and Part 2, safety will be assessed through monitoring of adverse events (AEs) and serious adverse events (SAEs) from the signing of informed consent to 30 days after the last dose of defibrotide. Other safety assessments include vital signs, physical examinations, clinical laboratory tests, and Eastern Cooperative Oncology Group performance status. Disease status of DLBCL will be assessed by modified International Working Group criteria (Cheson et al. 2016).
STATISTICAL ANALYSIS	The primary objective of the study is to assess the efficacy of defibrotide for the prevention of CAR-T-associated neurotoxicity by CAR-T Day +30. 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. A Simon's optimal 2-stage design is employed to test the response rate of administration with defibrotide in the target subject population (Simon 1989). The historical rate of CAR-T-associated neurotoxicity post-CAR-T-cell therapy is 64% (Neelapu et al. 2017); it is hypothesized that administration with defibrotide will reduce this incidence by half, to a CAR-T-associated neurotoxicity rate of 32% by CAR-T Day +30 (ie, a no CAR-T-associated neurotoxicity rate of 68%). The sample size calculation is based on testing the null and alternative hypotheses with an overall 1-sided Type I error of 0.05 and a statistical power of at least 92% when the no CAR-T-associated neurotoxicity rate is ≥ 68%. In the first stage, 10 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 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. Estimation of the no CAR-T-associated neurotoxicity rate will use the method of Koyama and Chen (Koyama & Chen 2008), which incorporates the 2-stage design. The corresponding confidence interval and the p-value will also be calculated using the method of Koyama and Chen. A sensitivity analysis will be performed for the primary efficacy endpoint using all enrolled subjects treated at the RP2D. The total sample size 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 1 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 noneligible for the efficacy evaluation, a planned maximum total of 38 subjects will be required.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANG2	Angiopoietin-2
aPTT	Activated partial thromboplastin time
ASBMT	American Society of Blood and Marrow Transplant
AST	Aspartate aminotransferase
ATIII	Antithrombin III
BiPAP	Bilevel positive airway pressure
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T-cell
CAR-T Day 0	The day of Yescarta infusion
CEC	central ethics committees
CFR	Code of Federal Regulations
CI	Confidence interval
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CR	Complete response
CRO	Contract Research Organization
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
D5W	5% dextrose in water
DF	Defibrotide
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity

DMP	Data Management Plan
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EEG	Electroencephalography
EU	European Union
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
HLGT	High Level Group Term
H_a	Alternative hypothesis
H_o	Null hypothesis
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
ICF	Informed consent form
ICH	International Council for Harmonisation
ICP	Intracranial pressure
ICU	Intensive care unit
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IL-1	Interleukin 1
IL-6	Interleukin 6
IL-8	Interleukin 8
IL-15	Interleukin 15
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

NA	Not applicable
NCSE	Nonconvulsive status epilepticus
NE	Not evaluable
NEC	Not elsewhere classified
NO	Nitric oxide
PAI-1	Plasminogen activator inhibitor-1
PD	Progressive disease
PET	Positron emission tomography
PGE_2	Prostaglandin E2
PGI_2	Prostaglandin I2
PK	Pharmacokinetic(s)
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
QD	Once dailiy
QID	4 times a day
RP2D	Recommended Phase 2 dose
SAC	Safety Assessment Committee
SAE	Serious adverse event
SAS	Subarachnoid space
SD	Stable disease
SOC	System Organ Class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFPI	Tissue factor pathway inhibitor
TNF-α	Tumor necrosis factor alpha
t-PA	Tissue plasminogen activator
TM	Thrombomodulin
US	United States
VCAM-1	Vascular cell adhesion molecule-1

VOD	Veno-occlusive disease
vWF	von Willebrand factor
WBC	White blood cell

1. INTRODUCTION

1.1. Background and Rationale

1.1.1. Defibrotide

Defibrotide (Defitelio®) will be investigated for the prevention of chimeric antigen receptor T-cell (CAR-T)-associated neurotoxicity in adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) receiving axicabtagene ciloleucel (Yescarta®). Defibrotide is a highly complex polydisperse collection of predominantly single-stranded polydeoxyribonucleotides prepared by controlled depolymerization of DNA from porcine intestinal tissue. While the mechanism of action of defibrotide has not been fully elucidated, nonclinical and clinical data have shown that defibrotide protects endothelial cells. Defibrotide (defibrotide sodium; brand name Defitelio) has been approved in the US and Canada for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, with evidence of renal or pulmonary dysfunction following hematopoietic stem cell transplantation (HSCT). Defibrotide is also currently marketed in Europe, Israel, and South Korea with the brand name Defitelio for the treatment of severe hepatic VOD post-HSCT therapy.

1.1.2. CAR-T-cell Therapy and Associated Complications

Engineering the T-cells with genetically modified chimeric antigen receptor (CAR) targeting cancer antigen revolutionized the way B-cell neoplasm is treated. Currently, 2 products have been approved by the US Food and Drug Administration (FDA) for the treatment of this condition. One is tisagenlecleucel (Kymriah® [Novartis]) for patients ≤ 25 years of age with B-cell acute lymphoblastic leukemia that is refractory or in second or later relapse and for adult patients with relapsed or refractory DLBCL after 2 or more lines of systemic therapy (Kymriah US Prescribing Information, 2018). Another is axicabtagene ciloleucel (Yescarta [Kite Pharma/Gilead]) for adult patients with relapsed or refractory DLBCL after 2 or more lines of systemic therapy (Yescarta US Prescribing Information).

While such an approach with a unique mechanism of action can induce rapid and durable clinical responses, it is often associated with a serious complication called cytokine release syndrome (CRS). Cytokine release syndrome is characterized by high fever, hypotension, hypoxia and/or multiorgan toxicity. CAR-T-associated neurotoxicity is another common toxicity observed after CAR-T-cell therapy. This toxicity was once referred to as “CAR-T related encephalopathic syndrome” (Neelapu et al. 2018), and most recently referred to as “immune effector cell associated neurotoxicity syndrome (ICANS)” in the American Society of Blood and Marrow Transplant (ASBMT) consensus guideline (Lee et al. 2018). In this protocol we use the most widespread and self-explanatory term “CAR-T-associated neurotoxicity” to describe this condition.

1.1.2.1. Incidence of CAR-T-associated Neurotoxicity and CRS

The incidence and severity of toxicities reported varied in different multicenter trials. Whether this variation is because of differences in trial designs, subject populations, disease types, the

toxicity grading systems used, or the CAR-T-cell platform is currently unclear. In the pivotal multicenter Phase 2 trial (ZUMA-1 Trial) of axicabtagene ciloleucel in 101 subjects with large B-cell lymphoma, DLBCL, and primary mediastinal B-cell lymphoma or transformed follicular lymphoma, the incidence rates of any grade CAR-T-associated neurotoxicity, Grade 3 or greater CAR-T-associated neurotoxicity, and CRS were 64%, 28%, and 13%, respectively, according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (Neelapu et al. 2017). Conversely, in an interim analysis of the JULIET trial of tisagenlecleucel in 51 subjects with relapsed or refractory DLBCL, the rates of Grade 3 or greater CAR-T-associated neurotoxicity and CRS were 13% and 26%. Of note, the grading systems for CRS differed between these 2 trials.

1.1.2.2. Presentation and Pathophysiology of CAR-T-associated Neurotoxicity

CAR-T-associated neurotoxicity typically manifests as a toxic encephalopathy, with the earliest signs being diminished attention, language disturbance, and impaired handwriting. Other symptoms and signs include confusion, disorientation, agitation, aphasia, somnolence, and tremors. In severe cases of CAR-T-associated neurotoxicity (greater than Grade 2), seizures, motor weakness, incontinence, mental obtundation, increased intracranial pressure, papilledema, and cerebral edema can also occur. The manifestation of CAR-T-associated neurotoxicity can be biphasic; the first phase occurs concurrently with high fever and other CRS symptoms, typically within the first 5 days after cellular immunotherapy, and the second phase occurs after the fever and other CRS symptoms subside, often beyond 5 days after cell infusion. Notably, delayed neurotoxicity with seizures or episodes of confusion occurred during the third or fourth week after CAR-T-cell therapy in approximately 10% of patients. The pathophysiological mechanism underlying CAR-T-associated neurotoxicity remains to be determined. Two potential explanations can be postulated. Firstly, passive diffusion of cytokines into the brain supported by the finding that high serum levels of interleukin 6 (IL-6) and interleukin 15 (IL-15) are associated with severe neurotoxicity in patients treated with CAR-T-cell therapy. Secondly, trafficking of T-cells into the central nervous system (CNS), as indicated by the detection of CAR-T cells in cerebrospinal fluid (CSF) from patients with neurotoxicity, in the absence of malignant CNS disease. Indeed, in 1 study, CAR-T-cell numbers were found to be significantly higher in CSF from patients with neurotoxicity versus those without neurotoxicity ($p=0.0039$). The numbers of circulating CAR-T cells also tend to be higher in patients who develop neurotoxicity than in those who do not. Of note, protein levels in the CSF are usually elevated in patients with CAR-T-associated neurotoxicity, compared with baseline measurements, suggesting disruption of the blood-brain barrier. Other organ dysfunctions (hepatic and renal), as well as hypoxemia, and infection, might also contribute to the encephalopathy.

The incidence of nonconvulsive status epilepticus (NCSE) in patients treated with CAR-T-cell therapy is approximately 10%, with some patients (< 5%) developing NCSE after convulsive status epilepticus. Seizure prophylaxis with levetiracetam 750 mg orally or intravenously every 12 hours is recommended for 30 days, starting on the day of infusion for patients undergoing CAR-T-cell therapies that are known to cause CAR-T-associated neurotoxicity (Keppra US Prescribing Information, 2017). Levetiracetam is the preferred agent for seizure prophylaxis because it has a better drug-drug interaction profile and lower risk of cardiotoxicity compared with those of other antiepileptic agents, and can be administered safely to patients with hepatic dysfunction; although, dose adjustments might be needed for those with renal

dysfunction. Furthermore, cytokine levels are not affected by levetiracetam treatment. Of note, not all CAR or T-cell receptor-engineered T-cell products have been associated with CAR-T-associated neurotoxicity. Thus, for patients undergoing treatment with new agents that have an unknown risk of CAR-T-associated neurotoxicity, seizure prophylaxis can be omitted until data from initial clinical trials have been analyzed. Magnetic resonance imaging (MRI) and computed tomography scans of the brain are usually negative for any anatomical pathology that would account for the neurotoxicity symptoms observed in patients treated with CAR-T-cell therapy, although rare cases of reversible T2/fluid attenuated inversion recovery MRI hyperintensity (involving the thalami, dorsal pons, and medulla) and cerebral edema have been reported. Of note, life-threatening cerebral edema, although very rare in patients treated with cellular immunotherapy, tends to have a very rapid course with ensuing brain death within 24 hours. Notably, in March 2017, 5 deaths attributed to cerebral edema were reported following treatment of patients with 1 anti-CD19 CAR-T-cell product (JCAR015) as part of a multicenter clinical trial. The sponsor (Juno Therapeutics/Celgene) has now halted development of this agent. Why deaths relating to cerebral edema have been observed with certain anti-CD19 CAR-T-cell products but not others remains unclear. Additional investigations are needed to better understand the pathophysiology of this fatal complication, for which anti-IL-6 therapy is not effective.

A recent humanized mouse model of anti-CD19 CAR-T-cell gives some insight into this matter. (Norelli et al. 2018) The team treated humanized mice with high leukemia burden with anti-CD19 CAR-T cells. In this model they observed CAR-T-cell-mediated clearance of cancer triggered high fever and elevated IL-6 levels, which are hallmarks of CRS. Human monocytes were the major source of interleukin 1 (IL-1) and IL-6 during CRS. Accordingly, the syndrome was prevented by monocyte depletion or by blocking IL-6 receptor with tocilizumab. Nonetheless, tocilizumab failed to protect mice from delayed lethal neurotoxicity, characterized by meningeal inflammation. Instead, the IL-1 receptor antagonist anakinra abolished both CRS and neurotoxicity, resulting in substantially extended leukemia-free survival. This study suggests the important role of IL-1 in CAR-T-associated neurotoxicity, but also confirms that the cytokine diffusion appears to play a role in CAR-T-associated neurotoxicity.

1.1.2.3. Grading of CAR-T-associated Neurotoxicity

Previous reports on neurotoxicity related to CAR-T-cell therapy have typically graded neurotoxocity based on CTCAE. Sections of “Nervous sytem disorders” and “Psychiatric disorders” apply to this condition (Appendix 3).

Since the grading system was not designed for CAR-T-associated neurotoxicity, Neelapu et al. proposed a new grading system of CAR-T-associated neurotoxicity based on a new (but mini-mental status examination based) assessment tool called CARTOX10 (Neelapu et al. 2018). More recently, ASBMT issued a new consensus guideline for assessment and grading of CAR-T-associated neurotoxicity based on the CARTOX10. Refer to Appendix 4 for details.

1.1.2.4. Management of CAR-T-associated Neurotoxicity

Early CAR-T-associated neurotoxicity that occurs with CRS may respond to tocilizumab, and thus, tocilizumab is recommended when CRS is present. However, the efficacy of tocilizumab in CAR-T-associated neurotoxicity is generally limited and is usually ineffective in

CAR-T-associated neurotoxicity that is observed after CRS. Therefore, the mainstay of the treatment of CAR-T-associated neurotoxicity is corticosteroid use. The approach to CAR-T-associated neurotoxicity is not fully established, but Neelapu et al. suggests the use of corticosteroid for Grade 2 or higher toxicity (Neelapu et al. 2018). Given the possible rapid clinical deterioration, hospitalization is recommended for any grade CAR-T-associated neurotoxicity, and intensive care unit (ICU) stay is recommended for Grade 3 or greater CAR-T-associated neurotoxicity.

1.1.2.5. Presentation and Pathophysiology of CRS

Cytokine release syndrome, the most common toxicity of cellular immunotherapy, is triggered by the activation of T-cells on engagement of their T-cell receptors or CARs with cognate antigens expressed by tumor cells. The activated T-cells release cytokines and chemokines as do bystander immune cells. Cytokine release syndrome typically manifests with constitutional symptoms, such as fever, malaise, anorexia, and myalgias, but can affect any organ system in the body, including cardiovascular, respiratory, integumentary, gastrointestinal, hepatic, renal, hematological, and nervous systems. Findings have demonstrated that high serum levels of IL-6, soluble glycoprotein 130, interferon gamma (IFNγ), IL-15, interleukin 8 (IL-8), and/or interleukin 10 either before or 1 day after CAR-T-cell infusion are associated with subsequent development of severe CRS.

Patient hospitalization with close monitoring is recommended for at least 7 days after CAR-T-cell infusion. Owing to a high risk of arrhythmias, cardiac monitoring by telemetry is advised from the time of CAR-T-cell infusion until resolution of any emergent CRS symptoms. Additional investigations, such as chest radiography, electrocardiography, echocardiography, electroencephalography (EEG), and imaging studies, can be performed as needed, depending on the toxicities that arise. For detailed grading system, refer to Section 1.8.3.

1.1.2.6. Management of CRS

Strong positive correlations of peak blood CAR-T-cell levels and serum IL-6 levels with the severity of CRS after CAR-T-cell therapy have been reported. Together with the approval of tisagenlecleucel, the FDA approved tocilizumab (marketed as Actemra® [Genentech]) for the treatment of CAR-T-cell-induced severe or life-threatening CRS in adult and pediatric patients (> 2 years of age) (Actemra US Prescribing Information, 2018). The approval was based on a retrospective study of 45 subjects treated with Yescarta. Median time from CRS to tocilizumab was 4 days. Resolution of CRS (lack of fever and off vasopressor for 24 hours) was observed within 14 days in 69%. Use of tocilizumab does not seem to affect the efficacy of CAR-T-cell therapy, in terms of response rates or the durability of responses.

General supportive care plays a significant role in the management of CRS including hydration, antipyrexias, antibiotics, oxygen supplementation and ICU monitoring. In addition, use of tocilizumab is considered generally depending on the grade of CRS and duration. Tocilizumab is usually considered for persistent Grade 1 CRS > 3 days despite supportive care, persistent Grade 2 CRS > 6 hours despite supportive care, and any Grade 3 or 4 CRS. Corticosteroid is also considered for CRS of Grade 2 to 4 not responding to tocilizumab. However, this is an example of the way to use tocilizumab, and should not be used as a guidance at each clinical setting.

