

Protocol Number: ADCT-402-201

**Official Title: Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and
Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory
Diffuse Large B-Cell Lymphoma (DLBCL)**

NCT Number: NCT03589469

Document Date: 09 July 2019

CLINICAL STUDY PROTOCOL

IND: 126138

EudraCT Number: 2017-004288-11

A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

PROTOCOL NO.: ADCT-402-201

Sponsor:

ADC Therapeutics SA
[Redacted]

Sponsor Contact:

[Redacted]

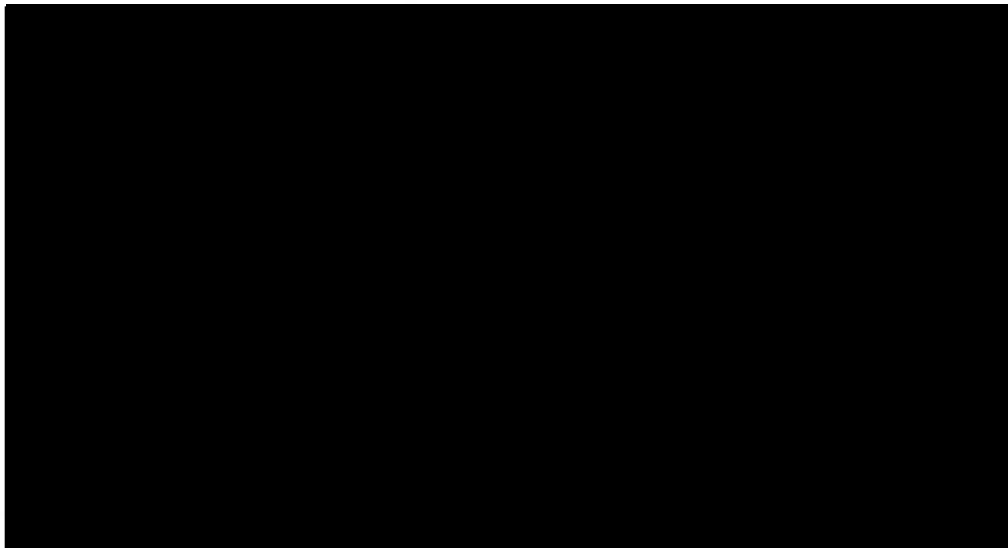
Date of Original Protocol:	09 March 2018
Protocol Amendment 1:	05 April 2018
Protocol Amendment 2:	24 September 2018
Protocol Amendment 3:	07 June 2019
Protocol Amendment 4:	09 July 2019

Confidentiality Statement

The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the express written consent of ADC Therapeutics SA.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)
Protocol Number	ADCT-402-201
Date of Original Protocol:	09 March 2018
Protocol Amendment 1:	05 April 2018
Protocol Amendment 2:	24 September 2018
Protocol Amendment 3:	07 June 2019
Protocol Amendment 4:	09 July 2019



Declaration of Investigator

I have read and understood all sections of the protocol entitled: “A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)” and the accompanying Investigator’s Brochure (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol, dated 09 July 2019, the current version of International Council for Harmonisation (ICH) harmonised tripartite guideline E6: Good Clinical Practice, and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer the study drug only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ADC Therapeutics SA.

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

Protocol Amendment Summary of Changes

Overall Changes and Rationale from Amendment 2

- [Section 6.3](#) was updated to include text regarding monitoring for extravasation during or after study drug infusion because of updated safety information.
- [Section 6.4](#) was modified to clarify dose delays and modifications for non-hematologic and hematologic toxicities.
- [Section 8.1](#) was modified to allow for capture of response information during the follow-up period for patients who receive CAR-T therapy after loncastuximab tesirine treatment.
- [Section 8.2.2](#) was modified to add AE/SAE reporting requirements for patients who receive CAR-T therapy after study drug discontinuation.
- Editorial corrections and clarifications were applied throughout.

Note: Amendment 3 was approved internally by ADC Therapeutics but not submitted to any trial sites, regulatory agencies, or ethics committees. All changes from Amendment 2 are included in Amendment 4.

Table of Contents

Protocol Amendment Summary of Changes.....	4
Table of Contents	5
List of Tables.....	8
List of Figures	8
List of Abbreviations.....	9
Protocol Synopsis.....	12
Schedule of Events.....	18
1 Introduction and Background.....	20
1.1 Diffuse Large B-Cell Lymphoma	20
1.2 Description of Investigational Study Drug	21
1.3 Safety and Efficacy of Loncastuximab Tesirine in Phase 1 Study, ADCT-402-101	22
2 Study Rationale	24
2.1 Rationale for Study Design.....	24
2.2 Rationale for Dose Selection	24
3 Study Objectives and Endpoints.....	26
4 Study Design	27
4.1 Overview.....	27
4.2 Screening Period.....	27
4.3 Treatment Period.....	27
4.4 End of Treatment.....	28
4.5 Follow-up Period	28
4.6 End of Study	28
5 Patient Population.....	29
5.1 Inclusion Criteria	29
5.2 Exclusion Criteria	30
5.3 Screening Failures.....	31
6 Treatment.....	32
6.1 Study Drug.....	32
6.2 Management of Clinical Supplies.....	32

6.2.1	Packaging and Storage	32
6.2.2	Preparation and Administration.....	33
6.2.3	Accountability	33
6.3	Loncastuximab Tesirine Dosing.....	33
6.4	Dose Delays and Modifications	33
6.5	Overdose Management	34
6.6	Premedication and Supportive care	34
6.6.1	Premedication	34
6.6.2	Treatment of Edema and Pleural Effusion.....	34
6.6.3	Treatment and Prophylaxis of Infusion-Related Hypersensitivity Reactions.....	35
6.6.4	Skin Rash.....	35
6.6.5	Other Supportive Care.....	35
6.7	Concomitant Medications and Procedures.....	35
6.7.1	Permitted During Study.....	36
6.7.2	Prohibited During Study.....	36
7	Discontinuation.....	37
7.1	Discontinuation from Study Treatment.....	37
7.2	Discontinuation from the Study	37
7.3	Loss to Follow-Up	37
8	Study Assessments and Procedures	38
8.1	Efficacy Assessments.....	38
8.2	Adverse Events	39
8.2.1	Definition of Adverse Events and Serious Adverse Events.....	39
8.2.2	Eliciting and Reporting Adverse Events/Serious Adverse Events	39
8.2.3	Assessment of Severity.....	40
8.2.4	Assessment of Causality.....	41
8.2.5	Regulatory Reporting	41
8.2.6	Pregnancy	41
8.2.7	Overdose.....	41
8.3	Safety Assessments	41
8.3.1	Physical Examination	42
8.3.2	ECOG Performance Status	42
8.3.3	Height and Weight	42
8.3.4	Vital Signs	42
8.3.5	Laboratory Tests	42
8.3.6	Pregnancy Test.....	43

8.3.7	ECG	43
8.4	Pharmacokinetics, Pharmacodynamics, and Immunogenicity.....	44
8.4.1	Pharmacokinetics.....	44
8.4.2	Immunogenicity.....	45
	[REDACTED]	
	[REDACTED]	
	[REDACTED]	
8.5	Health-Related Quality of Life (HRQoL) Questionnaires.....	46
8.5.1	EuroQol-5 Dimensions-5 Levels (EQ-5D-5L).....	46
8.5.2	Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym).....	46
9	Statistical Considerations	47
9.1	Sample Size Calculation	47
9.2	Analysis Populations.....	47
9.3	Interim Analysis for Futility.....	47
9.4	Final Analysis.....	48
9.5	Demographics and Baseline Characteristics.....	48
9.6	Efficacy Analyses.....	48
9.6.1	Overall Response Rate	48
9.6.2	Duration of Response	49
9.6.3	Complete Response Rate.....	49
9.6.4	Relapse-free Survival	49
9.6.5	Progression-Free Survival	49
9.6.6	Overall Survival.....	49
9.6.7	Subgroup analysis.....	50
9.7	Safety Analyses.....	50
9.7.1	Adverse Events.....	50
9.7.2	Clinical Laboratory Results.....	50
9.7.3	Additional Safety Assessments.....	51
9.8	Pharmacokinetic Analyses	51
9.9	Immunogenicity Analyses.....	51
	[REDACTED]	
10	Data Management and Quality Assurance	53
11	Ethical, Regulatory, and Study Management Considerations	54
11.1	Regulatory and Ethical Conduct of the Study.....	54
11.2	Independent Ethics Committee or Institutional Review Board	54

11.3	Patient Information and Consent	54
11.4	Confidentiality	55
11.5	Financial Disclosure and Obligations	55
11.6	Serious Adverse Events Report Requirements	55
11.7	Study Conduct.....	55
11.8	Protocol Amendments.....	55
11.9	Monitoring of the Study.....	56
11.10	Records Retention.....	56
11.11	Publications.....	56
12	Reference List.....	57
13	Appendices	59
13.1	Appendix 1. Eastern Cooperative Oncology Group Performance Status	59
13.2	Appendix 2. Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Classification).....	60

List of Tables

Table 1.	Schedule of Events	18
Table 2.	Study Objectives and Endpoints.....	26
Table 3.	Definition of Severity Grades for CTCAE	40
Table 4.	Schedule for Triplicate ECG Collection.....	43
Table 5.	Sampling Schedule for PK and ADA	45

List of Figures

Figure 1.	Schematic Representation and Chemical Structure of Loncastuximab Tesirine .	21
Figure 2.	Anti-drug Antibody Tiered Immunogenicity Testing Strategy	52

List of Abbreviations

Abbreviation	Definition
ABW	adjusted body weight
ADA	anti-drug antibody
ADC	antibody drug conjugate
ADR	adverse drug reaction
AE	adverse event
AI	accumulation index
Ala	Alanine
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AlloSCT	allogeneic stem cell transplant
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC _{0-∞}	area under the concentration-time curve from time zero to infinity
AUC _{0-last}	area under the concentration-time curve from time zero to the last quantifiable concentration
AUC _{0-τ}	area under the concentration-time curve from time zero to the end of the dosing interval
BID	twice daily
BMI	body mass index
BOR	best overall response
BP	blood pressure
CAR	chimeric antigen receptor
CD	cluster of differentiation
C1D1	Cycle 1 Day 1
CFR	Code of Federal Regulations
cfDNA	circulating cell-free DNA
CI	confidence interval
CL	Clearance
C _{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CRR	complete response rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Definition
EOT	end of treatment
EQ-5D-5L	EuroQol–5 Dimensions–5 Levels
EU	European Union
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
gDNA	genomic DNA
GGT	gamma glutamyl transferase
H0	null hypothesis
H1	first hypothesis
H2	second hypothesis
Ha	alternate hypothesis
HBV	hepatitis B virus
β-HCG	beta human chorionic gonadotropin
HCV	hepatitis C virus
HD-ASCT	high-dose chemotherapy and autologous stem cell transplant
HIV	human immunodeficiency virus
hr	hour
HRQoL	health-related quality of life
IB	Investigator’s Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
MRI	magnetic resonance imaging
MSD-ECL	Meso-Scale Discovery Electrochemiluminescence
MTD	maximum tolerated dose
NHL	non-Hodgkin lymphoma
ORR	overall response rate
OS	overall survival
PBD	pyrrolbenzodiazepine
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic(s)
PO	per os
pp	predicted probability
PR	partial response
PTT	partial thromboplastin time

Abbreviation	Definition
QT	measure between Q wave and T wave in the electrocardiogram
QTcF	Fridericia correction of the QT measure
Q3W	every 3 weeks
RBC	red blood cell
RFS	relapse-free survival
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplantation
SD	stable disease
SOC	standard of care
SoE	schedule of events
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
T _{max}	time to maximum concentration
μL	microliter
ULN	upper limit of normal
US	United States
Val	valine
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
wk	week
WOCBP	woman of childbearing potential

Protocol Synopsis

Protocol Number:	ADCT-402-201
Title:	A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 2
Indication:	Diffuse Large B-Cell Lymphoma (DLBCL)
Rationale:	<p>Non-Hodgkin lymphoma (NHL) is the seventh most common type of cancer in the US, and account for an estimated 4.3% of new cancer cases in 2017. DLBCL accounts for nearly one-third (32.5%) of NHL. Chemo-immunotherapy, with or without radiotherapy, is the most common initial treatment for DLBCL. Response to initial treatment is high; however, a significant proportion of patients relapse. The current standard of care for relapsed DLBCL is additional chemotherapy, which can be followed by stem cell transplantation (SCT). The poor prognosis for relapsed patients, especially those with chemo-refractory disease with a short interval between remission and relapse, or those who relapse after high-dose therapy and SCT, highlights the unmet needs for patients with relapsed or refractory DLBCL.</p> <p>Human CD19 antigen is a 95 kd transmembrane glycoprotein belonging to the immunoglobulin superfamily. In normal human tissue, expression of CD19 continues through pre-B and mature B-cell differentiation until it is finally down-regulated during terminal differentiation into plasma cells; however, expression of CD19 is maintained in hematologic B-cell malignancies, including DLBCL.</p> <p>Loncastuximab tesirine (ADCT-402) is an antibody drug conjugate (ADC) that has been designed to target and kill CD19-expressing malignant B-cells. Preliminary data from a Phase 1 study of loncastuximab tesirine in relapsed or refractory B-cell NHL shows significant activity in patients with DLBCL.</p>
Objectives:	<p>Primary Objective</p> <ul style="list-style-type: none">• Evaluate the efficacy of single agent loncastuximab tesirine in patients with relapsed or refractory DLBCL <p>Secondary Objectives</p> <ul style="list-style-type: none">• Characterize the safety profile of loncastuximab tesirine• Characterize the pharmacokinetic (PK) profile of loncastuximab tesirine• Evaluate the immunogenicity of loncastuximab tesirine• Evaluate the impact of loncastuximab tesirine treatment on health-related quality of life (HRQoL) <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

Endpoints:

Primary Endpoint

Overall response rate (ORR) according to the 2014 Lugano classification as determined by central review in all treated patients; ORR is defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR)

Secondary Endpoints

- Duration of response (DOR) defined as the time from the first documentation of tumor response to disease progression or death
- CR rate defined as the percentage of treated patients with a BOR of CR
- Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death
- Progression-free survival (PFS) defined as the time between start of treatment and the first documentation of recurrence, progression, or death
- Overall survival (OS) defined as the time between the start of treatment and death from any cause
- Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
- Changes from baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs)
- Concentrations and PK parameters of loncastuximab tesirine total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated warhead SG3199
- Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine after treatment with loncastuximab tesirine
- Change from baseline in HRQoL as measured by EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

[REDACTED]

[REDACTED]

[REDACTED]

Study Design:

This is a Phase 2, multi-center, open-label, single-arm study. The study will enroll approximately 140 patients.

A 2-stage design will be used, with an interim analysis for futility on the first 52 patients. If ≥ 10 patients respond (CR+PR), the study will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment will be halted if futility is confirmed.

Patient Selection:

Inclusion Criteria:

1. Male or female patient aged 18 years or older
2. Pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification, to include: DLBCL not otherwise specified; primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements
3. Relapsed or refractory disease following two or more multi-agent systemic treatment regimens
4. Patients who have received previous CD19-directed therapy must have a biopsy that shows CD19 protein expression after completion of the CD19-directed therapy
5. Measurable disease as defined by the 2014 Lugano Classification
6. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block (or minimum 10 freshly cut unstained slides if block is not available)

Note: Any biopsy since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred.