Corticosteroids suppress inflammatory responses. However, because corticosteroids suppress T-cell function and/or induce T-cell apoptosis, use of these drugs should be avoided for other indications (such as premedication for blood transfusions) after adoptive T-cell therapy. But preliminary data suggest that corticosteroid use for the management of toxicities resulting from CAR-T-cell therapy does not affect objective and complete response (CR) rates, or the durability of responses. In any case, given these concerns, the use of corticosteroids is generally considered only when the toxicities of CAR-T-cell therapy are refractory to anti-IL-6 therapy.

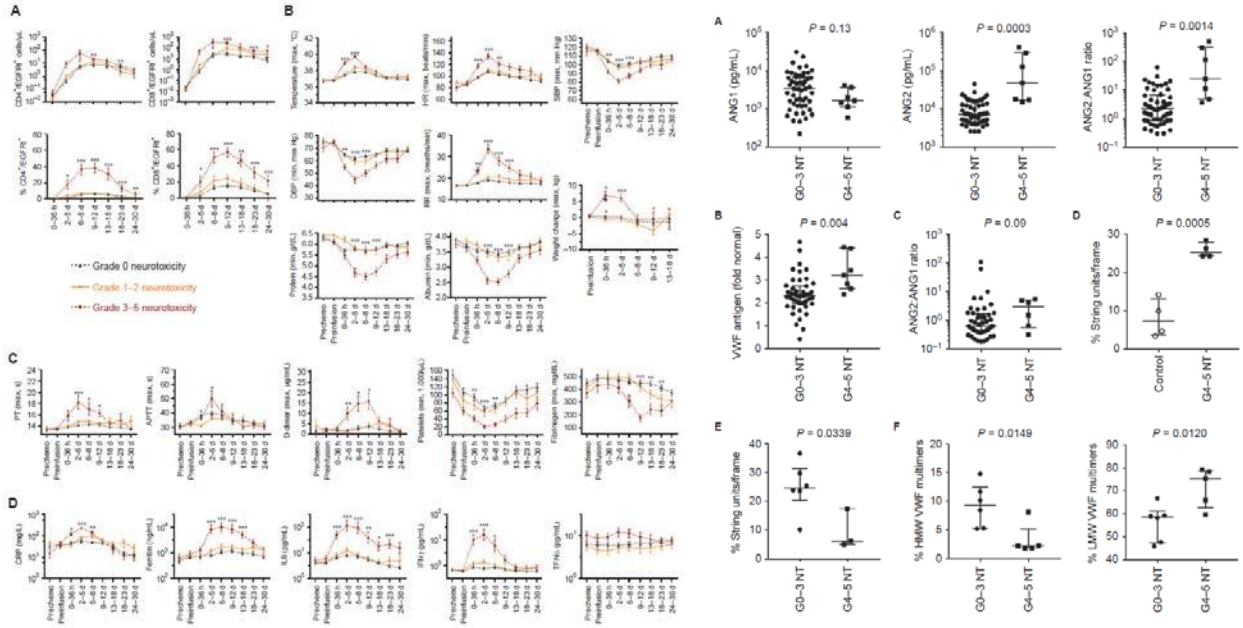
1.1.2.7. Endothelial Damage in CRS and CAR-T-associated Neurotoxicity

Emerging evidence suggests that the endothelial damage plays an important role in development and progression of both CRS and CAR-T-associated neurotoxicity (Gust et al. 2017; Hay et al. 2017; Santomasso et al. 2018).

Hay et al. analyzed the kinetics and biomarkers of severe CRS after CD19-CART-cell therapy (Hay et al. 2017). In 133 subjects analyzed, CRS developed in 70% of subjects (Grade 1, 26%; Grade 2, 32%; Grade 3, 4.5%; Grade 4, 3.8%; and Grade 5, 3.8%). A large panel of serum biomarkers was analyzed during this period of treatment with CAR-T cells, and it was found that severe CRS was associated with elevated levels of angiopoietin-2 (ANG2) and von Willebrand factor (vWF), which are released from Weibel-Palade bodies on endothelial activation. These cytokines are elevated in severe illnesses including infection or thrombotic microangiopathy, and are related to poor outcomes. This is in accordance with the clinical characterization of severe CRS with hemodynamic instability, capillary leak and consumptive coagulopathy. It should be noted that the levels of these biomarkers are elevated not only during CRS but also before lymphodepletion in subjects who subsequently developed CRS.

The same group also performed analysis focusing on CAR-T-associated neurotoxicity (Gust et al. 2017). In this study, 7 (5%) subjects developed Grade 4 or greater neurotoxicity, and 4 subjects died with neurotoxicity including multifocal brainstem hemorrhage with edema, acute cerebral edema and cortical laminar necrosis. With the exception of these fatal cases and 1 subject whose Grade 1 neurotoxicity persisted over 2 months, neurotoxicity completely resolved in all subjects by Day 28. Severe CAR-T-associated neurotoxicity is associated with disseminated intravascular coagulation, capillary leak, and increased blood-brain barrier permeability. Similar to the analysis of CRS, ANG2 and vWF levels were higher in subjects who developed severe neurotoxicity (Grade 4 or greater) than in those with no or mild toxicity (Grade 0 to 3) (Figure 3). In addition, they evaluated cytokine concentrations in paired blood and CSF samples, obtained before lymphodepletion and during acute neurotoxicity. During acute neurotoxicity, concentrations of IFNɣ, tumor necrosis factor alpha (TNF-α), IL-6, and TNF receptor p55 had increased markedly and were comparable between serum and CSF, suggesting that the blood-brain barrier did not prevent high plasma cytokine concentrations from transitioning into CSF or that there was local cytokine production in the CSF.

Figure 3: Changes in the Serum Cytokine Levels During Treatment Per CAR-T-associated Neurotoxicity Grade



Upon autopsy of 2 patients who developed fatal CRS and CAR-T-associated neurotoxicity, multifocal microhemorrhages and patchy parenchymal necrosis in the pons, medulla, and spinal cord were observed. Intravascular vWF binding and CD61+ platelet microthrombi were observed, consistent with endothelial activation (Gust et al. 2017).

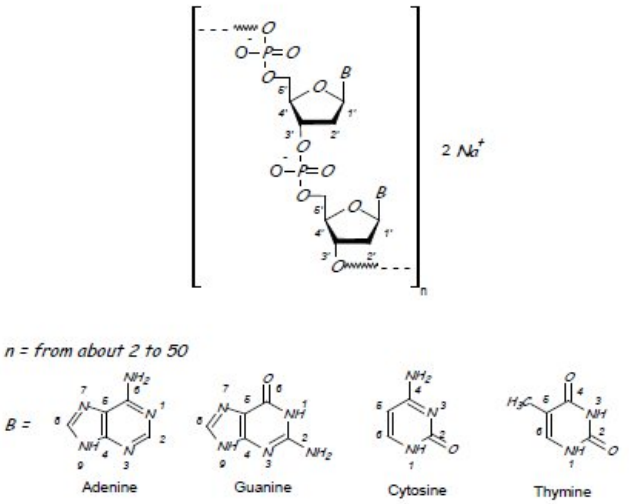
More recently, the group of Memorial Sloan Kettering Cancer Center published the detailed description of neurologic symptoms, blood, CSF, and neuroimaging correlates of neurotoxicity associated with CD19 CAR-T cells (Santomasso et al. 2018). The results suggest novel links between systemic inflammation and characteristic neurotoxicity symptoms. One important aspect of the mechanisms of neurotoxicity is the disruption of blood-CSF barrier. This finding also indicates that the endothelial damage is strongly associated with the development of neurotoxicity after CAR-T-cell therapy.

1.2. Defibrotide's Protective Effect on Endothelial Cells

1.2.1. Chemical Structure of Defibrotide

Defibrotide is a highly complex polydisperse collection of polydeoxyribonucleotides (predominantly single stranded and approximately 10% double stranded) that is purified from the porcine intestinal mucosa (Figure 4). It is believed that defibrotide has pleiotropic biologic effect leading to the stabilization of endothelial cells.

Figure 4: Chemical Structure of Defibrotide



1.2.2. Mechanism of Action of Defibrotide

Defibrotide sodium is an oligonucleotide mixture with demonstrated actions on multiple pathways affecting endothelial homeostasis. Endothelial cell activation promotes thrombogenesis, fibrinogenesis, leukocyte and platelet adhesion, vasoconstriction, and vascular permeability. Excessive endothelial cell activation (endothelial dysfunction) can become a liability to the host. Defibrotide reduces endothelial cell activation by mechanisms that are antithrombotic, fibrinolytic, anti-adhesive, and anti-inflammatory, thereby restoring the thrombotic-fibrinolytic balance and preserving endothelial homeostasis (Coccheri et al. 1988; Cella et al. 2001; Falanga et al. 2003; Corbacioglu et al. 2004; Benimetskaya et al. 2008; Echart et al. 2009; Pescador et al. 2013).

Defibrotide sodium has demonstrated antithrombotic and fibrinolytic properties. In vitro, defibrotide increases tissue plasminogen activator (t-PA) and thrombomodulin (TM) expression, enhancing the enzymatic activity of plasmin to hydrolyze fibrin clots. It also decreases vWF and plasminogen activator inhibitor-1 (PAI-1) expression, resulting in a decrease in procoagulant activity (by reducing endothelial cell activation) and an increase in the fibrinolytic potential of endothelial cells. Defibrotide sodium increases systemic tissue factor pathway inhibitor (TFPI) in clinical and nonclinical settings (Coccheri et al. 1988; Cohen et al. 1989; Zhou et al. 1994; Coccheri & Nazzari 1996; Falanga et al. 2003; Echart et al. 2009; Umemura et al. 2016).

In vitro, defibrotide inhibits leukocyte adhesion to endothelium by suppressing P-selectin and vascular cell adhesion molecule-1 (VCAM-1) and by interfering with lymphocyte function-associated antigen 1-intercellular adhesion molecule mediated leukocyte transmigration. Platelet adhesion is inhibited via increases in nitric oxide (NO), Prostaglandin I2 (PGI_2) and Prostaglandin E2 (PGE_2) (Biagi et al. 1991; Ferraresso et al. 1993; Vera et al. 2018).

Anti-inflammatory properties have been demonstrated with defibrotide that attenuates the production of inflammatory mediators such as IL-6, thromboxane A2, leukotriene B4, TNF-α, and reactive oxygen species (Ferraresso et al. 1993; Bracht & Schror 1994; Palomo et al. 2011; Yakushijin et al. 2018).

Defibrotide also protected endothelial cells from damage caused by chemotherapy-related toxicities. In vitro, defibrotide decreases fludarabine-mediated apoptosis of endothelial cells while maintaining its anti-leukemic effect (Eissner et al. 2002). Additionally, defibrotide inhibits the expression of heparanase, contributing to extracellular matrix integrity and, thereby, tissue homeostasis (Barash et al. 2018).

1.3. Overview of Defibrotide Clinical Development

The clinical program for defibrotide spans more than 20 years, with clinical studies evaluating the safety and efficacy of defibrotide for the treatment of adult and pediatric subjects with hepatic VOD (beginning in April 2000) and for the prevention of hepatic VOD in high-risk pediatric subjects (starting in January 2006). Additional clinical pharmacology studies have evaluated defibrotide in healthy and renally impaired subjects and have evaluated the effect of defibrotide on QTc intervals.

The defibrotide clinical development program includes 2 ongoing clinical studies in a post-HSCT setting. The first is a Phase 3 randomized study (Study 15-007) that is evaluating the efficacy and safety of defibrotide in the prevention of VOD in adult and pediatric subjects undergoing HSCT. The second is a Phase 2 randomized study (Study JZP963-201) that is evaluating the efficacy and safety of defibrotide added to standard of care immunoprophylaxis for the prevention of acute graft-versus-host disease in adult and pediatric subjects.

For additional information on the defibrotide clinical development program, refer to the Investigator's Brochure (IB) for defibrotide.

1.4. Clinical Experience on Safety of Defibrotide

The primary clinical safety information for defibrotide comes from 3 studies evaluating defibrotide in a VOD treatment setting (Studies 2005-01, 99-118, and 2006-05) and 1 study evaluating defibrotide in the VOD prevention setting (Study 2004-000592-33). The administration doses and durations of treatment are described in Table 1.

Table 1: Defibrotide Administration Dose and Duration of Treatment – Clinical Studies

Study Number	Study Objective(s)	Defibrotide Dosage Regimen; Route of Administration	Number of Subjects Who Received Defibrotide	Duration of Treatment
2005-01	Safety and efficacy of DF vs. historical control in the treatment of severe VOD	DF 25 mg/kg/day IV (in 4 divided doses)	102	Minimum 21 days (range: 1 to 83 days)
99-118	Safety and efficacy, dose-finding 25 mg/kg/day or 40 mg/kg/day in treatment of severe VOD	DF 10 mg/kg/day IV (Day 1) followed by DF 25 mg/kg/day IV or DF 40 mg/kg/day IV. Regimen for all subjects: in 4 divided doses, each over 2 hours	149 total: 75 DF 25 mg/kg/day 74 DF 40 mg/kg/day	Minimum 14 days
2004-000592-33	DF vs. control in the prevention of hepatic VOD	DF 25 mg/kg/day IV (in 4 divided doses, each over 2 hours)	180	Median duration: 35 days (from start of conditioning until 30 days HSCT)
2006-05	Safety and efficacy in subjects with severe VOD	DF 25 mg/kg/day IV (in 4 divided doses, each over 2 hours)	1154	Minimum 21 days

Abbreviations: DF = defibrotide; HSCT = hemopoeitic stem cell transplantation; IV = intravenous; VOD = veno-occlusive disease.

As reported in the pooled safety population (Studies 2005-01 and 99-118), the most frequent adverse events (AEs; incidence ≥ 10% and independent of causality) observed during the treatment of hepatic VOD were hypotension, diarrhea, vomiting, nausea, and epistaxis. The most common serious adverse events (SAEs; incidence ≥ 5% and independent of causality) were hypotension (11%) and pulmonary alveolar hemorrhage (7%). Hemorrhage events of any type and any grade were reported for 104 (59%) of the subjects, and the events were Grade 4 to 5 in 35 (20%) of the subjects. There were no clinically important influences of gender, race, or body mass index on the overall incidence of hemorrhage. One case of an anaphylactic reaction was reported in a subject who had received previously marketed formulation of defibrotide for chronic venous insufficiency. In Study 2006-05, reports of hemorrhage (any type, any grade) were received for 339 (29.4%) of the 1154 subjects treated with defibrotide, with more hemorrhagic events reported in adults (32.4%) than in children (27.4%). The most commonly reported hemorrhage AEs were pulmonary hemorrhage and gastrointestinal hemorrhage, reported in 73 (6.3%) and 55 (4.8%) subjects, respectively. Overall, the results from this

expanded access study were consistent with safety profile from Studies 2005-01 and 99-118. In the VOD treatment studies, more than 50% of subjects were children. The frequency, nature, and severity of adverse reactions in children were comparable with those in adults. In doses above the recommended dose of 25 mg/kg/day, higher dose (above 25 mg/kg/m^2) was numerically associated with higher rate of bleeding events observed, but since many events occurred in the follow-up period, a clear relationship with defibrotide treatment could not be determined.

In the prevention of VOD setting (Study 2004-000592-33), the most commonly reported AEs during the prophylactic phase of the study were typical for a high-risk pediatric population undergoing HSCT and were generally balanced between the study arms. The overall incidence of AEs was similar between subjects who received defibrotide prophylaxis and subjects in the control arm who received no VOD prophylaxis. The incidence of SAEs was somewhat higher in the defibrotide prophylaxis arm compared with the control arm during the prophylactic phase of the study (53% vs. 45%); however, the majority of SAEs were considered unrelated to defibrotide. Related SAEs were reported in 4% of subjects receiving defibrotide prophylaxis, and were generally hemorrhagic events. One subject had an AE leading to death that was considered possibly related to defibrotide prophylaxis (gastrointestinal hemorrhage). One subject in the control arm also died from a gastrointestinal hemorrhage during the prophylactic phase of the study. There was no meaningful difference in the incidence of any specific hemorrhage event or in the overall incidence of hemorrhage between the defibrotide prophylaxis arm (18%) and the control arm (14%). Defibrotide was generally safe and well tolerated in this study.