7. ECOG performance status 0-2
8. Adequate organ function as defined by screening laboratory values within the following parameters:
 - a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu\text{L}$ (off growth factors at least 72 hours)
 - b. Platelet count $\geq 75 \times 10^3/\mu\text{L}$ without transfusion in the prior 7 days
 - c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) $\leq 2.5 \times$ the upper limit of normal (ULN)
 - d. Total bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's syndrome may have a total bilirubin up to $\leq 3 \times$ ULN)
 - e. Blood creatinine $\leq 1.5 \times$ ULN or calculated creatinine clearance ≥ 60 mL/min by the Cockcroft and Gault equation

Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.

9. Negative beta-human chorionic gonadotropin (β -HCG) pregnancy test within 7 days prior to start of study drug (C1D1) for women of childbearing potential
10. Women of childbearing potential must agree to use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of loncastuximab tesirine. Men with female partners who are of childbearing potential must agree that they will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of loncastuximab tesirine

Exclusion Criteria:

1. Previous treatment with loncastuximab tesirine
2. Known history of hypersensitivity to or positive serum human ADA to a CD19 antibody
3. Pathologic diagnosis of Burkitt lymphoma
4. Bulky disease, defined as any tumor ≥ 10 cm in longest dimension
5. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agree and document should not be exclusionary
6. Autologous stem cell transplant within 30 days prior to start of study drug (C1D1)
7. Allogeneic stem cell transplant within 60 days prior to start of study drug (C1D1)
8. Active graft-versus-host disease
9. Post-transplant lymphoproliferative disorders
10. Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other central nervous system (CNS) autoimmune disease
11. Known seropositive and requiring anti-viral therapy for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Note: Testing is not mandatory to be eligible
12. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
13. Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease
14. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
15. Breastfeeding or pregnant
16. Significant medical comorbidities, including but not limited to, uncontrolled hypertension (blood pressure [BP] $\geq 160/100$ mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease
17. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor
18. Use of any other experimental medication within 14 days prior to start of study drug (C1D1)
19. Planned live vaccine administration after starting study drug (C1D1)
20. Failure to recover to Grade ≤ 1 (Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) from acute non-hematologic toxicity (Grade ≤ 2 neuropathy or alopecia) due to previous therapy prior to screening

	<p>21. Congenital long QT syndrome or a corrected QTcF interval of >480 ms at screening (unless secondary to pacemaker or bundle branch block)</p> <p>22. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk</p>
<p>Estimated Duration of Patient Participation and Study Duration:</p>	<p>The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first.</p> <p>The study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 3 weeks), and a Follow-up Period (approximately every 12 week visits for up to 3 years after treatment discontinuation).</p> <p>Patients may continue treatment until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first.</p> <p>The end of study occurs at the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by Sponsor.</p>
<p>Efficacy Assessments:</p>	<ul style="list-style-type: none">• Disease assessments: Positron emission tomography - computed tomography (PET-CT) <p>Note: If disease is not PET-avid at baseline, CT or magnetic resonance imaging (MRI) may be used for follow-up disease assessments. The assessment method determined to identify sites of disease at baseline should be used for all subsequent assessments.</p>
<p>Safety Assessments:</p>	<ul style="list-style-type: none">• Physical examination• ECOG Performance status• Height and weight• Vital signs• Safety laboratories (hematology, chemistry, coagulation, urinalysis)• Pregnancy test, if applicable• 12 Lead-ECG (triplicate)• AEs/SAEs, graded according to CTCAE version 4.0.
<p>Other Assessments:</p>	<ul style="list-style-type: none">• Blood sampling for PK, ADA, [REDACTED]• [REDACTED]• [REDACTED]• HRQoL: EQ-5D-5L and FACT-Lym
<p>Study Drug, Dosage, and Mode of Administration:</p>	<p>Loncastuximab tesirine will be administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle. Patients will receive 150 µg/kg every 3 weeks (Q3W) for 2 cycles, then 75 µg/kg Q3W for subsequent cycles.</p> <p>Patients with a body mass index (BMI) ≥ 35 kg/m² will have their dose calculated based on an adjusted body weight.</p>
<p>Sample Size:</p>	<p>Approximately 140 patients.</p>

**Statistical
Considerations:**

Study Hypotheses:

H1: ORR based on central review for patients treated with loncastuximab tesirine is significantly greater than 20% (i.e., H0: $p \leq 0.2$ vs. Ha: $p > 0.2$).

Sample Size Justification:

Using nQuery exact test for single proportion, a sample size of 140 patients has >99% power to achieve a 1-sided significance level of 0.025 (2-sided significance level of 0.05). This sample size will provide adequate precision for observed ORR in the expected range and a robust population for safety evaluation.

Statistical Analysis:

ORR and CR rate with 95% CI from all treated patients will be presented. DOR, PFS, RFS, and OS will be analyzed by Kaplan-Meier approach. Safety analyses will be presented descriptively.

Schedule of Events

Table 1. Schedule of Events

	Protocol Section	Screening	Treatment Period				EOT	Follow-up Period (up to 3 years from EOT) Every 12 weeks
			Cycle 1 and Cycle 2 (C1 and C2)		C3 and beyond			
(1 Cycle = 3 weeks)			Cycle 1	Cycle 2				
Day (D)		-28 to -1	1	8	15	1		
Informed consent	11.3	X						
Eligibility criteria	5	X						
Demography	9.5	X						
Medical/Cancer history	9.5	X						
██████████	██████████	██████████						
Physical examination	8.3.1	X	X			X	X	
ECOG performance status	8.3.2	X	X			X	X	
Height	8.3.3	X						
Weight	8.3.3	X	X	X	X	X	X	
Vital signs (BP, HR, RR, Temp)	8.3.4	X	X	X	X	X	X	
Disease assessment ²	8.1	X	6 weeks and 12 weeks after C1D1, then every 9 weeks				X ²	Every 12 weeks until 1 year from EOT, then every 6 months until disease progression ³
Hematology and Chemistry	8.3.5	X	X ⁴	X	X	X ⁴	X	
Coagulation and Urinalysis	8.3.5	X						
Pregnancy test, if applicable	8.3.6	X	X ⁵			X	X	
12-lead ECG	8.3.7 Table 4	X	X (pre-infusion, EOI, and 4 h post-infusion)	X	X	Every other cycle (C3, pre-infusion and EOI; C5 and beyond, pre-infusion only)	X	
Premedication	6.6.1		D-1 to D2			D-1 to D2		
Loncastuximab tesirine administration	6.3		X			X		

	Protocol Section	Screening	Treatment Period				EOT	Follow-up Period (up to 3 years from EOT) Every 12 weeks
			Cycle 1 and Cycle 2 (C1 and C2)		C3 and beyond			
(1 Cycle = 3 weeks)			1	8	15	1		
Day (D)		-28 to -1	1	8	15	1		
PK sample	8.4.1 Table 5		X (pre-infusion, EOI, and 4 h post-infusion)	X	X	Every other cycle (C3, pre-infusion and EOI; C5 and beyond, pre-infusion only)	X	
ADA sample	8.4.2 Table 5		X (pre-infusion)		X ⁶	Every other cycle (C3 and beyond, pre-infusion only)	X ⁷	
gDNA and cfDNA samples	8.4.3		X				X	
HRQoL	8.5		X			X	X	
Concomitant medications	6.7	From ICF signature date or D-14 whichever is earlier, until at least 30 days after last dose of study drug						
Adverse events	8.2	CTCAE, Version 4.0 AE/SAEs from ICF signature date until at least 30 days after last dose of study drug; thereafter related SAEs only						
1 st New anticancer treatment							X	
Survival							X	

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BP, blood pressure; cfDNA, circulating cell-free DNA; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; EOT, end of treatment; gDNA, genomic DNA; HR, heart rate; HRQoL, health-related quality of life; ICF, informed consent form; PET-CT, Positron emission tomography - computed tomography; PK, pharmacokinetics; RR, respiratory rate; SAE, serious adverse event; Temp, temperature.

¹ Tumor tissue should be submitted once all other eligibility criteria have been met.

² Screening imaging (PET-CT) must be performed within 4 weeks prior to C1D1 and the same assessment method should be used throughout the study. Week 6 imaging should be performed within 5 days prior to C3D1 and Week 12 imaging should be performed within 5 days prior to C5D1. All other imaging for disease assessment for patients on study drug should be performed within ± 2 weeks of the scheduled timepoint. Disease assessments should be performed at the timepoints specified even if study drug dosing is delayed. If a scan has been performed within 8 weeks of EOT, it does not need to be repeated at EOT.

³ Disease assessments to be performed in patients having discontinued study drug for reasons other than disease progression.

⁴ ≤3 days prior to administration of study treatment, unless more frequent testing is clinically indicated.

⁵ Not needed if screening assessment was performed within 7 days prior to C1D1.

⁶ Cycle 1 only

⁷ Patients who test positive for ADAs will be requested to supply additional ADA samples as per [Section 8.4.2](#).

Visit Scheduling Windows:

- Treatment Period: visit day ± 2 days (excluding C1D1 which is the reference day)
- EOT: as soon as possible after decision to discontinue the study drug, preferably within 30 days after last dose of study drug, and before initiation of any new anticancer treatment
- Follow-up Period: visit day ± 14 days

1 Introduction and Background

1.1 Diffuse Large B-Cell Lymphoma

Non-Hodgkin lymphoma (NHL) represents a biologically and clinically diverse group of hematologic malignancies arising from precursor and mature B, T, and natural killer cells. It is the 7th most common type of cancer in the US and will account for an estimated 4.3% (n=72,240) of new cancer cases in 2017 (Siegel et al., 2017). Diffuse large B-cell lymphoma (DLBCL) accounts for an estimated 32.5% of NHL (Al-Hamadani et al., 2015).

Approximately 30% to 50% of patients with DLBCL are not cured, and most patients who fail a rituximab-containing chemotherapy regimen (e.g., R-CHOP) will die from their disease. Salvage therapy, including high-dose chemotherapy and autologous stem cell transplant (HD-ASCT), can be effective treatment for DLBCL patients with chemotherapy-sensitive relapse. However, over half of the patients treated in this fashion will not have long term disease control (Gisselbrecht et al., 2010). The prognosis of patients whose disease is refractory to initial chemotherapy and are therefore not eligible for HD-ASCT, or who relapse early after HD-ASCT, is extremely poor. These patients have a poor response to salvage therapy, with an objective response rate (ORR) of 26% (complete response [CR] rate 7%) and a median survival of approximately 6 months (Crump et al., 2017). The management of patients with DLBCL who are ineligible for HD-ASCT or who relapse after HD-ASCT is difficult. Palliation, second HD-ASCT, or allogeneic stem cell transplant (AlloSCT) are some of the options available for these patients but results are dismal and toxicity significant. The poor prognosis for relapsed patients, especially those with chemotherapy-refractory disease with a short interval between remission and relapse or those who relapse after high-dose therapy and stem cell transplant (SCT), highlights the unmet needs for patients with relapsed or refractory DLBCL (Coiffier, 2016; Epperla, 2017).

In late 2017, the US Food and Drug Administration (FDA) granted approval to the autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, axicabtagene ciloleucel (Yescarta[®]), for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. While this therapy does provide disease control in a portion of patients (51% CR, 21% partial response [PR]), and provides durable responses in patients who achieve a CR, the duration of response (DOR) is short for patients who only achieve a PR (2.1 months), meaning that a significant fraction of patients (approximately 50%) treated with this therapy will not have long-term disease control. In addition, this therapy has significant toxicity, with 94% of patients having cytokine release syndrome (13% Grade 3 or higher) and 57% having encephalopathy (29% Grade 3 or higher). It is only available at specialized centers and requires substantial lead-time for preparation, with approximately 10% of patients being unable to receive the planned therapy. Thus, the development of more effective salvage treatment remains an unmet medical need.

1.2 Description of Investigational Study Drug

Loncastuximab tesirine (ADCT-402) is an antibody drug conjugate (ADC), composed of a humanized monoclonal antibody (RB4v1.2) directed against human cluster of differentiation 19 (CD19) conjugated through a cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. The toxin SG3199 attached to the linker is designated as SG3249.

The schematic representation of loncastuximab tesirine is presented in [Figure 1](#).

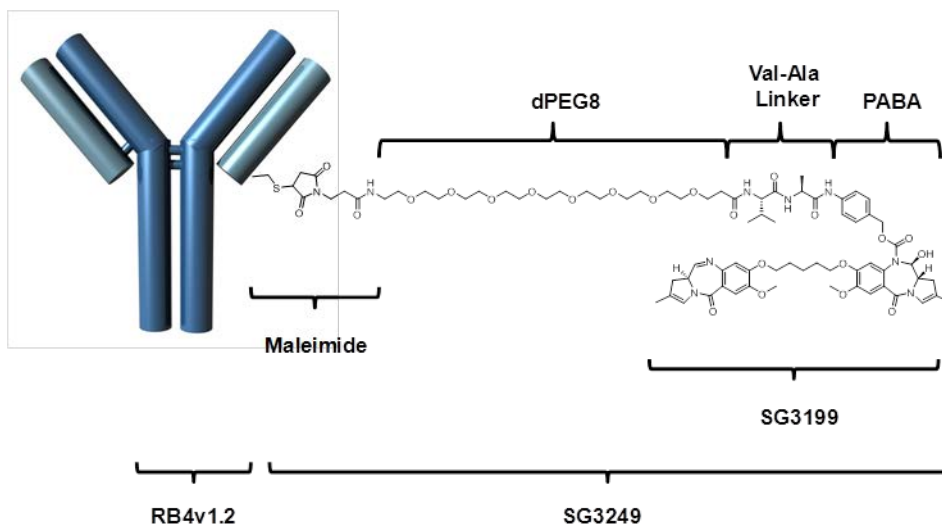


Figure 1. Schematic Representation and Chemical Structure of Loncastuximab Tesirine

Abbreviations: Ala, alanine; PABA, para-aminobenzoic acid; PEG, polyethylene glycol; RB4v1.2, human monoclonal antibody being studied; Val, valine.

Loncastuximab tesirine binds with picomolar affinity to human CD19. After binding and internalization, loncastuximab tesirine traffics to the lysosomes, where the protease-sensitive linker is cleaved and unconjugated PBD dimers (SG3199) are released inside the target cell. The released PBD dimers bind in the minor groove of DNA and form potent cytotoxic DNA interstrand cross-links. The cross-links result in a stalled DNA replication fork, blocking cell division and causing cell death ([Hartley, 2011](#)). The cross-links formed by PBD dimers are relatively non-distorting to the DNA structure, making them hidden to repair mechanisms ([Adair et al., 2012](#); [Beck et al., 2017](#)).

1.3 Safety and Efficacy of Loncastuximab Tesirine in Phase 1 Study, ADCT-402-101

ADCT-402-101 (NCT02669017) is a first-in-human Phase 1 dose-escalation study of loncastuximab tesirine in relapsed or refractory B-cell NHL patients, who have failed or are intolerant to established therapies, or have no other treatment options available. The study design involves a dose escalation phase (Part 1) followed by a dose expansion phase (Part 2). The primary objectives for Part 1 were to evaluate the safety and tolerability of loncastuximab tesirine and to determine the maximum tolerated dose (MTD) and/or the recommended dose(s) to use in Part 2. The primary objective for Part 2 was to evaluate the safety and tolerability of the dose(s) determined in Part 1. The secondary objectives include evaluating the clinical activity of loncastuximab tesirine as measured by ORR, DOR, progression free survival (PFS), and overall survival (OS).