For additional information, refer to the IB for defibrotide.

1.5. Hypothesis and Nonclinical Experience

The Sponsor hypothesizes that the use of defibrotide during CAR-T-cell therapy can contribute to the stabilization of endothelial cells, thereby reducing the incidence of severe CAR-T-associated neurotoxicity and CRS without affecting the anti-lymphoma effect of CAR-T-cell therapy.

While there is no direct nonclinical experience with defibrotide in the context of CAR-T-associated neurotoxicity, a number of in vitro and in vivo studies have demonstrated that defibrotide decreases endothelial cell activation and damage. Defibrotide modulates the activity and expression of thrombogenic and inflammatory mediators that are produced in response to endothelial cell or leukocyte activation. Defibrotide is hypothesized to reduce clotting and formation of microthrombi, as administration of defibrotide increases t-PA and TM expression, enhances the enzymatic activity of plasmin to hydrolyze fibrin clots, and decreases vWF and PAI-1. Defibrotide increases systemic TFPI in clinical and nonclinical settings. Platelet adhesion is inhibited via increases in NO, PGI_2, and PGE_2.

Anti-inflammatory properties have been demonstrated with defibrotide that attenuate the release of inflammatory mediators such as IL-6, thromboxane A2, leukotriene B4, TNF-α, and reactive oxygen species that are produced in response to endothelial cell or leukocyte activation (Ferraresso et al. 1993; Bracht & Schror 1994; Palomo et al. 2011; Yakushijin et al. 2018). Defibrotide inhibits leukocyte adhesion to endothelium by suppressing P-selectin (Scalia et al. 1996) and VCAM-1 (Vera et al. 2018). Defibrotide also protects endothelial cells from damage caused by chemotherapy-related toxicities. In vitro, defibrotide decreases

fludarabine-mediated apoptosis of endothelial cells while maintaining its antileukemic effect (Eissner et al. 2002). Additionally, defibrotide inhibits the expression of heparanase, contributing to extracellular matrix integrity and, thereby, tissue homeostasis (Barash et al. 2018).

1.6. Clinical Experience with Defibrotide Administration for Prevention of CAR-T-associated Neurotoxicity

There is no clinical experience with defibrotide administration for prevention of CAR-T-associated neurotoxicity. The current standard approach for CAR-T-associated neurotoxicity is supportive care and the use of steroids.

1.7. Justification for Dosage and Dosage Regimen

As summarized in Section 1.1, endothelial damage occurs prior to CAR-T-cell therapy, and is exacerbated as CAR-T-cell expansion. In particular, chemotherapeutic agents are known to cause endothelial damage. Therefore, the Sponsor considers that it is important to initiate the use of defibrotide around the time of lymphodepletion chemotherapy.

Specifically, 1 of the agents used for lymphodepletion, fludarabine, is known to damage human microvascular endothelial cells, dermal cells, and alveolar epithelial cell lines after 48 hours of culture in vitro. But pretreatment with defibrotide for 1 hour followed by washing protected the endothelial cells from damage by fludarabine (Eissner et al. 2002). This indicates that the efficacy of defibrotide may persist for longer than its actual serum half-life, which is less than 2 hours.

Therefore, in this clinical trial, defibrotide will be given over 2 hours (±15 min) once daily immediately prior to each lymphodepletion chemotherapy on CAR-T Days -5, -4, and -3 (Study Days 1, 2, and 3). This will permit the administration to be performed in an outpatient setting during lymphodepletion. On CAR-T Day -2 (Study Day 4) and CAR-T Day -1 (Study Day 5), defibrotide will not be administered. Once the subject is in the hospital (ie, day of Yescarta infusion [CAR-T Day 0]), defibrotide infusion will be started before Yescarta infusion. A minimum of 2 doses of defibrotide must be administered prior to Yescarta infusion. The defibrotide infusion will be repeated every 6 hours (4 times a day) until CAR-T Day +7 (Study Day 13), during which the subjects will be generally recommended to stay in the hospital for the observation of complications of Yescarta therapy (Request for New MS-DRGs for CAR-T Therapy for FY 2019, 2017).

More details on the timing of defibrotide administration relative to that of lymphodepletion and Yescarta are provided in Section 5.3.

The target dosage of defibrotide selected for this study is 6.25 mg/kg/dose infusions over 2 hours starting immediately prior to the start of the lymphodepletion chemotherapy. The window between the end of defibrotide infusion and start of lymphodepletion chemotherapy should not exceed 2 hours. The administration dose/schedule has been demonstrated to be generally safe and well tolerated when administered for 21-35 days or longer in studies in a VOD treatment setting (Studies 2005-01, 99-118, and 2006-05) and in a study evaluating defibrotide in the VOD prevention setting (Study 2004-000592-33). Refer to Table 1 for additional information.

However, defibrotide has not been tested in the context of CAR-T-cell therapy, so the Sponsor will perform a lead-in phase evaluating the safety of defibrotide by 3+3 design starting at a lower dose (2.5 mg/kg/dose) and then the target dose (6.25 mg/kg/dose).

1.8. Justification for Choice of Primary and Secondary Efficacy Endpoints

The primary endpoint of any grade CAR-T-associated neurotoxicity was selected because even Grade 1 neurotoxicity requires close monitoring in an inpatient setting, leading to significant hospital resource utilization.

Severe neurotoxicity (Grade 3 or greater) carries the most clinical significance, and as such, is a secondary endpoint.

A universally established grading system of neurotoxicity, however, has not been established. Previous resports are mostly based on CTCAE, which is not designed to describe the unique presentation of neurotoxicity related to CAR-T-cell therapy. Therefore, recently ASBMT formed a working group and issued a consensus grading system of neurotoxicity in the context of immune effector cell therapy, including CAR-T-cell therapy (Lee et al. 2018). Therefore, the Sponsor will use this grading system for the secondary endpoints.

1.8.1. CTCAE v5.0 Grading of Neurotoxicity

The Medical Dictionary for Regulatory Activities (MedDRA) High Level Group Terms (HLGTs) that are indicative of neurotoxicity are shown in Appendix 2 and AEs that code to these HLGTs will be captured in this study. Each of these HLGTs is either in the MedDRA System Organ Class (SOC) of 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 3, and this will be used to grade events of neurotoxicity (Appendix 2).

1.8.2. ASBMT Consensus Grading System of CAR-T-associated Neurotoxicity

The ASBMT consensus grading of CAR-T-associated neurotoxicity is shown in Appendix 4.

1.8.3. Grading of CRS by ASBMT Consensus Criteria

Grading of CRS proposed by ASBMT (Lee et al. 2018) is shown in Appendix 5.

1.8.4. Use of High Dose Steroid

Use of steroid inhibits T-cell expansion and survival. Therefore, it is generally considered important that the use of steroid be limited. In this study, the Sponsor will monitor the use of high dose steroid, which is 1 of the secondary efficacy endpoints. The Sponsor defines high dose steroid as dexamethasone (7.5 mg/day). This is considered equivalent to hydrocortisone (200 mg/day) or methylprednisolone (40 mg/day) or prednisone (50 mg/day). This allows reasonable use of low dose steroid for premedication for transfusion or immunoglobulin products in case they are needed.

1.9. Justification for Selection of Subject Populations

While CAR-T-cell therapy provides high response rate with durable duration in patients with B-cell neoplasm, the use of this approach is often complicated with CAR-T-associated neurotoxicity and CRS. While CRS is generally well managed with the use of tocilizumab, an anti-IL6 antibody, there has not been an effective therapy for CAR-T-associated neurotoxicity except for high dose steroid use, which generally is not preferred after CAR-T-cell therapy as steroid inhibits CAR-T-cell survival and expansion. Therefore, CAR-T-associated neurotoxicity is a major challenge for patients undergoing CAR-T-cell therapy, making it an area of unmet need.

While all CD19 targeted CAR-T-cell therapy are reported to be associated with CAR-T-associated neurotoxicity to date, the incidence and severity of CAR-T-associated neurotoxicity seems to depend on the construct of the CAR-T cells. The first CAR-T-cell product that was approved for DLBCL, Yescarta, has been associated with the highest incidence of CAR-T-associated neurotoxicity, as high as 64% (any grade, Neelapu et al. 2017). Therefore, the Sponsor selected a study population that was limited to Yescarta, and to not include other types of CAR-T-cell therapy. The inclusion criteria is primarily based on the current labeled indication of Yescarta (adult patients with relapsed or refractory DLBCL).

The endothelial damage occurs with lymphodepletion chemotherapy and CAR-T-cell expansion (Gust et al. 2017; Hay et al. 2017; Santomasso et al. 2018). The Sponsor's hypothesis of endothelial protection by defibrotide makes use of defibrotide before or with chemotherapy reasonable. In addition, the progression of CAR-T-associated neurotoxicity can be rapid and thus, progression from the first sign of CAR-T-associated neurotoxicity to severe CAR-T-associated neurotoxicity may be within a matter of hours. This small window allows use of the investigational drug, defibrotide, in the evaluation of prevention of CAR-T-associated neurotoxicity.

1.10. Summary of Potential Benefits and Risks

As described in Section 1.1, emerging evidence suggests that the endothelial damage plays an important role in development and progression of both CRS and CAR-T-associated neurotoxicity (Gust et al. 2017; Hay et al. 2017; Santomasso et al. 2018). This makes defibrotide an attractive treatment option as nonclinical and clinical data have shown that defibrotide protects endothelial cells in multiple different scenarios in case of endothelial injury caused by chemotherapeutic agents or immune activation (Palomo et al. 2016).

CAR-T-associated neurotoxicity is a significant morbidity during the CAR-T-cell therapy, and even a Grade 1 CAR-T-associated neurotoxicity would require close observation in an inpatient setting, leading to prolonged hospital resource utilization. The potential benefit of the use of defibrotide in this context is reduced risk of CAR-T-associated neurotoxicity, less requirement of high dose steroid use potentially leading to improved efficacy of CAR-T-cell therapy, and shorter hospital stay after CAR-T-cell therapy.

The defibrotide clinical development program, spanning over 20 years, comprises 8 clinical studies, as well as expanded access/compassionate use programs, examining defibrotide in both the VOD treatment and prevention settings. As of 18 October 2018, over 8,000 adult, adolescent, and pediatric patients have been exposed to defibrotide. Through clinical study use,

approximately 1,855 subjects have received defibrotide: approximately 1,459 subjects for treatment of VOD, 314 subjects for prevention of VOD, 12 subjects for severe or end-stage renal disease, 12 subjects for prevention of aGvHD, and 58 healthy volunteers. The estimated postapproval exposure from all sources is 7,033 patients.

The safety profile is consistent across clinical studies and postapproval use. A review of the literature has revealed a similar safety profile. Defibrotide has been generally well tolerated, and the overall safety profile of defibrotide appears to be acceptable. The principal toxicity of concern continues to be the potential for increased risk of hemorrhage. Since this is the first study that evaluates defibrotide in the context of CAR-T therapy, a safety evaluation will be performed in Part 1 that starts at a low dose.

The current study in CAR-T-associated neurotoxicity will target a similar defibrotide dose and frequency but shorter duration. The duration of the treatment in this study is up to CAR-T Day +7, such that it covers the peak timing of CAR-T cell expansion and initiation of CAR-T-associated neurotoxicity, during which the subjects are hospitalized for monitoring.

Therefore, given the potential benefit of defibrotide in protecting endothelial cells and decreasing endothelial cell activation and an acceptable safety profile, the benefit-risk evaluation is considered to be positive for this study of defibrotide.

Although there is no preclinical or clinical reason to suspect that defibrotide will impair the antilymphoma activity of CAR-T-cell therapy, 1 unknown risk is the effect of defibrotide on the expansion and trafficking of CAR-T cells. The Sponsor, therefore, plans to follow the disease status as a secondary endpoint, as a marker of CAR-T-cell activity. This is a part of standard of care performed by positron emission tomography (PET) scan with or without bone marrow evaluation.

Please refer to Section 6 of the defibrotide IB for additional details and guidance for the Investigator.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

To assess the safety and efficacy of defibrotide for the prevention of CAR-T-associated neurotoxicity.

2.2. Study Endpoints

2.2.1. Primary Endpoint

Incidence of CAR-T-associated neurotoxicity (any grade, defined by CTCAE v5.0 [Appendix 3]) by CAR-T Day +30.

2.2.2. Secondary Endpoints

2.2.2.1. Efficacy

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 (Appendix 3) 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. 2018; Appendix 4) by CAR-T Day +30
- Incidence of CRS (any grade, according to the ASBMT consensus grading system [Lee et al. 2018; Appendix 5]) by CAR-T Day +30
- Use of high dose steroid by CAR-T Day +30

2.2.2.2. Safety

The following secondary safety endpoints will be evaluated:

- Incidence of treatment-emergent adverse events (TEAEs) that occur up to 30 days after the last dose of defibrotide
- Incidence of treatment-emergent serious adverse events (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

2.2.2.3. Pharmacokinetics

The pharmacokinetics (PK) of defibrotide will be assessed as a secondary endpoint.

2.2.3. 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

3. STUDY DESIGN

3.1. Overall Study Design and Plan

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. Subjects are considered enrolled into the study after signing of informed consent and meeting the eligibility criteria.

This is a 2-part study consisting of a low-dose safety lead-in phase (Part 1) that will determine the final treatment dose to be used in all subsequent eligible subjects (Part 2) to enroll a total of 32 subjects at the final treatment dose.

To ensure the safety of defibrotide administration in this subject population, Part 1 (lead-in phase) of the study is based on a standard 3+3 design and will evaluate 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. After establishing the recommended phase 2 dose (RP2D), Part 2 will enroll subjects at the RP2D to obtain a total of 29 efficacy evaluable subjects, including Part 1 subjects who were treated at the RP2D. 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. The Efficacy Evaluable Analysis Set will include:

- All subjects 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
- All subjects who discontinued treatment due to post-CAR-T-associated neurotoxicity before receiving 18 doses of defibrotide.

In addition, subjects whose Yescarta infusion is delayed by more than 2 days from the original schedule are considered not evaluable (NE) for efficacy.

The dose-limiting toxicity (DLT) assessment period is from the start of the first dose of defibrotide to 7 days after the last dose of defibrotide during Part 1 of the study. In addition, through Part 1 and Part 2, safety will be assessed through the collection of AEs and SAEs from the signing of informed consent to 30 days after the last dose of defibrotide. Other safety assessments (as described in Section 6.7) will also be performed up to 30 days after the last dose of defibrotide. Lymphoma response by Cheson criteria (Cheson et al. 2016) will also be captured by CAR-T Day +60 as a safety endpoint of this study when performed per standard of care.