As of data cut-off date of 03 December 2017, a total of 144 patients with relapsed or refractory B-cell NHL received at least one infusion of loncastuximab tesirine. The median age was 63.5 years (range: 23-86). The median number of previous chemotherapy regimens was 3 (range: 1-10) with 24.3% of patients having prior stem cell transplant.

Treatment-emergent adverse events (TEAEs) were reported in 137 (95.1%) out of 144 patients treated with loncastuximab tesirine. The most common TEAEs (observed in at least in 15% of patients), regardless of relationship to study treatment, were fatigue (42.4%); nausea (27.1%); gamma-glutamyltransferase (GGT) increased (26.4%); anemia (25.7%); edema peripheral (25.0%); dyspnea (18.8%); neutrophil count decreased, platelet count decreased, and thrombocytopenia (18.1% each); rash (17.4%); abdominal pain (16.0%); neutropenia (16.0%); and constipation (15.3%). Grade ≥ 3 TEAEs were reported in 92 (63.9%) patients. The most common Grade ≥ 3 TEAEs (observed in at least in 5% of patients) were neutrophil count decreased (16.0%); GGT increased (14.6%); anemia (12.5%); platelet count decreased (11.8%); neutropenia (11.1); and thrombocytopenia (8.3%).

The following events were considered non-serious adverse drug reactions (ADRs): GGT increased, edema (includes peripheral and facial), neutrophil count decreased, platelet count decreased, thrombocytopenia, neutropenia, and skin-related events (such as rash, maculopapular rash, and erythema).

TEAEs in 16 (11.1%) patients led to treatment discontinuation.

Dose-limiting toxicity was reported in 3 patients (2 thrombocytopenia and 1 febrile neutropenia).

Serious adverse events (SAEs) were reported in 54 (37.5%) out of 144 patients. Of these, 24 patients experienced an SAE(s) considered at least possibly related to study drug. Six of the possibly related events were observed in multiple patients (febrile neutropenia in 5 patients, pyrexia in 3 patients, dyspnea in 2 patients, lung infection in 2 patients, pleural effusion in 2 patients, and sepsis in 2 patients). Preliminary data indicate an acceptable safety profile. Febrile neutropenia and pleural effusion have been classified as expected serious ADRs.

Out of 126 evaluable patients, 33 (26.2%) achieved CR and 25 (19.8%) achieved PR, for an ORR of 58/126 (46.0%).

Out of 92 evaluable patients with DLBCL, 22 (23.9%) achieved CR and 16 (17.4%) achieved PR, for an ORR of 38/92 (41.3%).

Additional details may be found in the current loncastuximab tesirine Investigator's Brochure (IB).

2 Study Rationale

Human CD19 antigen is a 95 kd transmembrane glycoprotein belonging to the immunoglobulin superfamily. In normal human tissue, expression of CD19 continues through pre-B and mature B-cell differentiation until it is finally down-regulated during terminal differentiation into plasma cells (Scheuermann, 1995); however, expression of CD19 is maintained in hematologic B-cell malignancies, including DLBCL.

Loncastuximab tesirine is an ADC that has been designed to target and kill CD19-expressing malignant B-cells. Preliminary data from a Phase 1 study of loncastuximab tesirine in relapsed or refractory B-cell NHL (Section 1.3) shows significant activity of loncastuximab tesirine with an acceptable safety profile in patients with DLBCL.

2.1 Rationale for Study Design

This is a Phase 2, open-label, single-arm study and will enroll approximately 140 patients. The primary objective will be to evaluate the efficacy of single agent loncastuximab tesirine in patients with relapsed or refractory DLBCL who have failed at least 2 multi-agent systemic therapy regimens.

The primary hypothesis is that the ORR based on central review in all patients treated with loncastuximab tesirine is significantly greater than 20%. With the null hypothesis that the true response rate is 20%, and the alternative hypothesis that the true response rate is significantly greater than 20% (40% is used for calculation), the design controls the type I error rate at 0.025 and yields a power of >99%.

To enhance patient safety, a 2-stage design will be used, with an interim analysis for futility on the first 52 patients. If ≥ 10 patients respond, the study will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment will be halted if futility is confirmed to minimize exposure of patients in the study.

Given the encouraging ORR reported with loncastuximab tesirine in the Phase 1 study at dose levels below the MTD and the acceptable safety profile to date, loncastuximab tesirine presents a positive risk-benefit for further evaluation in relapse and refractory DLBCL.

2.2 Rationale for Dose Selection

For patients with relapsed or refractory non-Hodgkin lymphoma, available data support a loncastuximab tesirine dosing regimen of 150 $\mu\text{g}/\text{kg}$ every 3 weeks (Q3W) \times 2 cycles, followed by a 50% reduction to 75 $\mu\text{g}/\text{kg}$ Q3W for the Phase 2 trial. For safety, particular differences in predicted probabilities (pp) were apparent between the 200 $\mu\text{g}/\text{kg}$ Q3W and 150 $\mu\text{g}/\text{kg}$ Q3W doses, respectively, including Grade ≥ 3 edema (pp=0.2817 vs. 0.1070 in patients with prior stem cell transplant), liver function test-related toxicities (pp=0.4018 vs. 0.1644 in patients with prior relapsed disease; 0.4018 vs. 0.1644 in patients without prior stem cell transplant; pp=0.5208 vs. 0.2203 in patients with body mass index [BMI] of 35 kg/m^2 , and pp=0.4018 vs. 0.1644 in patients with baseline Eastern Cooperative Oncology Group [ECOG] of 0 or 1, respectively), and neutropenia or neutrophil decrease (pp=0.4383 vs. 0.2865).

For efficacy, the decision for initial dosing at the 150 µg/kg dose level is predicated on higher observed and predicted ORR as compared to the 120 µg/kg and lower doses. The decision to dose reduce following 2 cycles of treatment was based on the rapid onset of response observed in a majority of patients (median 2 cycles), and desire to mitigate onset of late-developing and difficult to manage toxicities, such as edema. Initial dosing for 2 cycles is anticipated to optimize the frequency of objective response, while dose reduction in subsequent cycles will permit continued exposure with manageable toxicity to optimize the durability of response.

3 Study Objectives and Endpoints

Table 2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the efficacy of single agent loncastuximab tesirine in patients with relapsed or refractory DLBCL	ORR according to the 2014 Lugano classification (Cheson et al. 2014) as determined by central review in all treated patients; ORR is defined as the proportion of patients with a best overall response (BOR) of CR or PR
Secondary	
Further evaluate the efficacy of loncastuximab tesirine	<ul style="list-style-type: none"> • DOR defined as the time from the first documentation of tumor response to disease progression or death • CR rate defined as the percentage of treated patients with a BOR of CR • Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death • PFS defined as the time between start of treatment and the first documentation of recurrence, progression, or death • OS defined as the time between the start of treatment and death from any cause
Characterize the safety profile of loncastuximab tesirine	<ul style="list-style-type: none"> • Frequency and severity of adverse events (AEs), and SAEs • Changes from baseline of safety laboratory variables, vital signs, ECOG performance status, and 12-lead electrocardiograms (ECGs)
Characterize the pharmacokinetic (PK) profile of loncastuximab tesirine	Concentrations and PK parameters of loncastuximab tesirine total antibody, PBD-conjugated antibody, and unconjugated warhead SG3199
Evaluate the immunogenicity of loncastuximab tesirine	Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine after treatment with loncastuximab tesirine
Evaluate the impact of loncastuximab tesirine treatment on health-related quality of life (HRQoL)	Change from baseline in HRQoL as measured by EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

4 Study Design

4.1 Overview

This is a Phase 2, multi-center, open-label, single-arm study of the efficacy and safety of loncastuximab tesirine used as monotherapy in patients with relapsed or refractory DLBCL. The study will enroll approximately 140 patients.