3.1.1. Treatment Assignment

3.1.1.1. Definition of Dose-Limiting Toxicity

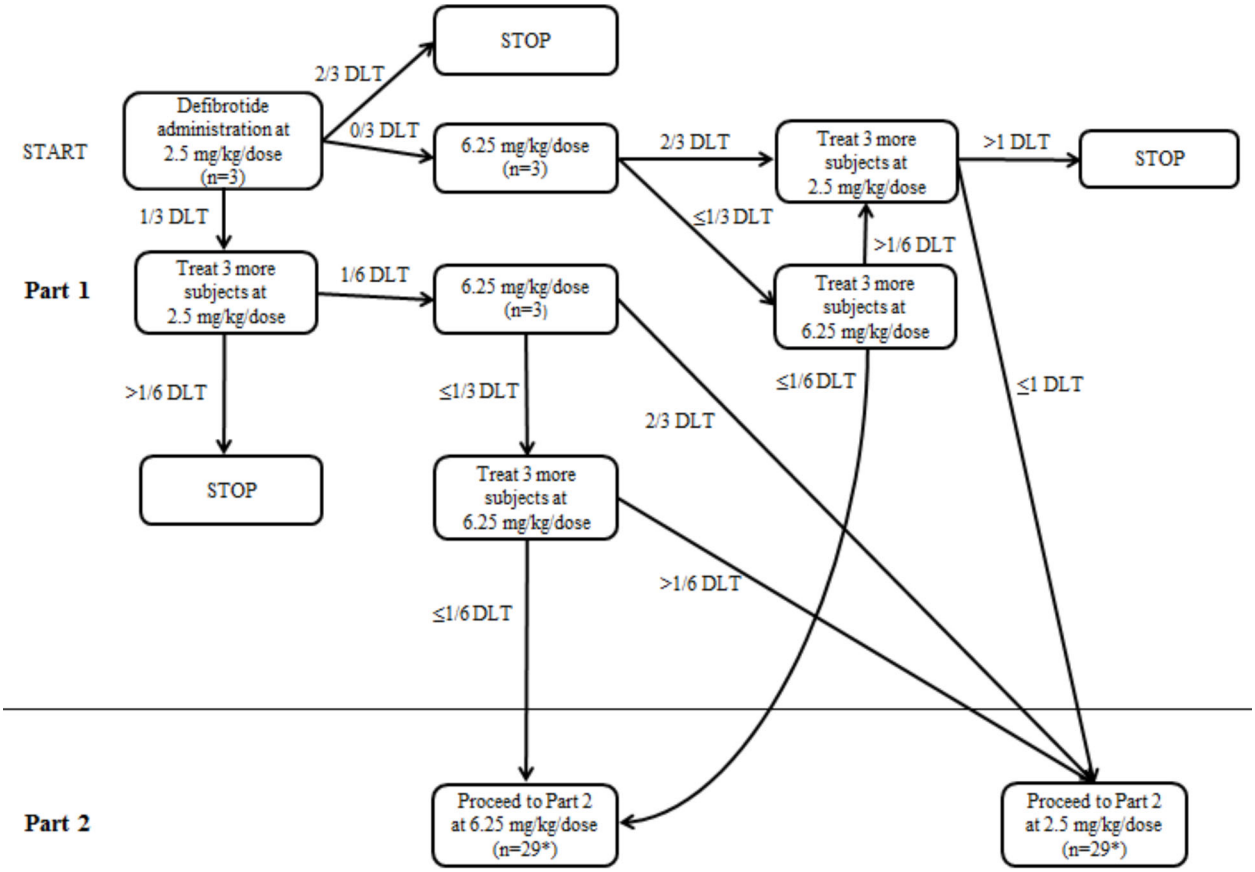
A Safety Assessment Committee (SAC) will be formed for the determination of any dose DLTs during Part 1 of the study. The significant toxicity from CAR-T treatment may not be distinguishable from TEAEs attributable to defibrotide, as the safety profile of defibrotide in this subject population has not 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 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 focus on any grade (per CTCAE v5.0) of intracranial hemorrhage and any other hemorrhage of Grade 2 or greater. The SAC will also focus all nonhemorrhagic TEAEs of Grade 3 or greater as possible DLTs in this clinical setting. Of note, CAR-T-associated neurotoxicity is not a DLT. Refer to Section 9.5 for more details on the SAC.

3.1.1.2. Part 1: Lead-in Phase and Determination of Recommended Phase 2 Dose

The study will begin with a lead-in phase in which defibrotide at 2.5 mg/kg/dose is evaluated (Figure 5). Three subjects will be enrolled in this cohort initially. If no subject experiences a DLT, then the next dose (6.25 mg/kg/dose) will be assessed. If ≥ 2 of the 3 subjects experience a DLT at 2.5 mg/kg/dose, the study will be placed on hold and the SAC will discuss the potential next steps, including possible study termination. If 1 of the 3 subjects experiences a DLT at 2.5 mg/kg/dose, 3 more subjects will be enrolled at this dose. If > 1 of the 6 subjects experience a DLT at 2.5 mg/kg/dose, the study will be placed on hold and the SAC will be consulted. If only 1 of the 6 subjects experiences a DLT at 2.5 mg/kg/dose, then 6.25 mg/kg/dose will be tested using a similar schema as described below.

Three subjects will receive 6.25 mg/kg/dose initially. If > 1 of the 3 subjects experiences a DLT at 6.25 mg/kg/dose, then 6.25 mg/kg/dose is considered to exceed the maximum tolerated dose, and the lower dose cohort will reopen to accrue a total of 6 subjects (including subjects previously tested) at 2.5 mg/kg/dose, unless 6 subjects had already been treated at 2.5 mg/kg/dose prior to dose escalation. If < 2 of the 3 subjects experience a DLT, then 3 more subjects will be enrolled at 6.25 mg/kg dose to further evaluate toxicity at this dose. If < 2 of the 6 subjects experience a DLT at 6.25 mg/kg/dose, then 6.25 mg/kg will be the RP2D. If > 1 of 6 subjects experience a DLT, then 6.25 mg/kg/dose is considered to exceed the maximum tolerated dose, and the lower dose cohort will reopen to accrue a total of 6 subjects (including subjects previously tested) at 2.5 mg/kg/dose, unless 6 subjects had already been treated at 2.5 mg/kg/dose prior to dose escalation. If > 1 of the 6 subjects experience a DLT at 2.5 mg/kg/dose, then the study will be placed on hold and the SAC will discuss the potential next steps, including possible study termination. If < 2 of the 6 subjects experience a DLT at 2.5 mg/kg/dose, then 2.5 mg/kg will be the RP2D.

Figure 5: Dose Escalation Algorithm



* Efficacy evaluable; subjects in Part 1 treated at the RP2D will be included in the efficacy and safety analyses.
Abbreviations: DLT = dose-limiting toxicity; RP2D = recommended Phase 2 dose.

3.1.1.3. Part 2: Evaluating Safety and Efficacy of Defibrotide at the Recommended Phase 2 Dose for Prevention of CAR-T-associated Neurotoxicity

Once the RP2D is determined, a total of 32 subjects (anticipating 29 efficacy evaluable) are to be treated at that dose (Figure 5). Subjects treated at the RP2D in Part 1 will be included in the efficacy and safety analyses of the study. The SAC will continue to monitor safety data, including serious and Grade 3 or greater TEAEs throughout Part 2 of the study.

3.2. Rationale for Study Design

Given the rarity of the disease, lack of preclinical models, significant unmet medical need with clear diagnostic criteria, a single-arm study approach is appropriate for evaluation of defibrotide in this subject population.

The reported incidence of CAR-T-associated neurotoxicity (any grade) in the pivotal multicenter Phase 2 trial (ZUMA-1 Trial with axicabtagene ciloleucel) was 64%; 28% reported Grade 3 or greater neurotoxicity according to CTCAE v4.03 criteria (Neelapu et al. 2017). The Sponsor targets the reduction of all grades of neurotoxicity by 50% (ie, from 64% to 32%). This is a clinically relevant reduction in the incidence of CAR-T-associated neurotoxicity.

Since defibrotide has not been tested in this context, the Sponsor will start with a lead-in phase (Part 1) in order to assess the safety of defibrotide in the subjects who have received Yescarta. The target dose is 6.25 mg/kg/dose, given over 2 hours once daily prior to lymphodepletion chemotherapy on CAR-T Days -5, -4, and -3 (or Study Days 1, 2, and 3), and 4 times a day (beginning on CAR-T Day 0) as given in the currently approved indication for the treatment of hepatic VOD with renal or pulmonary dysfunction following HSCT and as previously used in the prevention of VOD pediatric study (Study 2004-000592-33).

3.3. Study Duration and Dates

The study is expected to be approximately 21 months in duration, with an estimated enrollment period of 18 months and participation for each subject of approximately 3 months (observation for CAR-T-associated neurotoxicity up to CAR-T Day +30, AEs assessed up to CAR-T Day +37, and lymphoma response captured up to CAR-T Day +60).

End of study for each subject is the time at which the subject completes the study or the time of death, lost to follow-up, or early termination from the study. 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 will be considered to have completed the study on CAR-T Day +60.

The study will be considered completed once all enrolled subjects have reached the end of study.

4. SELECTION OF STUDY POPULATION

Subjects aged ≥18 years are considered eligible for the study if they are planned to receive lymphodepletion chemotherapy followed by infusion of CAR-T-cell product, Yescarta, for the treatment of relapsed or refractory DLBCL for labeled indication (DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma).

Approximately 35 to 38 adult subjects are planned for enrollment.

4.1. Inclusion Criteria

Subjects must meet the following criteria to be enrolled in this study:

1. Subject must be ≥ 18 years of age at signing of informed consent.
2. Subject must be diagnosed with relapsed or refractory DLBCL (including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma) and scheduled to receive treatment with Yescarta.
3. Female subjects of childbearing potential who are sexually active and male subjects who are sexually active and have female partners of childbearing potential must agree to use a highly effective method of contraception with their partners during exposure to defibrotide and for 30 days after the last dose of defibrotide. Highly effective methods of contraception include abstinence (when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence, eg, calendar, postovulation, symptothermal methods, and withdrawal are not acceptable methods]), combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (ie, birth control pills, patches, vaginal ring), progestogen-only hormonal contraception associated with inhibition of ovulation (ie, progestin implant or injection), intrauterine device, intrauterine hormone-releasing system, surgical sterilization, and vasectomy (> 6 months before CAR-T Day -5 [Study Day 1]). Surgically sterile women and men and postmenopausal women (ie, women with > 2 years of amenorrhea) do not need to use contraception.
4. Subject must be able to understand and sign written informed consent.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Subject is currently receiving dialysis or expected to receive dialysis.
2. Subject has used any investigational anticancer agent within 3 weeks prior to the first dose of defibrotide, or is using or plans to use any investigational agent during the study.
3. Subject has previously been treated with CAR-T therapy.
4. Hemodynamic instability requiring vasopressors or uncontrolled hypertension with persistent systolic blood pressure > 180.

5. Subject has clinically significant active bleeding, history of intracranial bleeding, or is at risk for intracranial bleeding as determined by the Investigator.
6. Subject plans to use any medication that increases the risk of bleeding, including, but not limited to, systemic heparin, low molecular weight heparin, heparin analogs, alteplase, streptokinase, urokinase, antithrombin III (ATIII), oral anticoagulants including warfarin, and factor Xa inhibitors. Subjects may receive heparin (up to 100 U/kg/day) or other anticoagulants for routine central venous line management and/or intermittent dialysis or ultrafiltration.
7. Subject, in the opinion of the Investigator, may not be able to comply with the study protocol, including appropriate supportive care, follow-up, research tests, and safety monitoring requirements.
8. Subject has a serious active disease or comorbid medical condition, as judged by the Investigator, that is likely to interfere with the conduct of this study.
9. Subject is pregnant or lactating and does not agree to stop breastfeeding.
10. Subject has a known history of hypersensitivity to defibrotide or any of the excipients.
11. Subject has primary CNS lymphoma.

4.3. Removal of Subjects from the Study or Study Drug

4.3.1. Handling of Early Terminations

All subjects may withdraw from participation in this study at any time, for any reason, and without prejudice. The Investigator must withdraw any subject from the study if the subject states that he/she wants to stop participating in the study. In addition, the Investigator or the Sponsor or its designee may remove a subject from the study treatment or the study at any time and for any reason, for example, in the case of disease relapse, noncompliance with study treatment regimen, or protocol deviation.

However, subjects must prematurely discontinue study drug or early terminate from the study if any of the following occur:

Reasons to prematurely discontinue study drug	Reasons to early terminate from the study
• Withdrawal of consent by subject • Adverse event that, in the opinion of the Investigator, precludes continuation of study drug for subject safety • Investigator considers it not in the subject's best interest to continue study treatment • Death • Pregnancy • Sponsor (or its designee) decision to terminate study	• Withdrawal of consent by subject • Death • Lost to follow-up • Investigator considers it not in the subject's best interest to continue the study • Sponsor (or its designee) decision to terminate study

The specific reason for the early termination from the study or premature discontinuation of study drug will be documented on the corresponding electronic case report forms (eCRFs). Subjects who prematurely discontinue study drug will continue to be followed for all efficacy

and safety assessments unless they also early terminate from the study. If a subject withdraws informed consent, the specific reason for withdrawing the informed consent should be stated.

Adverse events resulting in premature discontinuation of study drug will be followed to the satisfactory resolution and determination of outcome as ascertained by the Investigator (and/or the Sponsor or its designee). The data will be recorded on the appropriate eCRF.

4.3.2. Sponsor's Termination of the Study

The Sponsor reserves the right to terminate the study at any time for clinical or administrative reasons, including but not limited to, the following:

- Inability to enroll
- Concern for subject safety
- Recommendation from the SAC

Upon notification by the Sponsor, such a termination must be implemented promptly by the Investigator, if instructed to do so by the Sponsor, in a timeframe that is compatible with the subjects' well-being.

5. STUDY TREATMENT

5.1. Description of Treatment

5.1.1. Study Drug

Defibrotide (defibrotide sodium) is a clear, light yellow to brown solution supplied as 200 mg/2.5 mL (concentration of 80 mg/mL) in single-patient-use clear, glass vials. After dilution with 0.9% sodium chloride or 5% dextrose in water (D5W), the final solution should be free of particulates and turbidity.

Excipients include sodium citrate dihydrate, hydrochloric acid and sodium hydroxide (for pH adjustment), and water for injection.

5.2. Treatments Administered

Subjects will receive defibrotide (study drug) 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).

5.2.1. Defibrotide Administration

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 min. Individual doses of defibrotide are determined for individual subjects based on body weight at baseline. Baseline is defined as the day 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.

After dilution with D5W or 0.9% sodium chloride, the final concentration of defibrotide for administration should be in the range of 4 mg/mL to 20 mg/mL, as appropriate for infusion over 2 hours (±15 min). Detailed procedures for preparation of study drug will be provided separately.

5.3. Selection and Timing of Defibrotide Dosing for Each Subject

To minimize the endothelial damage from lymphodepletion chemotherapy, defibrotide is to start on the first day (CAR-T Day -5 [Study Day 1]) 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) prior to Yescarta infusion, 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. 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). A delay of > 2 days should be discussed with the Sponsor's Study Medical Monitor.

Each defibrotide dose (infused over a 2 hour ±15 min infusion period) 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 Table 2.

Table 2: 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 chemotherpy	X[b]	X[b]	X[b]						
Yescarta						X[c]			
Defibrotide[d]	QD[e]	QD[e]	QD[e]			QID[f]	QID[f]		

[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). A delay of > 2 days should be discussed with the Sponsor's Study Medical Monitor.
[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.
Abbreviations: CAR-T = chimeric antigen receptor T-cell; QD = once daily; QID = 4 times a day.

5.4. Treatment Discontinuation

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 (see Section 1.9). If the subject experiences Grade 3 or greater CAR-T-associated neurotoxicity, the treatment must be discontinued, 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.

5.5. Blinding

Blinding is not applicable in this open-label study.

5.6. Prior and Concomitant Therapy

5.6.1. Prior and Concomitant Medications

All medications and therapies received between the date of the first screening procedure and before baseline (but not during treatment with defibrotide), and all prior therapies for the primary disease will be recorded as prior medications. All medications and therapies (including lymphodepletion chemotherapy) taken between baseline and until 30 days after the subject's last dose of defibrotide, inclusive, will be recorded as concomitant medications. This includes medications and therapies started before treatment with defibrotide and continuing after the first dose of defibrotide.

5.6.2. Transfusions

Subjects' requirements for platelet and/or red blood cell transfusions will be recorded from baseline through 30 days after the subject's last dose of defibrotide.

5.6.3. Prohibited Medications

Medications that increase the risk of hemorrhage are prohibited throughout the study. These include, but are not limited to, systemic heparin, low molecular weight heparin, heparin analogs, alteplase, streptokinase, urokinase, ATIII, and oral anticoagulants, including warfarin, factor Xa inhibitors, and other agents that increase the risk of bleeding. Note: Subjects may receive heparin or other anticoagulants for routine central venous line management, and intermittent dialysis or ultrafiltration. Fibrinolytic instillation for central venous line occlusion is also permitted. Heparin use is allowed throughout the study (up to a maximum of 100 U/kg/day).

Concomitant use of any other investigational product or procedure is prohibited during this study.

The Sponsor must be notified of any instances in which excluded therapies are administered.

5.7. Treatment Compliance

Defibrotide will be administered by study site personnel, and all administrations will be recorded in the eCRF.

5.8. Packaging and Labeling

Defibrotide will be supplied to the study sites by the Sponsor in vials containing 200 mg defibrotide at a concentration of 80 mg/mL. All defibrotide provided for this study will be labeled for investigational use only.

All packaging and labeling operations will be performed according to current Good Manufacturing Practices, Good Clinical Practice (GCP), and local requirements.

5.9. Storage and Accountability

Defibrotide will be stored, inventoried, reconciled, and retained or destroyed according to applicable state and federal regulations and instructions from the Sponsor.

Defibrotide solution does not contain preservatives. Unopened vials of defibrotide are to be stored according to the carton/vial label. Diluted defibrotide solution must be used within 4 hours if stored at room temperature, or within 24 hours if stored under refrigeration (2°C to 8°C), and then subsequently discarded. Use of diluted defibrotide is not permitted outside of these time ranges. Partially used vials should also be discarded, and must not be used across subjects.

Do not coadminister defibrotide and other intravenous (IV) drugs concurrently within the same IV line.

The Investigator or pharmacist will maintain accurate records of receipt of all defibrotide, including dates of receipt. Defibrotide must be kept in a secure area. Unused (or partially used) supplies must be accounted for on the drug inventory record. The receipt and dispensing of all defibrotide must be documented throughout the study and reconciled at study completion.

After the study has been completed and all drug accountability records have been completed and reviewed, all unused clinical supplies are to be disposed of per instructions from the Sponsor. The Investigator must provide a written explanation for any missing study drug. One copy of the drug inventory record will be retained at the study site and the other will be retained by the Sponsor.

6. STUDY PROCEDURES

6.1. Informed Consent

All subjects will provide their written informed consent, as applicable, before any study-related procedures are performed.

Each subject's chart will have his or her signed informed consent form (ICF) attached to it. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the Investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder. All subjects will be given a copy of their signed ICF.

6.2. Medical History, Information Pertaining to Underlying Disease, and Information Pertaining to Yescarta Therapy

6.2.1. Medical History

A complete medical history including diseases and conditions by standard body systems, and information on resolved conditions, intermittent conditions, concurrent illnesses, and previous surgeries will be collected.

6.2.2. Information Pertaining to Underlying Disease

Information pertaining to the underlying disease, including date of initial diagnosis and date of recurrent disease, if applicable, will be collected.

6.2.3. Information Pertaining to Yescarta Therapy

Information pertaining to current Yescarta therapy, including date of Yescarta infusion and infused cell count, will be collected.

6.3. Efficacy Assessments

Efficacy will be assessed through monitoring of subject symptoms, physical examinations, laboratory testing, imaging studies and EEG to assess neurotoxicity as needed, and recording survival status.

On CAR-T Day 0 (Study Day 6) until discharge (ie, during hospitalization), neurological evaluation is performed every 8 hours (±2 hours) as per the recommended standard of care. If hospitalization is prolonged beyond CAR-T Day +7 (Study Day 13) for reasons other than neurotoxicity, neurological evaluation can be as less frequent as once every visit, that happens at least every 7 days until CAR-T Day +30.

6.3.1. Primary Efficacy Assessment

Primary efficacy assessment is the incidence of CAR-T-associated neurotoxicity (any grade, defined by CTCAE v5.0) after CAR-T-cell therapy by CAR-T Day +30.

6.3.2. Secondary Efficacy Assessments

Secondary efficacy assessments include incidence of Grade 3 or greater CAR-T-associated neurotoxicity defined by CTCAE v5.0 by CAR-T Day +30; incidence of any grade CAR-T-associated neurotoxicity according to ASBMT consensus grading system (Lee et al. 2018) by CAR-T Day +30; incidence of Grade 3 or greater CAR-T-associated neurotoxicity according to ASBMT consensus grading system (Lee et al. 2018) by CAR-T Day +30; incidence of CRS (any grade, according to ASBMT criteria [Lee et al. 2018]) by CAR-T Day +30; and use of high dose steroid by CAR-T Day +30.

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

The use of high dose steroids is defined as a dose of dexamethasone of at least 7.5 mg/day or equivalent. This dose of dexamethasone is generally equivalent to hydrocortisone (200 mg/day) or methylprednisone (40 mg/day) or prednisone (50 mg/day). This allows reasonable use of low dose steroid for premedication for transfusion or immunoglobulin products.

6.4. Biomarker Analysis

Serum cytokines including markers of endothelial damage will be analyzed from serial blood samples (Table 3), which will be collected once daily on CAR-T Days -5 and -3 (Study Days 1 and 3) and once every other day starting from CAR-T Day 0 (Study Day 6) to discharge, but not beyond CAR-T Day +14. In addition, blood collection will be peformed once on CAR-T Day +14 (±3 days) and once on CAR-T Day +30 (±3 days), which may be performed either in the hospital or as an outpatient.

Potential biomarkers for investigation include, but are not limited to, AAT, ANG2, ATIII, E-selectin, FVII, fibrinogen, hyaluronic acid, homocysteine, ICAM-1, MMP-1, MMP-2, MMP-9, PAI-1, ST2, TIMP1, TNFR1, VCAM-1, VEGF, vWF, IL-6, IL-8, IL-1 RA, MCP-1, IFN-γ, CRP, TNF-α, ferritin, endothelin-1, TM, GM-CSF, and heparin sulfate.

Table 3: Biomarker Sample Collection

Collection Study Part	Study Day/Visit	Sample Type[a]	Timepoint
Part 1 and Part 2	CAR-T Day -5	Blood	Pre-infusion (any time prior to the start of defibrotide infusion)
	CAR-T Day -3	Blood	Any time on the specified day
	CAR-T Day 0	Blood	Pre-CAR-T (any time prior to Yescarta administration)
	CAR-T Day +2	Blood	Any time on the specified day
	CAR-T Day +4	Blood	Any time on the specified day
	CAR-T Day +6	Blood	Any time on the specified day
	CAR-T Day +8 (if hospitalized)	Blood	Any time on the specified day
	CAR-T Day +10 (if hospitalized)	Blood	Any time on the specified day

Collection Study Part	Study Day/Visit	Sample Type[a]	Timepoint
	CAR-T Day +12 (if hospitalized)	Blood	Any time on the specified day
	CAR-T Day +14	Blood	Any time on the specified day (±3 days)
	CAR-T Day +30	Blood	Any time on the specified day (±3 days)

[a] 7 mL collected per time point

Abbreviations: CAR-T = chimeric antigen receptor T-cell.

6.5. Health Economics (Hospital Length of Stay)

The hospital length of stay (including any re-admissions before CAR-T Day +30) will be recorded in the eCRF as the date of admission and the date of discharge for both the initial hospitalization as well as any re-admissions during the follow-up period. As a subset of hospitalization days, the duration of days spent in the ICU will be recorded in the eCRF as the date of admission to the ICU and the date of discharge from the ICU.

6.6. Pharmacokinetics Assessments

Blood samples will be obtained from all subjects as described in Table 4. Blood samples will be collected before and after the first morning defibrotide infusion on CAR-T Day -5 (Study Day 1) during Part 1 of the study and on CAR-T Day 0 (Study Day 6) and CAR-T Day +7 (Study Day 13) during Parts 1 and 2 of the study. Plasma defibrotide concentrations will be measured using a validated bioanalytical method. The PK of plasma defibrotide will be assessed.

Table 4: Pharmacokinetics Sample Collection

Collection Study Part	Study Day/Visit	Sample Type[a,b]	Timepoint	Time Window
Part 1 only	CAR-T Day -5	Blood	Pre-defibrotide (prior to start of defibrotide infusion)	Within 15 min prior to start of infusion
	CAR-T Day -5	Blood	1.0 hour post start of defibrotide infusion	±10 min (during infusion)
	CAR-T Day -5	Blood	2.0 hours post start of defibrotide infusion	Within 15 min prior to end of infusion
	CAR-T Day -5	Blood	4.0 hours post start of defibrotide infusion	±30 min
	CAR-T Day -5	Blood	6.0 hours post start of defibrotide infusion	±30 min
	CAR-T Day -4	Blood	24.0 hours post start of CAR-T Day -5 defibrotide infusion	±60 min
Part 1 and Part 2	CAR-T Day 0	Blood	Pre-defibrotide (prior to start of defibrotide infusion)	Within 15 min prior to start of infusion
	CAR-T Day 0	Blood	2.0 hours post start of defibrotide infusion	Within 15 min prior to end of

Collection Study Part	Study Day/Visit	Sample Type[a,b]	Timepoint	Time Window
				infusion
	CAR-T Day 0	Blood	4.0 hours post start of defibrotide infusion	±30 min
	CAR-T Day +7	Blood	Pre-defibrotide (prior to start of defibrotide infusion)	Within 15 min prior to start of infusion
	CAR-T Day +7	Blood	2.0 hours post start of defibrotide infusion	Within 15 min prior to end of infusion
	CAR-T Day +7	Blood	4.0 hours post start of defibrotide infusion	±30 min

[a] Plasma to be harvested within 30 minutes after blood collection
[b] 3 mL collected per time point
Abbreviations: CAR-T = chimeric antigen receptor T-cell; min = minutes.

6.7. Safety Assessments

Safety will be assessed through monitoring of AEs, SAEs, vital signs, physical examinations, clinical laboratory tests, and Eastern Cooperative Oncology Group (ECOG) performance status (PS).

Response to treatment with Yescarta for relapsed or refractory DLBCL in subjects who received defibrotide will also be captured if assessed per standard of care (Section 6.7.5).

6.7.1. Adverse Events

6.7.1.1. Reporting of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related to study drug or procedure.

Adverse events include, but are not limited to, the following: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; (4) drug interaction; and/or (5) laboratory values that appear or worsen after written informed consent is obtained and are assessed as clinically significant by the Investigator.

All AEs, whether observed by the Investigator, reported by the subject, determined from laboratory findings, vital signs, physical examinations, or other means, must be recorded.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The Investigator should attempt to establish a diagnosis (including syndromes) based on signs, symptoms, and/or other clinical information. When a diagnosis or syndrome is established or confirmed, the diagnosis or syndrome, not the individual signs/symptoms, should be documented as the AE.

Following questioning and evaluation, all AEs, whether believed by the Investigator to be related or unrelated to the study drug or procedure, must be documented in the subject's medical records, in accordance with the Investigator's normal clinical practice. Each AE is to be

evaluated for duration, severity, seriousness, outcome, action taken with study drug, and causal relationship to defibrotide or procedure.

6.7.1.2. Severity Assessment

Adverse events will be classified by the Investigator using the National Cancer Institute CTCAE v5.0. All appropriate treatment areas should have access to a copy of the CTCAE v5.0. A copy of the CTCAE v5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

If the CTCAE grade is not specified for a particular event or if the event term does not appear in the CTCAE, general guidelines for grading severity of AEs are provided in Table 5.

When the severity of an AE increases over time, the increase in the severity will be recorded as a new AE, and the original AE will stop when the new AE starts.

Table 5: National Cancer Institute Common Terminology Criteria for Adverse Events Severity Grades General Guidelines

Severity Grade	Terminology Criteria
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

[a] Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
Abbreviations: ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.
Source: CTCAE v5.0 Accessed at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

6.7.1.3. Serious Adverse Events

An SAE is an AE that fulfills any of the following criteria, as per International Council for Harmonisation (ICH) E2A.II.B:

- Is fatal (results in death)
- Is life-threatening (Note: The term “life-threatening” refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe. Grade 4 laboratory values are not necessarily serious unless the subject was at immediate risk of death.)
- Requires inpatient hospitalization or prolongs existing hospitalization

- Results in persistent or significant incapacity or disability, defined as substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly/birth defect
- Is an important medical event

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above in the definition of an SAE.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and the development of drug dependency or drug abuse.

Suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An AE should be recorded as an SAE when it meets at least 1 of the criteria for seriousness. A subject's underlying disease that results in the initial hospitalization is not considered an SAE. The following reasons for hospitalization are also NOT considered SAEs:

- Procedures that were planned prior to the subject entering the study
- Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Procedures that are elective in nature and not related to worsening of an underlying condition

Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

"Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. Emergency room care without admission to a hospital is considered outpatient care.

Overdose, medication errors, and drug misuse of the study drug are considered reportable experiences and should be reported by study site personnel. The reporting form and contact information for submission of the form, will be provided to the study sites separately.

6.7.1.4. Causal Relationship to Study Drug or Procedure

The Investigator's assessment of the relationship of AE to study drug (ie, defibrotide) and to study procedures is required. The relationship or association of the study drug or procedure in causing or contributing to the AE will be characterized using the following classification and criteria:

Related to Study Drug or Procedure	***There is a reasonable possibility that the study drug or procedure caused the event—ie, there is evidence to suggest a causal relationship between the study day or procedure and the AE.*** Some temporal relationship exists between the event and the administration

of the study drug or procedure and the event is unlikely to be explained by the subject's medical condition, other therapies, or accident.

The event follows a reasonable temporal sequence from administration of the study drug or procedure and at least 1 of the following instances of clinical evidence:

- The event follows a known or suspected response pattern to the study drug or procedure.
- The event improves upon stopping the study drug or procedure or decreasing the dose (positive dechallenge).
- The event reappears upon repeated exposure, if medically appropriate (positive rechallenge).

Not Related to Study Drug or Procedure

There is not a reasonable possibility or clinical evidence that the study drug or procedure caused the event.

The event can be readily explained by other factors such as the subject's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event.

6.7.1.5. Adverse Event Recording and Reporting

The Investigator must record all AEs that occur from the time written informed consent is obtained until 30 days after the subject's last dose of defibrotide, regardless of their relationship to study drug or procedure.

In addition, any SAE assessed as related to study drug or study procedures by the Investigator that occur more than 30 days after the last dose of study drug, must be reported as described below.

Serious AEs must be reported to the Sponsor or its designee using an SAE Reporting Form within 24 hours of first knowledge of the event by study site personnel. The reporting form and contact information for submission of the form, will be provided to the study sites separately.

The reporting form must be completed as thoroughly as possible before transmittal to the contact provided on the form. The Investigator must provide his/her assessment of causality to the study drug and to the study procedure at the time of an initial SAE report. If the Investigator's assessment of causality changes after the initial report, it must be provided as follow-up information to the Sponsor.

6.7.1.6. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs assessed as not related to study drug or procedure, including clinically significant laboratory tests, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

Adverse events and SAEs assessed as related to study drug or procedure should be followed for as long as necessary to adequately evaluate the subject's safety, or until the event stabilizes, or the subject is lost to follow-up. If the event resolves, a resolution date should be recorded. The

outcome at that time of the final study visit should be recorded, if the event is not resolved at that time.

Adverse events and SAEs resulting in discontinuation of study drug or termination from the study should be followed to the satisfactory resolution and determination of outcome as ascertained by the Investigator (and/or the Sponsor or its designee).

The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the event. This may include additional clinical laboratory testing or investigations, examinations, histopathological examinations, or consultation with other health care professionals as is practical, according to the Sponsor's requests.

The Investigator should provide follow-up SAE information for any updates to information previously provided to the Sponsor or as requested by the Sponsor.

6.7.1.7. Pregnancy

Subjects' treatment preparative regimens commonly include agents which, while known to have teratogenic effects, may cause infertility. As such, there is a low likelihood that subjects may become pregnant. However, due to the teratogenic effects of the preparative regimens, and the unknown effects of defibrotide use during pregnancy, highly effective methods of contraception are required (see Section 4.1, Inclusion Criterion No. 3).

If a female subject (or female partner of a male subject) of childbearing potential becomes pregnant at any time after the first dose of study drug and up to 30 days after the subject's last dose of study drug, it must be reported to the Sponsor or its designee using the Pregnancy Report Form within 24 hours of first knowledge of the event by study site personnel. Study drug must be stopped for any pregnant subject (see Section 4.3.1).

The pregnancy of a female subject (or female partner of a male subject) must be followed until the outcome of the pregnancy is known, and in the case of a live birth, for 6 months following the birth of the child. The Infant Follow-up Form should be used to report information regarding the status of the infant.