A 2-stage design will be used ([Simon, 1989](#)), with an interim analysis for futility using the data on the first 52 patients (see [Section 9.3](#)). If ≥ 10 patients respond (CR+PR), the study will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment will be halted if futility is confirmed.

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first.

The study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 3 weeks), and a Follow-up Period (approximately every 12 week visits for up to 3 years after treatment discontinuation).

4.2 Screening Period

Informed consent must be obtained for each patient and documented with a signed informed consent form (ICF) prior to any study procedures. Procedures that are performed as part of standard of care (SOC) may be used to satisfy screening requirements if they are performed in the appropriate window.

The screening period is from 28 days to 1 day prior to the start of the study drug. The screening assessments should be performed within this period in order to assess the eligibility of the patient against the inclusion and exclusion criteria ([Sections 5.1](#) and [5.2](#), respectively).

See [Section 5.3](#) for the information to be collected on screening failures.

4.3 Treatment Period

The treatment period starts on the date when a patient receives the first dose of study drug and continues until the date of discontinuation from treatment.

A treatment cycle is defined as 3 weeks (i.e., 21 days). Loncastuximab tesirine will be administered as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle. Patients will receive 150 $\mu\text{g}/\text{kg}$ Q3W for 2 cycles, then 75 $\mu\text{g}/\text{kg}$ Q3W for subsequent cycles.

Patients may continue treatment for up to one year or until disease progression, unacceptable toxicity, or other discontinuation criteria ([Section 7](#)), whichever occurs first. Additionally, patients benefitting clinically at 1 year may continue treatment after a case by case review with the Sponsor.

4.4 End of Treatment

End of Treatment visit (EOT) should be performed as soon as possible after the decision to discontinue the study drug, preferably within 30 days after last dose of study drug and before initiation of any new anticancer treatment.

When EOT coincides with a scheduled visit, the scheduled visit will become EOT.

4.5 Follow-up Period

All patients, regardless of disease status, will be followed every 12 weeks for up to 3 years, or until withdrawal of consent, loss to follow-up, or death, whichever occurs first.

When disease assessments are not planned for a follow-up visit, the visit can be done by phone.

4.6 End of Study

The end of study occurs at the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by Sponsor.

5 Patient Population

Patients must meet all inclusion criteria and none of the exclusion criteria to be eligible for the study. All criteria have to be assessed at Screening, unless otherwise specified (e.g., criterion to be confirmed within 28 days to 1 day prior to the start of study drug on Cycle 1 Day 1 [C1D1]).

5.1 Inclusion Criteria

1. Male or female patient aged 18 years or older.
2. Pathologic diagnosis of DLBCL, as defined by the 2016 WHO classification, to include: DLBCL not otherwise specified; primary mediastinal large B-cell lymphoma; and high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements
3. Relapsed or refractory disease following two or more multi-agent systemic treatment regimens
4. Patients who have received previous CD19-directed therapy must have a biopsy that shows CD19 protein expression after completion of the CD19-directed therapy.
5. Measurable disease as defined by the 2014 Lugano Classification ([Appendix 2](#)).
6. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block (or minimum 10 freshly cut unstained slides if block is not available).

Note: Any biopsy since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred.

7. ECOG performance status 0-2.
8. Adequate organ function as defined by screening laboratory values within the following parameters:
 - a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu\text{L}$ (off growth factors at least 72 hours).
 - b. Platelet count $\geq 75 \times 10^3/\mu\text{L}$ without transfusion in the prior 7 days.
 - c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) $\leq 2.5 \times$ the upper limit of normal (ULN).
 - d. Total bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's syndrome may have a total bilirubin up to $\leq 3 \times$ ULN).
 - e. Blood creatinine $\leq 1.5 \times$ ULN or calculated creatinine clearance ≥ 60 mL/min by the Cockcroft and Gault equation.

Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.

9. Negative beta-human chorionic gonadotropin (β -HCG) pregnancy test within 7 days prior to start of study drug (C1D1) for women of childbearing potential.

10. Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of loncastuximab tesirine. Men with female partners who are of childbearing potential must agree that they will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of loncastuximab tesirine.

* Women of childbearing potential are defined as sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

** Highly effective forms of birth control are methods that achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include: hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.

Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

5.2 Exclusion Criteria

1. Previous treatment with loncastuximab tesirine
2. Known history of hypersensitivity to or positive serum human ADA to a CD19 antibody
3. Pathologic diagnosis of Burkitt lymphoma
4. Bulky disease, defined as any tumor ≥ 10 cm in longest dimension
5. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agree and document should not be exclusionary
6. ASCT within 30 days prior to start of study drug (C1D1)
7. AlloSCT within 60 days prior to start of study drug (C1D1)
8. Active graft-versus-host disease
9. Post-transplant lymphoproliferative disorders
10. Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other central nervous system (CNS) autoimmune disease
11. Known seropositive and requiring anti-viral therapy for human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV).
Note: Testing is not mandatory to be eligible
12. History of Stevens-Johnson syndrome or toxic epidermal necrolysis

13. Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease
14. Clinically significant third space fluid accumulation (i.e., ascites requiring drainage or pleural effusion that is either requiring drainage or associated with shortness of breath)
15. Breastfeeding or pregnant
16. Significant medical comorbidities, including but not limited to uncontrolled hypertension (blood pressure [BP] $\geq 160/100$ mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease
17. Major surgery, radiotherapy, chemotherapy or other anti-neoplastic therapy within 14 days prior to start of study drug (C1D1), except shorter if approved by the Sponsor
18. Use of any other experimental medication within 14 days prior to start of study drug (C1D1)
19. Planned live vaccine administration after starting study drug (C1D1)
20. Failure to recover to Grade ≤ 1 (Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]) from acute non-hematologic toxicity (Grade ≤ 2 neuropathy or alopecia) due to previous therapy prior to screening
21. Congenital long QT syndrome or a corrected QTcF interval of >480 ms at screening (unless secondary to pacemaker or bundle branch block)
22. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk

5.3 Screening Failures

Patients who signed the ICF but were found not eligible for the study prior to receiving study drug are defined as screening failures.

For these patients, only limited information will be collected in the electronic case report form (eCRF):

- Informed consent
- Demographics
- Inclusion/exclusion criteria
- SAE and/or death occurring during the screening period

6 Treatment

6.1 Study Drug

The study drug is loncastuximab tesirine, which will be provided as a frozen liquid or a refrigerated lyophilized formulation.

- The liquid formulation will be provided in 10 mL glass vials designed to deliver 3.2 mL of loncastuximab tesirine at a concentration of 5 mg/mL (16 mg loncastuximab tesirine per vial) and stored at -65°C or below. It is a sterile, frozen liquid formulated in 30 mM histidine, 200 mM sorbitol, and 0.02% polysorbate 20, at pH 6.0. Prior to use, the frozen formulation is thawed at ambient temperature, gently swirled to ensure homogeneity, and visually inspected.
- The lyophilized formulation will be provided as a lyophilized white to off-white powder in 8 mL glass vials (10 mg loncastuximab tesirine per vial) and stored at 2-8°C. The lyophilized loncastuximab tesirine is formulated in 20 mM histidine, 175 mM sucrose, and 0.02% polysorbate 20, at pH 6.0. Prior to use, the study drug is reconstituted with 2.2 mL of Sterile Water for Injection to deliver 2.0 mL at a concentration of 5 mg/mL, gently swirled to ensure complete dissolution and homogeneity, and visually inspected. Sterile Water for Injection is to be provided by study sites.

Individual patients will receive the same formulation for their entire treatment.

6.2 Management of Clinical Supplies

Detailed instructions regarding study drug shipment, handling, storage, and preparation are included in the pharmacy manual.