The Pregnancy Report Form, Infant Follow-up Form, and contact information for submission of the form, will be provided to the study sites separately.

6.7.1.8. Regulatory Reporting

The Sponsor or its designee is responsible for reporting to the relevant regulatory authorities, central ethics committees (CECs), and participating Investigators, and will report in accordance with ICH guidelines, the US Code of Federal Regulations (CFR), the EU Clinical Trial Directive, and local regulatory requirements.

The reference safety information to determine expectedness of SAEs is in the IB for defibrotide.

All suspected unexpected serious adverse reactions (SUSARs) will be reported to the relevant regulatory authorities, CECs, and all participating Investigators no later than 15 days after first knowledge of the event.

SUSARs that are fatal or life-threatening will be reported to the relevant regulatory authorities, CECs, and participating Investigators (if required by local regulation), no later than 7 days after knowledge of such a case, and relevant follow-up information provided within an additional 8 days.

Once a year throughout the clinical study, a report listing of all SUSARs (and SAEs if required by local regulation) that have occurred during this period and a report of the subject's safety will be submitted to the applicable authorities, and as otherwise required by local laws.

Reporting of SAEs by the Investigator to his/her local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be done in accordance with the standard operating procedures (SOPs) and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified.

6.7.2. Clinical Laboratory Tests

Clinical laboratory tests will be performed at local laboratories. It is anticipated that subjects will undergo laboratory testing both as an inpatient and an outpatient. The Investigator will provide to the Sponsor or its designee the current licensure and laboratory reference ranges for all laboratories used during the study.

Clinical laboratory tests will include serum chemistry, hematology, pregnancy, urinalysis, and coagulation (Table 6). Collection frequency is outlined in the Schedule of Procedures and Assessments in Appendix 1. If a subject is at risk for exceeding maximal allowable blood draw limits, the blood draw schedules for laboratory assessments may be adjusted per local physician's practice to ensure subject safety and to remain below the blood draw maximums.

Table 6: Clinical Laboratory Tests

Serum Chemistry	**Hematology**
ALT	Hemoglobin
Albumin	Hematocrit
ALP	MCV
AST	Platelet count
BUN	WBC count with differential
Calcium	
Chloride	
Creatinine	**Coagulation**
Glucose	aPTT
Inflammatory markers[a]	INR
Magnesium	
Phosphorus	
Potassium	**Urine Tests**
Pregnancy (by local blood or urine test)[b]	Urinalysis

Serum Chemistry	Hematology
Sodium	
Total bilirubin, direct bilirubin, and indirect bilirubin	
Total protein	

[a] Inflammatory markers including, but not limited to, c-reactive protein and ferritin, will be examined at the treating physician's discretion.
[b] Test will not be part of statistical analysis.
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; MCV = mean corpuscular volume; WBC = white blood cell.

Laboratory values that appear or worsen after written informed consent is obtained and are assessed as clinically significant by the Investigator are AEs and must be recorded as AEs (see Sections 6.7.1.1 and Section 6.7.1.5).

6.7.3. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, peripheral capillary oxygen saturation, and body temperature. The method for measuring body temperature (eg, oral, tympanic, rectal, or axillary) is to be recorded. Vital signs will be measured at least once daily through CAR-T Day +7 (Study Day 13) or until discharge post-start of defibrotide treatment/early termination visit.

Adverse events determined from vital sign measurements must be recorded (see Section 6.7.1.5).

6.7.4. ECOG PS

Functional impairment will be assessed using the ECOG PS (Table 7).

Table 7: ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Abbreviations: ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al. 1982.

6.7.5. Response to Treatment with Yescarta

Although unlikely, the negative impact of defibrotide on Yescarta efficacy cannot be excluded. When done as part of standard of care by PET scan (with or without bone marrow evaluation), data from Investigator assessed lymphoma response (CR, partial response [PR], stable disease [SD], progressive disease [PD], NE) to Yescarta therapy will be captured in the eCRF. Subjects who complete the CAR-T Day +37 visit but do not yet have lymphoma response data available will remain on the study until data become available or until CAR-T Day +60, whichever occurs first.

6.8. Appropriateness of Measurements

The safety assessments used in this study are typical for a Phase 2 study and are based on the safety profile of defibrotide, as characterized in several clinical studies and postmarketing experience in another indication.

The efficacy endpoint of incidence and severity of CAR-T-associated neurotoxicity is measured by the CTCAE and ASBMT consensus grading systems. CTCAE is a widely accepted method of documenting toxicity grades and was used in previous CAR-T clinical studies. In addition, the ASBMT consensus grading is a relatively new grading system, but is based on expert discussions published by the ASBMT. Therefore, these methods are complementary for evaluating CAR-T-associated neurotoxicity.

7. STUDY ASSESSMENTS

A schedule of study procedures and assessments for subjects is provided in Appendix 1.

7.1. Screening Evaluations

Note: Subjects who failed screening may be rescreened if deemed eligible at a later time.

The following evaluations should be completed during screening (CAR-T Days -28 to -6 [Study Days -22 to -1]), unless otherwise indicated:

- Informed consent (obtained prior to any study activities).
- Inclusion/exclusion criteria (eligibility must be confirmed before enrollment).
- Demographics.
- Medical history: Medical history, information pertaining to underlying disease, and any information pertaining to Yescarta therapy should be collected.
- Prior medications: Include those current at the time of screening, and all prior therapies for the primary disease within 90 days of signing informed consent.
- Vital signs.
- Physical examination, height, weight, and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests).

  Labs obtained during screening or within 14 days prior to screening on a non-screening test if the test was performed as part of subject's routine standard of care will be acceptable. All laboratory criteria must be met concurrently. Screening labs can be repeated 2 additional times.
- Pregnancy test (by local blood or urine test; Table 6) is required for females of childbearing potential (ie, not postmenopausal or surgically sterile), and may be performed per institutional practices.
- AEs. All AEs from the time written informed consent is obtained must be recorded.

7.2. Baseline (CAR-T Day -5) Evaluations

Study drug administration (QD) will begin on CAR-T Day -5 (Study Day 1). Initiation of defibrotide administration is not to occur until all other visit-specific assessments have been performed.

The following evaluations should be completed at baseline (defined as the day of the first defibrotide infusion [CAR-T Day -5 (Study Day 1)], but prior to the start of infusion):

- Vital signs.

- Physical examination, weight, and subject symptoms. Note: Baseline weight is the weight used to calculate the dose of defibrotide.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests).
- Pregnancy test (by local blood or urine test; Table 6) must be performed at baseline, and at 30 days after the last dose of study drug. Pregnancy test is required for females of childbearing potential (ie, not postmenopausal or surgically sterile), and may be performed per institutional practices.
- Neurological evaluation
  - Subjects will be assessed for CAR-T-associated neurotoxicity using the ASBMT consensus grading system . If necessary, neurologist evaluation will be recommended.
  - Details from imaging studies and EEG to assess neurotoxicity done as part of standard of care will be collected.
- Hospitalization data: Includes dates of hospitalization, dates in ICU, and dates of readmissions.
- Biomarkers: Blood samples will be collected for biomarker analysis (refer to Section 6.4 for details).
- Blood samples will be collected for PK analysis as described in Section 6.6.
- Concomitant medications.
- AEs. AEs that are ongoing should be followed up to determine whether they have resolved.
- Survival status.

7.3. During Defibrotide Administration Evaluations

7.3.1. Physical Examination

Complete physical examination, including weight and assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, extremities, and a general assessment (including edema) will be performed. Height will be measured at screening only.

Adverse events determined from physicial examinations must be recorded (see Section 6.7.1.5).

7.3.2. Pre-lymphodepletion Chemotherapy (CAR-T Days -4 and -3)

Study drug administration (QD) will occur on CAR-T Days -4 and -3 (Study Days 2 and 3). Initiation of defibrotide administration on each day is not to occur until all other visit-specific assessments have been performed.

The following evaluations should be completed on CAR-T Days -4 and -3 (Study Days 2 and 3) according to Appendix 1:

- Vital signs.
- Physical examination and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests).
- Hospitalization data.
- Biomarkers: Blood samples will be collected for biomarker analysis (refer to Section 6.4 for details).
- Concomitant medications.
- AEs. AEs that are ongoing should be followed up to determine whether they have resolved.
- Survival status.

7.3.3. CAR-T Day 0

Study drug administration (QID) will occur on CAR-T Day 0 (Study Day 6). Initiation of defibrotide administration can occur at any time relative to other visit-specific assessments.

At least 2 doses of defibrotide must be administered on CAR-T Day 0 (Study Day 6) prior to administration of CAR-T-cell therapy (Yescarta). CAR-T-cell therapy (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). All visit assessments are to be performed prior to CAR-T therapy.

The following evaluations should be completed on CAR-T Day 0 (Study Day 6) and as describedin Appendix 1:

- Vital signs.
- Physical examination, weight, and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests). Laboratory samples will be collected daily while inpatient only.
- Neurological evaluation
  - Subjects will be assessed for CAR-T-associated neurotoxicity using the ASBMT consensus grading system and seizures. If necessary, neurologist evaluation will be recommended. On CAR-T Day 0 (Study Day 6) until discharge (ie, during hospitalization), neurological evaluation is performed every 8 ±2 hours as a standard of care.
  - Details from imaging studies and EEG to assess neurotoxicity done as part of standard of care will be collected.
- Hospitalization data.

- Biomarkers: Blood samples will be collected for biomarker analysis (refer to Section 6.4 for details).
- Blood samples will be collected for PK analysis as described in Section 6.6.
- Concomitant medications.
- AEs. AEs that are ongoing should be followed up to determine whether they have resolved.
- Survival status.

7.3.4. CAR-T Days +1 to +7

Study drug administration (QID) will occur on CAR-T Days +1 to +7 (Study Days 7 to 13). Initiation of defibrotide administration on each day can occur at any time relative to other visit-specific assessments.

The following evaluations should be completed daily on CAR-T Days +1 to +7 (Study Days 7 to 13) and as described in Appendix 1:

- Vital signs.
- Physical examination and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests). Laboratory samples will be collected daily while inpatient only.
- Neurological evaluation
  - Subjects will be assessed for CAR-T-associated neurotoxicity using the ASBMT consensus grading system and seizures. If necessary, neurologist evaluation will be recommended. On CAR-T Day 0 (Study Day 6) until discharge (ie, during hospitalization), neurological evaluation is performed every 8 ±2 hours as a standard of care.
  - Details from imaging studies and EEG to assess neurotoxicity done as part of standard of care will be collected.
- Hospitalization data.
- Biomarkers: Blood samples will be collected for biomarker analysis (refer to Section 6.4 for details).
- Blood samples will be collected for PK analysis as described in Section 6.6.
- Concomitant medications.
- AEs. AEs that are ongoing should be followed up to determine whether they have resolved.
- Survival status.

7.4. Post-defibrotide Administration Evaluations

7.4.1. Inpatient until Discharge (Daily)

Discharge from the hospital is determined by the treating physician.

The following evaluations should be completed daily as described in Appendix 1:

- Vital signs.
- Physical examination and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests). Laboratory samples will be collected daily while inpatient only.
- Neurological evaluation
  - Subjects will be assessed for CAR-T-associated neurotoxicity using the ASBMT consensus grading system and seizures. If necessary, neurologist evaluation will be recommended. On CAR-T Day 0 (Study Day 6) until discharge (ie, during hospitalization), neurological evaluation is performed every 8 ±2 hours as a standard of care. If the hospitalization is prolonged beyond CAR-T Day +7 (Study Day 13) for reasons other than neurotoxicity, neurotoxicity evaluation can be as less frequent as once daily.
  - Details from imaging studies and EEG to assess neurotoxicity done as part of standard of care will be collected.
- Hospitalization data.
- Biomarkers: Blood samples will be collected for biomarker analysis (refer to Section 6.4 for details).
- Concomitant medications.
- AEs. AEs that are ongoing should be followed to determine whether they have resolved.
- Survival status.

7.4.2. Outpatient until CAR-T Day +29

Outpatient follow-up is per standard of care.

Any of the following evaluations performed per standard of care should be captured in the appropriate eCRF:

- Vital signs.
- Physical examination and subject symptoms.
- ECOG PS.

- Clinical laboratory tests (please refer to Table 6 for list of tests). Clinical laboratory tests will be completed as part of standard of care.
- Neurological evaluation
  - Subjects will be assessed for CAR-T-associated neurotoxicity using the ASBMT consensus grading system and seizures. If necessary, neurologist evaluation will be recommended.
  - Details from imaging studies and EEG to assess neurotoxicity done as part of standard of care will be collected.
- Hospitalization data.
- Concomitant medications.
- AEs. AEs that are ongoing should be followed up to determine whether they have resolved.
- Survival status.

7.4.3. Primary Efficacy Evaluation Visit

7.4.3.1. CAR-T Day +30

The CAR-T Day +30 evaluation visit needs to occur regardless of inpatient/outpatient visits or variance in window (±3 days) of preceding visit.

The following evaluations should be completed as described in Appendix 1:

- Vital signs.
- Physical examination and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests).
- Pregnancy test (by local blood or urine test; Table 6) must be performed at CAR-T Day +30, and at 30 days after the last dose of study drug. Pregnancy testing is required for females of childbearing potential (ie, not postmenopausal or surgically sterile), and may be performed per institutional practices.
- Neurological evaluation
  - Subjects will be assessed for CAR-T-associated neurotoxicity using the ASBMT consensus grading system and seizures. If necessary, neurologist evaluation will be recommended.
  - Details from imaging studies and EEG to assess neurotoxicity done as part of standard of care will be collected.
- Hospitalization data.
- Concomitant medications.

- AEs. AEs that are ongoing should be followed up to determine whether they have resolved. If any AEs are not resolved, the outcome at the time of the visit should be recorded.
- Survival status.

7.5. End of Study Evaluations

End of study for each subject is the time at which the subject completes the study or the time of death, lost to follow-up, or early termination from the study. 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 will be considered to have completed the study on CAR-T Day +60.

7.5.1. Final Safety Follow-up (CAR-T Day +37)

The following evaluations should be completed on CAR-T Day +37 (+6 days) (either by clinic visit or telephone):

- Hospitalization data.
- Concomitant medications.
- AEs. AEs that are ongoing should be followed up to determine whether they have resolved. If any AEs are not resolved, the outcome at the time of the visit should be recorded.
- Survival status.

7.5.2. Early Study Termination Visit Evaluations

For subjects who prematurely terminate from the study for any reason, effort should be made to complete the following evaluations as described in Appendix 1.

For subjects who prematurely terminate from the study prior to receiving Yescarta, the following evaluations should be performed:

- Vital signs.
- Physical examination, and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests).
- Pregnancy test (by local blood or urine test; Table 6) must be performed at the early termination visit, and at 30 days after the last dose of study drug. Pregnancy test is required for females of childbearing potential (ie, not postmenopausal or surgically sterile), and may be performed per institutional practices.
- Hospitalization data.
- Concomitant medications (Note: Subjects who early terminate after 30 days after the last dose of defibrotide will not be required to report concomitant medications).

- AEs. AEs that are ongoing should be followed up to determine whether they have resolved. If any AEs are not resolved, the outcome at the time of the visit should be recorded.
- Survival status.

For subjects who prematurely terminate from the study after receiving Yescarta, the following evaluations should be performed:

- Vital signs.
- Physical examination, and subject symptoms.
- ECOG PS.
- Clinical laboratory tests (please refer to Table 6 for list of tests).
- Pregnancy test (by local blood or urine test; Table 6) must be performed at the early termination visit, and at 30 days after the last dose of study drug. Pregnancy test is required for females of childbearing potential (ie, not postmenopausal or surgically sterile), and may be performed per institutional practices.
- Neurological evaluation.
  - Subjects will be assessed for CAR-T-associated neurotoxicity using the ASBMT consensus grading system and seizures. If necessary, neurologist evaluation will be recommended.
  - Details from imaging studies to assess for neurotoxicity and EEG (if performed) done as part of standard of care will be collected.
- Hospitalization data.
- PET scan (Note: only performed if done as part of standard of care. Details will be recorded).
- Bone marrow evaluation will be completed if previously positive for lymphoma (Note: only performed as part of standard of care. Details will be recorded).
- Concomitant medications (Note: Subjects who early terminate after 30 days after the last dose of defibrotide will not be required to report concomitant medications).
- AEs. AEs that are ongoing should be followed up to determine whether they have resolved. If any AEs are not resolved, the outcome at the time of the visit should be recorded.
- Survival status.

8. PLANNED STATISTICAL METHODS

8.1. General Considerations

All study data will be summarized either by descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum) for continuous variables (eg, age, weight) or by the number and percentage of subjects for categorical variables (eg, gender, race). All summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.3 or later of the Statistical Analysis System (SAS Institute, Inc. Cary, NC). Baseline for efficacy and safety endpoints is defined as the date of the first dose of defibrotide.

8.2. Tests of Hypotheses and Significance Levels

The primary objective of the study is to assess the efficacy of defibrotide for the prevention of CAR-T-associated neurotoxicity by CAR-T Day +30. A Simon's optimal 2-stage design is employed to test the response rate of administration with defibrotide in the target subject population (Simon 1989). 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%. Simon's optimal 2-stage design requires that the null rate is less than the hypothesized rate, so the hypotheses are formulated using the arithmetic complements. Therefore, the study hypotheses are:

- H_o: The rate of no CAR-T-associated neurotoxicity ≤ 36% (ie, the rate of CAR-T-associated neurotoxicity is at least 64%).

  vs.

- H_a: The rate of no CAR-T-associated neurotoxicity $\underline{\geq}$ 68% (ie, the rate of CAR-T-associated neurotoxicity is no more than 32%).

The null hypothesis will be tested using the Simon's 2-stage design rejection rule (Section 8.3) with a Type I error rate of 0.05 in a 1-sided test.

8.3. Determination of Sample Size

Part 1 (initial lead-in phase) 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 3+3 design. If DLTs are observed in > 1 out of 3 or > 1 out of 6 subjects, then the dose is considered not safe (Figure 5). The highest dose that is determined to be safe (RP2D) will be given to subjects enrolled in Part 2 of the study and will be evaluated for 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 sample size calculation is based on testing the null and alternative hypotheses with an overall 1-sided Type I error of 0.05 and a statistical power of at least 92% when the rate of no CAR-T-associated neurotoxicity rate is ≥ 68%.

Simon's optimal 2-stage design (Simon 1989) is used to avoid unnecessarily exposing subjects to a nonefficacious therapy with defibrotide to prevent CAR-T-associated neurotoxicity. In the first stage, 10 evaluable subjects will be accrued. If there are ≤ 4 subjects without CAR-T-associated neurotoxicity post-CAR-T-cell therapy in these 10 subjects, the study will be stopped. Otherwise, 19 additional subjects will be accrued for a total of 29 subjects. The null hypothesis will be rejected if ≥ 15 subjects without CAR-T-associated neurotoxicity post-CAR-T-cell therapy are observed in these 29 subjects. This design yields a 1-sided Type I error rate of 0.0456 and a power of 92.47% when the true rate of no CAR-T-associated neurotoxicity is 68% (ie, the rate of CAR-T-associated neurotoxicity is 32%).

The operating characteristics of this design are illustrated in Table 8 and Table 9.

Table 8: Statistical Power for a Range of Rates of No CAR-T-associated Neurotoxicity

Null and Alternative Rates of No CAR-T-associated Neurotoxicity	Interpretation	Statistical Power
0.36 vs. 0.68	The historical CAR-T-associated neurotoxicity rate of 64% has been reduced to 32%	92.47%
0.36 vs. 0.64	The historical CAR-T-associated neurotoxicity rate of 64% has been reduced to 36%	86.12%
0.36 vs. 0.60	The historical CAR-T-associated neurotoxicity rate of 64% has been reduced to 40%	76.51%
0.36 vs. 0.56	The historical post-CAR-T-cell CAR-T-associated neurotoxicity rate of 64% has been reduced to 44%	63.65%

Abbreviations: CAR-T = chimeric antigen receptor T-cell.

Table 9: 90% Confidence Intervals for a Range of Subjects Without CAR-T-associated Neurotoxicity

Total Number of Subjects Without CAR-T-associated Neurotoxicity	Stage 1 (Need 5+ Subjects Without CAR-T-associated Neurotoxicity to Enter Stage 2) n_1=10	Stage 2 (Need 15+ Subjects Without CAR-T-associated Neurotoxicity) n_2=29	Estimated Rate of Subjects Without CAR-T-associated Neurotoxicity	p-value[a]	90% CI
17	5	12	57.7%	0.0098	42.19%, 73.09%
	9	8	57.9%	0.0083	42.62%, 73.00%
21	5	16	71.3%	<0.0001	56.05%, 83.87%
	9	12	70.3%	<0.0001	55.93%, 82.34%
24	5	19	85.1%	<0.0001	70.55%, 94.81%
	9	15	80.1%	<0.0001	66.81%, 90.03%
25	6	19	87.9%	<0.0001	74.27%, 96.41%
	9	16	83.5%	<0.0001	70.75%, 92.54%

[a] p-value for the test of H_o: The rate of no CAR-T-associated neurotoxicity ≤ 36% vs. H_a: The rate of no CAR-T-associated neurotoxicity ≥ 68%.

Abbreviations: CAR-T = chimeric antigen receptor T-cell; CI = confidence interval; H_a = alternative hypothesis; H_o = null hypothesis.

The sample size of 29 from the Simon's optimal 2-stage design will yield at least 75% power when the true of rate of no CAR-T-associated neurotoxicity is at least 60% (ie, the corresponding CAR-T-associated neurotoxicity rate is ≤ 40%).

The total sample size comprises the sum of subjects from Part 1 of the study, described in Section 3.1.1.2, and those from Part 2 of the study, described in Section 3.1.1.3. 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 1 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 noneligible for the efficacy evaluation (ie, not in the Efficacy Evaluable Analysis Set defined in Section 3.1 and Section 8.4), 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.

8.4. Analysis Sets

The Efficacy Evaluable Analysis Set will include:

- All subjects 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
- All subjects who discontinued treatment due to post-CAR-T-associated neurotoxicity before receiving 18 doses of defibrotide.

In addition, subjects whose Yescarta infusion is delayed by more than 2 days from the original schedule are considered NE for efficacy.

This is the primary analysis set for efficacy analyses.

The All Enrolled Analysis Set will include all enrolled subjects treated at the RP2D. This is the analysis set for the sensitivity analyses on the primary efficacy endpoint and the secondary efficacy endpoint on the incidence of CRS.

The Safety Analysis Set will include all subjects who received at least 1 dose of defibrotide. This is the primary analysis set for safety analyses.

The PK Analysis Set will include all subjects who received at least 1 dose of defibrotide and had at least 1 evaluable PK concentration. This analysis set will be used for all descriptive PK summaries.

The PK Evaluable Analysis Set will include all subjects in the PK Analysis Set whose key PK parameters such as AUC_{tau}, CL_{tot}, and $t_{½}$ can be determined.

8.5. Handling of Dropouts and Missing Data

Every effort will be made to minimize missing data. For the secondary endpoint on lymphoma response, missing data will be handled using a "Missing=Failure" approach.

8.6. Pooling of Investigation Centers

Data from all study centers will be pooled.

8.7. Demographics and Baseline Characteristics

The summaries of demographics and baseline characteristics will be provided for the Safety Analysis Set.

Relevant medical history findings and prior medications will be summarized by SOC and anatomical therapeutic chemical codes, respectively, using descriptive statistics.

8.8. Efficacy Endpoints and Analyses

All primary efficacy analyses (ie, the primary and secondary efficacy endpoints) will be performed using the Efficacy Evaluable Analyis Set. A sensitivity analysis will be performed for the primary efficacy endpoint using the All Enrolled Analysis Set.

8.8.1. Primary Efficacy Endpoint and Analyses

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. The study hypotheses are:

- H_o: The rate of no CAR-T-associated neurotoxicity $\leq$ 36% (ie, the rate of CAR-T-associated neurotoxicity is at least 64%).

  vs.

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

These hypotheses will be tested using the Simon's 2-stage design rejection rule (Section 8.3) with a Type I error rate of 0.05 in a 1-sided test.

Estimation of the rate of no CAR-T-associated neurotoxicity will use the method of Koyama and Chen (Koyama & Chen 2008), which incorporates the 2-stage design. The corresponding confidence interval (CI) and the p-value will also be calculated using the method of Koyama and Chen. If the Stage 2 actual sample size is not the planned sample size, the method that takes into account the planned and actual sample size for the Simon's design used will be employed to calculate the rate, CI, and p-value for no CAR-T-associated neurotoxicity (Koyama & Chen 2008), and rejection of the null hypothesis after Stage 2 will be based on the p-value from the Koyama and Chen method.

8.8.2. Secondary Efficacy Endpoints and Analyses

8.8.2.1. Incidence of CAR-T-associated Neurotoxicity by CAR-T Day +30

Incidence of CAR-T-associated neurotoxicity by CAR-T Day +30 will be summarized descriptively based on the following grading criteria: Grade 3 or greater by CTCAE v5.0, any grade by the ASBMT consensus grading system (Lee et al. 2018), and Grade 3 or greater by the ASBMT consensus grading system. All 3 incidence rates will be reported.

8.8.2.2. Incidence of CRS by CAR-T Day +30

Incidence of CRS (all grades, according to ASBMT criteria, defined by the ASBMT consensus grading system [Lee et al. 2018]) by CAR-T Day +30 will be summarized descriptively.

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

The proportion of subjects using high dose steroids, the time in days to the start of high dose steroids, and the duration of use will be summarized descriptively.

8.8.3. Sensitivity Efficacy Analyses

Sensitivity analyses will be performed for the primary efficacy endpoint and the secondary efficacy endpoint on the incidence of CRS using the All Enrolled Analysis Set.

8.9. Pharmacokinetics Assessments

Defibrotide plasma concentrations will be measured using validated bioanalytical methods. Pharmacokinetic parameters for each individual will be calculated using non-compartmental analysis. Individual plasma concentrations will be listed by subject and summarized by dose level, day and nominal time point using descriptive statistics (ie, N, arithmetic mean, standard deviation, percent coefficient of variation, median, minimum, maximum, and geometric mean). Individual and summary figures of plasma concentration-time profiles will be provided in semi-log and linear scales. A summary of PK concentrations will be conducted on the PK Analysis Set.

Individual plasma PK parameters will be listed by subject and summarized for each study cohort using the descriptive statistics as mentioned above. Summary of PK parameters will be conducted on the PK Evaluable Analysis Set.

8.10. Safety Endpoints and Analyses

Safety analyses will be conducted using the Safety Analysis Set.

8.10.1. Adverse Events

Adverse events will be coded using the MedDRA to classify events under primary SOC and preferred term.

The number and percentage of subjects who experienced TEAEs, TESAEs, TEAEs leading to discontinuation of study drug, Grade 3 and 4 TEAEs, and deaths will be summarized using the Safety Analysis Set. Results will be presented by SOC and preferred term. The overview will also report TEAEs by maximum severity.

The number and percentage of subjects with treatment-related TEAEs (including AEs associated with abnormal physical examination findings), TESAEs, TEAEs leading to discontinuation of study drug, Grade 3 and 4 TEAEs, and subjects who have died will also be summarized.

For all AE summaries, if a subject has more than 1 AE within a preferred term, the subject is counted only once at the maximum severity and with the closest relationship to study drug. If a subject has more than 1 AE within a SOC, the subject is similarly counted once when reporting results for that SOC.

All AE data will be listed. The information presented will include subject number, primary SOC and preferred term, date of onset, severity, relationship to study drug, action taken, and stop date (if available).

8.10.2. Vital Signs, Clinical Laboratory Results, and ECOG Performance Status

Vital signs, clinical laboratory results, and ECOG PS measures will be listed.

8.10.3. Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary and will be summarized using descriptive statistics.

8.10.4. Response to Treatment with Yescarta

Although unlikely, the negative impact of defibrotide on Yescarta efficacy cannot be excluded. We will also record and report the Investigator assessed outcome of Yescarta response (CR, PR, SD, PD, NE) at each timepoint, which is generally determined by PET scan with or without bone marrow evaluation between CAR-T Day +30 and CAR-T Day +60 as standard of care.

8.11. Exploratory Endpoints and Analyses

Summaries for biomarkers will be provided by collection time. Additional exploratory analyses may be performed and will be specified in the Statistical Analysis Plan, as appropriate.

9. DATA QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor or its designee. Data are reviewed throughout the study through programmed checks, reports, and manual review. Any discrepancies will be resolved with the Investigator or designees as appropriate.

Quality assurance audits may be performed at the discretion of the Sponsor.

9.1. Clinical Data Management

The standard procedures for handling and processing clinical data will be followed in compliance with 21 CFR Part 11, FDA and ICH Regulations and Guidelines, GCP, and the SOPs of Jazz Pharmaceuticals or the contract research organization (CRO). A comprehensive Data Management Plan (DMP) will be developed to document data sources, systems, and handling.

9.2. Electronic Case Report Forms

All subject data required by the protocol to be reported to the sponsor on each trial subject will be recorded by clinical site staff in eCRFs developed by Jazz Pharmaceuticals or its designee, unless such data are transmitted to the sponsor or designee electronically (eg, central laboratory data, data from an Interactive Response Technology system). Electronic data sources will be identified in the DMP. The Principal Investigator must review the eCRFs and provide his/her signature certifying that he/she has reviewed the data and considers them complete and accurate to the best of his/her knowledge. Regardless of who signs or completes the forms, it is the Principal Investigator's responsibility to ensure their completeness and accuracy.

9.3. Retention of Data

The Investigator/institution will maintain the study documents as specified in Essential Documents for the Conduct of a Trial (ICH E6 Good Clinical Practice) and as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution when these documents no longer need to be retained.

9.4. Data and Safety Monitoring

Establishing a Data and Safety Monitoring Board is not planned for this trial on account of the small sample size, the short time frame and duration of treatment in the study, and the established safety profile of the study drug. The Sponsor recognizes the importance of ongoing

review of the accumulating safety data and will perform periodic data monitoring regularly by data listing review. In addition, safety data from the study will be reviewed on an ongoing basis as part of routine pharmacovigilance and safety surveillance activities. Reports of safety findings (from either single events or based on aggregate review) that suggest a significant risk to humans will be distributed to all participating Investigators and to the relevant regulatory authorities and IRBs/IECs.

The Sponsor acknowledges the role of Data and Safety Monitoring Boards in carrying out important aspects of clinical trial monitoring, especially related to evaluating the accumulating outcome data. However, on the basis of the study design (single arm, open-label, small number of treated subjects, short duration and treatment period) without consideration for early termination for efficacy and the established safety profile of the study drug, the Sponsor believes that a Data and Safety Monitoring Board is not required for the study, and that this opinion is in line with the FDA guidance (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees, March 2006).

9.5. Safety Assessment Committee

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. Dose-limiting toxicities will be identified by the SAC as described in Section 3.1.1.1. The SAC will review AEs in Part 1 of the study for each cohort of 3 subjects according to the escalation scheme described in Figure 5 to determine the RP2D. In Part 2 of the study, the SAC will continue monitoring safety. All roles and responsibilities of the SAC, as well as the timing of safety reviews, will be fully described in a charter.

10. ADMINISTRATIVE CONSIDERATIONS

10.1. Investigators and Study Administrative Structure

Parties (eg, Sponsor, CROs, and vendors) responsible for the various functions in this study will be listed in a separate document and filed in the Trial Master File.

10.2. Institutional Review Board or Independent Ethics Committee Approval

This study will be conducted in accordance with IRB regulations (eg, US 21 CFR 56.103) or IEC regulations. The final approved protocol and the ICF will be reviewed by the IRB/IEC. In addition, the IRB/IEC will review any other written information to be provided to the subject, advertisements for subject recruitment (if used), and subject compensation (if any). The committee's decision concerning conduct of the study will be sent in writing to the Investigator and a copy will be forwarded to the Sponsor. The Investigator will agree to make any required progress reports, as well as reports of SAEs, life-threatening problems, death, or any significant protocol deviations, as required by the IRB/IEC.