6.2.1 Packaging and Storage

The study drug will be supplied by the Sponsor through the designated packaging, labeling, and distribution center.

Once the package arrives at the study site, the receiving site pharmacy will complete the enclosed procedures to acknowledge receipt.

All study drugs must be stored in a secure area.

- Loncastuximab tesirine liquid formulation: loncastuximab tesirine should be protected from light and stored frozen (-65°C or below). Loncastuximab tesirine should be thawed under ambient conditions.
- Loncastuximab tesirine lyophilized formulation: should be protected from light and stored at 2-8°C.

6.2.2 Preparation and Administration

The study drug solution at the concentration of 5 mg/mL will be the basis for the preparation of the infusion solution. The amount of the product to be diluted will depend on the dose level and the body mass of the patient.

Patients will receive a 30 minutes IV infusion of loncastuximab tesirine on Day 1 of each cycle. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

6.2.3 Accountability

The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. All study drugs will be reconciled and retained or destroyed according to applicable regulations.

6.3 Loncastuximab Tesirine Dosing

Administration of loncastuximab tesirine will be performed by the Investigator or a qualified designee.

Loncastuximab tesirine will be administered as an IV infusion over 30 minutes on Day 1 of each cycle (every 3 weeks) at a dose of 150 µg/kg Q3W for 2 cycles, then 75 µg/kg Q3W. Refer to [Section 6.6](#) for premedication and supportive care.

Patients with a BMI ≥ 35 kg/m² will have their dose calculated based on an adjusted body weight as follows:

$$\text{Adjusted body weight (ABW) in kg} = 35 \text{ kg/m}^2 * (\text{height in meters})^2$$

$$\text{Dose to administer (mg)} = \text{dosage (}\mu\text{g/kg)} * \text{ABW} / 1000$$

Extravasation of loncastuximab tesirine may be associated with local irritation, swelling, pain, or tissue damage. The IV infusion site should be monitored for signs of IV infiltration or drug extravasation, and patients should be instructed to report immediately any signs of IV infiltration or drug extravasation during or after the infusion. Suspected extravasation of loncastuximab tesirine should be managed according to institutional protocol for management of extravasation of cytotoxic chemotherapy. For patients who have a central line, administration of loncastuximab tesirine via this central line should be considered.

6.4 Dose Delays and Modifications

If a patient experiences any Grade ≥ 3 (≥ 2 for edema, effusion, or increased AST/ALT/GGT) non-hematologic toxicity, loncastuximab tesirine must be held until the toxicity resolves to Grade ≤ 1 (Grade 1 or baseline for peripheral neuropathy). In addition, if a patient experiences hematological toxicity of Grade ≥ 3 neutropenia or thrombocytopenia, loncastuximab tesirine must be held until the toxicity resolves to Grade ≤ 2 .

If loncastuximab tesirine dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses of loncastuximab tesirine will be reduced by 50%. In addition, the Investigator may reduce the dose of loncastuximab tesirine by 50% for any Grade ≥ 3 (≥ 2 for edema, effusion, or increased

AST/ALT/GGT) toxicity that is possibly related to loncastuximab tesirine, but does not result in dosing delay of more than 3 weeks if they feel it is in the best interest of the patients.

If toxicity requiring dose reduction as described above occurs following the second dose of 150 µg/kg (C2D1), the patient should receive the per protocol-defined dose of 75 µg/kg for Cycle 3.

If toxicity as described above recurs at the reduced dose, subsequent doses of loncastuximab tesirine will be reduced by an additional 50%.

If toxicity as described above recurs after a second dose reduction, study drug must be discontinued permanently.

If loncastuximab tesirine dosing is delayed by more than 5 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, study drug must be discontinued permanently unless continued administration is approved by the Sponsor.

6.5 Overdose Management

An overdose is any dose of study drug given to a patient that exceeds the dose described in the protocol. There are no data available to determine what the effects of overdose are and whether they can be reversed. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

6.6 Premedication and Supportive care

6.6.1 Premedication

Unless contraindicated, administer dexamethasone 4 mg per os (PO) twice daily (BID) the day before loncastuximab tesirine administration (if possible), the day of loncastuximab tesirine administration (give at least 2 hours prior to administration when not given the day before; otherwise any time prior to administration), and the day after loncastuximab tesirine administration.

Patients who experience an infusion-related hypersensitivity reaction will receive the alternative premedication regimen specified in [Section 6.6.3](#).

6.6.2 Treatment of Edema and Pleural Effusion

Spironolactone at standard doses should be administered for patients with weight gain greater than 1 kg from C1D1, new or worsening edema, and/or new or worsening pleural effusion. The dose of spironolactone may be titrated as clinically indicated. Additional diuretic support may be added if there is further increase in weight, edema, or pleural effusion. Additionally, patients should be advised to monitor their weight on a daily basis, at around the same time (preferably in the morning), and to notify the study site if they gain >1 kg (2.2 pounds) over baseline.

6.6.3 Treatment and Prophylaxis of Infusion-Related Hypersensitivity Reactions

Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, should be available for immediate use and may be administered according to site standard treatment protocols.

Any patient who experiences an infusion-related hypersensitivity reaction should receive prophylactic treatment in subsequent cycles according to the guidelines below or institutional standard of care:

- On Day 1 of each cycle, patients will be instructed to take dexamethasone 20 mg PO 12 and 6 hours before the start of the loncastuximab tesirine infusion. When necessary, 12 and 6 hours before the first infusion may be defined as “immediately before sleeping” and “immediately after waking up.”
- On Day 1 of each cycle, patients will be given diphenhydramine hydrochloride 50 mg IV 30 minutes before the start of the loncastuximab tesirine infusion.
- On Day 1 of each cycle, patients will be given ranitidine (or equivalent) 50 mg IV 30 minutes before the start of the loncastuximab tesirine infusion.
- For 2 days following administration of loncastuximab tesirine on Day 1, patients are to take dexamethasone 4 mg PO BID.

6.6.4 Skin Rash

Skin rash has been reported in the ADCT-402-101 study, as well as with another investigational agent containing the same PBD warhead (Rudin et al., 2017). The rash has been reported in areas at risk for sun exposure; it is therefore recommended that precautions are taken to avoid prolonged exposure of skin to sunlight.

6.6.5 Other Supportive Care

- Although the study patient population has a low risk for development of tumor lysis syndrome (TLS) compared to patients with acute disease (Cairo et al., 2010), patients should be observed for development of TLS and treated according to site standard treatment protocols.
- As testing in animals showed testicular toxicity (atrophy with reduced spermatogenesis), male patients are advised to consider cryopreservation of sperm prior to treatment with loncastuximab tesirine, where applicable.

6.7 Concomitant Medications and Procedures

All medications (except for the study drug) and procedures will be recorded in the eCRF starting from the ICF signature date or from 14 days prior to C1D1, whichever is earlier, and continuing until at least 30 days after last dose of study drug.

6.7.1 Permitted During Study

All medications or procedures for the clinical care of the patient, including management of AEs, are permitted during the study, except for those listed in [Section 6.7.2](#).

Hematopoietic growth factors are permitted as per American Society of Clinical Oncology guidelines ([Smith et al., 2006](#)).

6.7.2 Prohibited During Study

- Other anticancer therapy with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Other investigational agents.
- Live vaccines.

7 Discontinuation

The reason for discontinuation and the date of discontinuation will be collected for all patients.

Note: Once discontinued from the study for any reason, patients are not permitted to be re-enrolled.

7.1 Discontinuation from Study Treatment

A patient may be discontinued from the study drug for any of the following reasons:

- Disease progression
- Unacceptable toxicity
- Patient decision
- Major protocol deviation
- The Investigator determines that it is in the best interest of the patient to discontinue study treatment.
- Discontinuation of the study by the Sponsor
- Pregnancy
- Death

IMPORTANT: Study drug discontinuation is not to be automatically considered as withdrawal from the study. Patients discontinuing the study drug will be asked to perform an EOT visit ([Section 4.4](#)) and continue with the Follow-up period ([Section 4.5](#)) as per protocol.