A list of the IRB/IEC members who actually participated in the review, their respective titles (occupational identification), and institutional affiliations or an IRB/IEC assurance number must be provided to the Sponsor. The approval letter or notice must be provided on IRB/IEC letterhead and contain the date of the meeting and sufficient information to identify the version of the protocol unambiguously (by name and number) and state that the ICF was also reviewed.

A clinical study may not be initiated before the proposed protocol and ICF have been reviewed and unconditionally approved by an IRB/IEC. The clinical study remains subject to continuing review by the IRB/IEC at least annually. The Sponsor or its designee will supply all necessary data for the Investigator to submit to the IRB/IEC. The Sponsor will not ship clinical supplies to an investigational site until written signed approval from the site's IRB/IEC has been received by the Sponsor.

The Investigator is responsible for ensuring initial and continued review and approval of the clinical study by the IRB/IEC at his/her site. The Investigator must also ensure that he/she will promptly report to the IRB/IEC and the Sponsor all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he/she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent hazards to human subjects. If the study remains in progress for more than 1 year, documentation of annual review by the IRB/IEC must be maintained.

10.3. Ethical Conduct of the Study

This study will be conducted in compliance with this protocol, GCP, and applicable regulatory requirements, and in accordance with the SOPs of the CRO or the Sponsor, as applicable.

Endorsement of the ethical principles embedded in the above guidances and regulations ensures that the rights, safety, and well-being of study subjects are protected and are consistent with the

principles that have their origin in the Declaration of Helsinki, World Medical Association – "Ethical Principles for Medical Research Involving Human Subjects."

Sponsor signatures indicating approval of this protocol are provided in Appendix 6.

10.4. Subject Information and Consent

All subjects will provide their written informed consent before the performance of any study-related procedures.

Written informed consent is to be obtained from each subject prior to enrollment into the study.

Each subject's chart will have his/her signed ICF for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF will be kept in the Investigator's central study file. Regulatory authorities may check the existence of the signed ICF in this central study folder if not having done so during the performance of the trial.

10.5. Subject Confidentiality

All reports and communications relating to the subjects in the study will identify each subject only by the subject's study number. These documents will be treated with strict adherence to professional standards of confidentiality and will be filed at the study site under adequate security and restricted access.

Portions of the subject's medical records pertinent to the study may be reviewed by the Sponsor or its designee, the governing IRB/IEC, and governmental agency to ensure accuracy and completeness of the source documents and data in the eCRFs.

10.6. Protocol Adherence and Protocol Amendments

The protocol must be read thoroughly and the instructions must be followed exactly.

The Investigator must not implement any deviation from the protocol. Any changes in the protocol will require a formal amendment. The IRB/IEC will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB/IEC approval has been received.

10.7. Required Documents

The Investigator must provide the Sponsor or its designee with the applicable regulatory documents before the enrollment of any subject (copies must be filed and maintained by the Investigator in the Investigator's regulatory document binder).

10.8. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the Investigator. This will include telephone calls and onsite visits. During the onsite visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data verification, source documents will be made available for review by the site. The study monitor will also perform drug accountability checks and will periodically request review of the

Investigator study file to assure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The Investigator or appointed delegate will receive the study monitor during these onsite visits and will cooperate in providing the documents for review and respond to inquiries. In addition, the Investigator will permit inspection of the study files by authorized representatives of the IRB/IEC and applicable regulatory agencies.

10.9. Protocol Deviations

All major protocol deviations must be reported to the IRB/IEC in an expedited fashion per the IRB/IEC guidelines. Reports of protocol deviations should be submitted to the Sponsor or designee continuously.

10.10. Access to Source Documentation

The Sponsor (or its designee) will be responsible for monitoring this clinical study. The Sponsor will monitor the study conduct, proper eCRF entry, source documentation completion and retention, and accuracy of study drug accountability. To this end, a monitor will visit the study site at suitable intervals and be in frequent contact with the site through verbal and written communication. It is essential that the monitor have access to all documents (related to the study and the individual subjects) at any time they are requested. In turn, the monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and his/her staff will be expected to cooperate with the monitor, to be available during the monitoring visit to answer questions, and to provide relevant information.

In addition, representatives of the Quality Assurance Department at the Sponsor (or equivalent), or appointed monitoring organization(s), and representatives of the FDA or other regulatory agencies may request to inspect the study documents (eg, study protocol, eCRFs, study drug accountability records, original medical records/files). All subject data will be treated confidentially.

10.11. Data Generation and Analysis

Information regarding data management and data collection is provided in Sections 9.1 and 9.2, respectively. Information on planned data analyses is provided in Section 8.

10.12. Publication and Disclosure Policy

Please refer to individual site contracts for specific contractual obligations and requirements.

All information concerning defibrotide, operations at Jazz Pharmaceuticals, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Jazz Pharmaceuticals to the Investigator and not previously published, are considered confidential and remain the sole property of Jazz Pharmaceuticals. Electronic CRFs also remain the property of Jazz Pharmaceuticals. The Investigator agrees to use this information only to complete this study and will not use it for other purposes without written consent of Jazz

Pharmaceuticals as further detailed in the Clinical Study Agreement signed by the Investigator and/or institution.

It is understood by the Investigator that Jazz Pharmaceuticals will use the information obtained in this clinical study in connection with the study of defibrotide, and therefore may disclose this information as required to other Jazz Pharmaceuticals Investigators, appropriate international regulatory agencies, or others. In agreeing to participate in this study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to Jazz Pharmaceuticals. Jazz Pharmaceuticals requires that permission to publish details of this study must be obtained in writing as further detailed in the Clinical Study Agreement signed by the Investigator and/or institution. It is intended that the results of this study may be published in scientific literature. In addition, results will be provided for Applicable Clinical Trials on ClinicalTrials.gov. The conditions noted here are intended to protect commercial confidential materials (patents, etc.) and not to restrict publication.

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APPENDIX 1. SCHEDULE OF PROCEDURES AND ASSESSMENTS

			During Defibrotide Administration			Post-defibrotide Administration			End of Study[a]	
	Screening	**Baseline[b]**	**Pre-lymphodepletion Chemotherapy[c]**	**CAR-T Therapy[d]**	**Post CAR-T Therapy**	**Inpatient until Discharge (Daily)[e]**	**Outpatient until CAR-T Day +29[f]**	**Primary Efficacy Evaluation Visit[g]**	**Final Safety Follow-Up[h]**	**Early Study Termination[i]**
CAR-T Day	**Prior to -5**	**-5**	**-4, -3**	**0**	**+1 to +7**	**+8 to discharge (daily)**	**Discharge to +29 (per standard of care)**	**+30**	**+37**	**NA**
Study Day	**Prior to 1**	**1**	**2, 3**	**6**	**7 to 13**	**14 to discharge (daily)**	**Discharge to 35 (per standard of care)**	**36**	**43**	**NA**
Window (days)	***-22***	***NA***	***NA***	***NA***	***NA***	***NA***	***NA***	***±3***	***+6***	***NA***
Informed consent	X									
Inclusion/exclusion criteria[j]	X									
Enrollment	X									
Demographics	X									
Medical history/underlying disease history/Yescarta therapy information[k]	X									
Prior medications[l]	X									
Vital signs	X	X	X	X	X	X	X	X		X
Physical exam and subject symptoms	X	X	X	X	X	X	X	X		X

			During Defibrotide Administration			Post-defibrotide Administration			End of Study[a]	
	Screening	**Baseline[b]**	**Pre-lymphodepletion Chemotherapy[c]**	**CAR-T Therapy[d]**	**Post CAR-T Therapy**	**Inpatient until Discharge (Daily)[e]**	**Outpatient until CAR-T Day +29[f]**	**Primary Efficacy Evaluation Visit[g]**	**Final Safety Follow-Up[h]**	**Early Study Termination[i]**
CAR-T Day	**Prior to -5**	**-5**	**-4, -3**	**0**	**+1 to +7**	**+8 to discharge (daily)**	**Discharge to +29 (per standard of care)**	**+30**	**+37**	**NA**
Study Day	**Prior to 1**	**1**	**2, 3**	**6**	**7 to 13**	**14 to discharge (daily)**	**Discharge to 35 (per standard of care)**	**36**	**43**	**NA**
Window (days)	***-22***	***NA***	***NA***	***NA***	***NA***	***NA***	***NA***	***±3***	***+6***	***NA***
Height and weight[m]	X	X		X						
ECOG PS	X	X	X	X	X	X	X	X		X
Clinical laboratory tests[n]	X	X	X	X	X	X	X	X		X
Pregnancy test[o]	X	X						X		X
Neurological evaluation[p]		X		X[q]	X[q]	X[q]	X	X		X
Hospitalization data[r]		X	X	X	X	X	X	X	X	X
Biomarkers[s]		X	X	X	X	X				
PK sampling[t]		X		X	X					
PET scan[u]										X
Bone marrow evaluation[v]										X
Concomitant medications		X	X	X	X	X	X	X	X	X[w]

	Screening	Baseline[b]	During Defibrotide Administration			Post-defibrotide Administration			End of Study[a]	
			Pre-lymphodepletion Chemotherapy[c]	CAR-T Therapy[d]	Post CAR-T Therapy	Inpatient until Discharge (Daily)[e]	Outpatient until CAR-T Day +29[f]	Primary Efficacy Evaluation Visit[g]	Final Safety Follow-Up[h]	Early Study Termination[i]
CAR-T Day	**Prior to -5**	**-5**	**-4, -3**	**0**	**+1 to +7**	**+8 to discharge (daily)**	**Discharge to +29 (per standard of care)**	**+30**	**+37**	**NA**
Study Day	**Prior to 1**	**1**	**2, 3**	**6**	**7 to 13**	**14 to discharge (daily)**	**Discharge to 35 (per standard of care)**	**36**	**43**	**NA**
Window (days)	***-22***	***NA***	***NA***	***NA***	***NA***	***NA***	***NA***	***±3***	***+6***	***NA***
Adverse events[x]	X	X	X	X	X	X	X	X	X	X
Study drug administration[y]		X (QD)[z]	X (QD)[z]	X (QID)[aa]	X (QID)[aa]					
Survival status		X	X	X	X	X	X	X	X	X

[a] End of study for each subject is the time at which the subject completes the study or the time of death, lost to follow-up, or early termination from the study. 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 will be considered to have completed the study on CAR-T Day +60.
[b] Baseline is defined as the day of the first defibrotide infusion (CAR-T Day -5 [Study Day 1]), but prior to the start of infusion.
[c] Defibrotide will be administered on CAR-T Days -5, -4, and -3 (Study Days 1, 2, and 3). The window between the end of defibrotide infusion and start of lymphodepletion chemotherapy should not exceed 2 hours.
[d] At least 2 doses of defibrotide must be administered on CAR-T Day 0 (Study Day 6) prior to administration of CAR-T-cell therapy (Yescarta). CAR-T-cell therapy (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). All visit assessments are to be performed prior to CAR-T therapy.
[e] Discharge from the hospital is determined by the treating physician.
[f] Outpatient follow-up is per standard of care, and any evaluations performed should be captured in the appropriate eCRF.
[g] Primary efficacy evaluation visit at CAR-T Day +30 needs to occur regardless of inpatient/outpatient visits or variance in window (±3 days) of preceding visit.
[h] The final safety follow-up visit may occur by clinic visit or telephone.
[i] If the subject prematurely terminates from the study prior to receiving Yescarta, neurological evaluation, PET scan, bone marrow evaluation do not need to be performed.
[j] Eligibility must be confirmed before enrollment.
[k] Medical history, information pertaining to underlying disease, and any information pertaining to Yescarta therapy should be collected.
[l] Prior medications include those current at the time of screening, and all prior therapies for the primary disease within 90 days of signing informed consent.

[m] Weight will be collected at Screening, on CAR-T Day -5 (Study Day 1) (baseline), and on CAR-T Day 0 (Study Day 6) only. Baseline weight is the weight used to calculate the dose of defibrotide. Height is only required at the screening visit.
[n] Clinical laboratory tests should include serum chemistry (ALT, albumin, ALP, AST, BUN, calcium, chloride, creatinine, glucose, inflammatory markers, magnesium, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, indirect bilirubin, and total protein), hematology (hemoglobin, hematocrit, MCV, platelet count, and WBC count with differential), coagulation parameters (aPTT, INR), and urinalysis. Note: Inflammatory markers including, but not limited to, c-reactive protein and ferritin, will be examined at the treating physician's discretion.
[o] Pregnancy test (by local blood or urine test) must be performed at screening, baseline, CAR-T Day +30, early termination visit, and at 30 days after the last dose of defibrotide. Pregnancy test is required for females of childbearing potential (ie, not postmenopausal or surgically sterile), and may be performed per institutional practices.
[p] Subjects will be assessed for CAR-T-associated neurotoxicity based on AEs (graded for severity by CTCAE v5.0), the ASBMT consensus guideline, and seizures. If necessary, neurologist evaluation will be recommended. Details from imaging studies and EEG to assess neurotoxicity done as part of standard of care will be collected.
[q] On CAR-T Day 0 (Study Day 6) until discharge (ie, during hospitalization), neurological evaluation is performed every 8 ±2 hours. If the hospitalization is prolonged beyond CAR-T Day +7 (Study Day 13) for reasons other than neurotoxicity, neurological evaluation can be as less frequent as once every visit, that happens at least every 7 days until CAR-T Day +30.
[r] Hospitalization data includes dates of hospitalization, dates in ICU, and dates of readmissions.
[s] Serum cytokines including markers of endothelial damage are analyzed from serial blood samples, which will be collected once daily on CAR-T Days -5 and -3 (Study Days 1 and 3) and once every other day starting from CAR-T Day 0 (Study Day 6) to discharge, but not beyond CAR-T Day +14. In addition, blood collection will be peformed once on CAR-T Day +14 (±3 days) and once on CAR-T Day +30 (±3 days), which may be performed either in the hospital or as an outpatient.
[t] Blood samples will be collected as described in Table 4.
[u] PET scan will only be performed if done per standard of care. Details will be recorded.
[v] Bone marrow evaluation will be completed if previously positive for lymphoma (only performed as part of standard of care). Details will be recorded.
[w] Subjects who early terminate after 30 days after the last dose of defibrotide will not be required to report concomitant medications.
[x] Investigator must record all AEs and SAEs that occur from the time written informed consent is obtained throughout the study drug administration and through 30 days after the last dose of study drug. AEs that are ongoing should be followed up at each visit to determine whether they have resolved. Only SAEs considered by the Investigator to be related to study drug or study procedures must be reported after 30 days from the last dose of study drug.
[y] Administered intravenously as 2-hour (±15 min) infusions.
[z] Initiation of defibrotide administration is not to occur until all other visit-specific assessments have been performed.
[aa] On CAR-T Days 0-7 (Study Days 6-13), initiation of defibrotide administration can occur at any time relative to other visit-specific assessments.
Abbreviaitons: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; ASBMT = American Society of Blood and Marrow Transplant; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CAR-T = chimeric antigen receptor T (in this study, Yescarta); CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EEG = electroencephalography; ICU = intensive care unit; INR = international normalized ratio; MCV = mean corpuscular volume; NA = not applicable; PET = positron emission tomography; PK = pharmacokinetic(s); PS = performance status; QD = once daily; QID = 4 times per day; SAE = serious adverse event; WBC = white blood count.

APPENDIX 2. MEDDRA HIGH LEVEL GROUP TERMS INDICATIVE OF NEUROTOXICITY

The high-level group terms that are indicative of neurotoxicity include (Topp 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 3. CTCAE VERSION 5.0

The severity of neurotoxicity events (defined in Appendix 2) 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 ventriculomegaly	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	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					

Nervous system disorders					
	Grade				
CTCAE Term	1	2	3	4	5
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 4. 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. 2018

APPENDIX 5. 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. 2018

APPENDIX 6. SIGNATURES OF AGREEMENT FOR PROTOCOL

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®)

Study Number: JZP395-201

Final Date: 09 February 2019

This clinical study protocol was subject to critical review and has been approved by Jazz Pharmaceuticals.

PI [redacted]

Date: 12 February 2019

Jazz Pharmaceuticals

PI [redacted]

12-Feb-2019

PI [redacted]

Date: 12 Feb 2019

Jazz Pharmaceuticals