The investigational site should make every effort to complete follow-up per protocol. If patients are unable to return to the site, patient status, including but not limited to survival status, may be obtained by site staff via phone, email, or mail.

7.2 Discontinuation from the Study

A patient may be discontinued from the study for any of the following reasons:

- Withdrawal of consent
- Investigator/Sponsor decision
- Death
- Loss to follow-up

If a patient withdraws informed consent, no additional data will be collected. The Sponsor may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

The study may be terminated at any time, for any reason, by the Sponsor. Patients still receiving study drug should have an EOT visit as described in [Section 4.4](#) and SoE ([Table 1](#)).

7.3 Loss to Follow-Up

Patients who fail to return for protocol follow-up are to be contacted by the investigative site. Following a minimum of two documented unsuccessful telephone calls, the investigative site should send a registered letter to the patient in a final attempt to ensure protocol compliance.

8 Study Assessments and Procedures

Informed consent, as documented by a signed and dated ICF, must be obtained prior to performing any study procedures. Results (e.g., from laboratory tests or radiographic evaluations, etc.) obtained prior to the date of informed consent but within the allowed timeframe for screening may be used for determination of patient eligibility only if obtained as part of standard care.

8.1 Efficacy Assessments

Disease assessments will occur as per schedule of events (SoE) ([Table 1](#)) until progression. Disease assessments should take place at the timepoints specified even if study drug dosing is delayed. Additional disease assessments may be obtained, if clinically indicated.

Imaging and clinical examination for lymphoma will be performed at all disease assessment timepoints. All patients will have positron emission tomography - computed tomography (PET-CT) of the neck/chest/abdomen/pelvis and other areas of known or suspected disease performed at baseline. Patients with PET-avid disease at baseline should have PET-CT for all subsequent disease assessments. If disease is not PET-avid at baseline, computed tomography (CT) or magnetic resonance imaging (MRI) may be used for subsequent disease assessments. Patients whose disease is not PET-avid should have a bone marrow biopsy as part of their baseline staging and disease assessment if clinically appropriate.

Screening (Baseline) imaging must be performed within 4 weeks prior to C1D1.

During the treatment period, imaging will be performed 6 weeks and 12 weeks after C1D1, then every 9 weeks until EOT. Week 6 imaging should be performed within 5 days prior to C3D1 and Week 12 imaging should be performed within 5 days prior to C5D1. All other imaging should be performed within ± 2 weeks of the scheduled time point.

During the follow-up period, patients who discontinued study drug for reasons other than disease progression or initiation of other anti-cancer therapy except stem cell transplant, will have imaging performed every 12 (± 2) weeks until 1 year from EOT, then every 6 months until disease progression, up to 3 years from EOT.

Response data will be collected for patients who receive CAR-T therapy until 90 days after receiving CAR-T therapy.

If a scan has been performed within 8 weeks of EOT, it does not need to be repeated at EOT.

In case of dose delays, disease assessment should be maintained at the frequencies defined above.

The patient's response to treatment will be determined according to the 2014 Lugano Classification Criteria ([Appendix 2](#)) as CR, PR, stable disease (SD), or progressive disease (PD). Images will be obtained according to local site imaging protocols and will be submitted for central review. Submission instructions for central review will be provided in a separate manual.

Central imaging review will be performed using two blinded independent reviewers with adjudication by a third blinded independent reviewer in cases of discordance.

8.2 Adverse Events

8.2.1 Definition of Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment.

Test results collected during the study (e.g., laboratory values, physical examination, ECGs, etc.) or identified from review of other documents may constitute AEs if deemed clinically significant.

A SAE is defined as any AE that:

- results in death.
- is life threatening.
- requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization for elective procedures or for protocol compliance is not considered an SAE).
- results in persistent or significant disability/incapacity.
- is a congenital anomaly/birth defect.
- important medical events that do not meet the preceding criteria but based on appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed above.

8.2.2 Eliciting and Reporting Adverse Events/Serious Adverse Events

Patients will be instructed to contact the Investigator at any time after ICF signature if any symptoms develop. At each study visit, patients will be asked a non-leading question to elicit any medically related changes in their well-being. Patients may also report AEs voluntarily and they will be instructed to contact the Investigator between visits if any symptoms develop or worsen.

AEs will be reported starting when the patient provides written informed consent. Clinically significant medical conditions present at the time of ICF signature will be reported as medical history. Clinically significant medical conditions that start or worsen after ICF signature will be reported as AEs.

All AE/SAEs, regardless of relationship to study drug, will be reported from the time the patient signs the ICF until 30 days after the last dose of study drug or start of new anti-cancer therapy, whichever is earlier; thereafter, only related SAEs will be reported, with 2 exceptions.

1. Patients who have responded to loncastuximab tesirine and undergo SCT (either autologous or allogeneic) after permanent discontinuation of loncastuximab tesirine treatment without any intervening anti-cancer therapy. These patients will have the following safety information reported until 180 days post-transplant regardless of relationship to loncastuximab tesirine:
 - Grade ≥ 3 AEs suggestive of hepatic toxicity, veno-occlusive disease/sinusoidal obstruction syndrome, graft-versus-host disease, infectious complications, prolonged cytopenia(s), and pulmonary toxicity
 - SAEs
 - Death

2. Patients who receive CAR-T therapy after permanent discontinuation of loncastuximab tesirine treatment will have the following safety information reported until 90 days after receiving CAR-T therapy regardless of relationship to loncastuximab tesirine:
 - Grade ≥ 3 AEs of cytokine release syndrome, encephalopathy, edema or effusion, rash, hepatic toxicity
 - SAEs
 - Death

Whenever possible, AEs should be reported as a diagnosis rather than individual signs and symptoms. If no diagnosis is available or has been identified, then the primary symptom is reported.

In general, the term ‘disease progression’ should not be used for reporting an AE/SAE. However, AEs/SAEs that are complications of disease progression should be reported.

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected will include event term, date of onset, assessment of severity ([Section 8.2.3](#)), seriousness ([Section 8.2.1](#)), relationship to study drug ([Section 8.2.4](#)), action taken with study drug, date of resolution of the event or ongoing (when no resolution by the end of the reporting period), any required treatment or evaluations, and outcome.

New SAEs and any recurrent episodes, progression, or complications of the original SAE must be reported to the pharmacovigilance department of the Sponsor or delegate (e.g., contract research organization [CRO]) within 24 hours after the time site personnel first learn about the event. Reporting will occur through the electronic data capture (EDC) system.

8.2.3 Assessment of Severity

AEs will be graded according to CTCAE v4.0. For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5 as shown in [Table 3](#).

Table 3. Definition of Severity Grades for CTCAE

Grade	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). ^a
3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. ^b
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

^a 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.

AEs characterized as intermittent do not require documentation of onset and duration of each episode.

8.2.4 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is an important part of safety reporting, but is not a factor in determining whether an AE is reported. An AE will be assessed as related to study drug if there is a reasonable possibility of causal relationship with the use of the study drug. For SAEs, whenever possible, the Investigator should provide a rationale for the causality assessment.

8.2.5 Regulatory Reporting

All SAEs considered at least possibly related to the study drug will be reported as Suspected Unexpected Serious Adverse Reactions (SUSARs), unless they have been defined as expected in the Reference Safety Information section of the IB. SUSARs will be reported to competent authorities and independent ethics committee (IEC) in accordance with current legislation.

8.2.6 Pregnancy

Any pregnancy in a participant or partner that occurs during the study must be reported using the Pregnancy Report Form. Pregnancy must be reported within 24 hours after the site personnel first learn of the pregnancy. The pregnancy itself is not considered an AE. However, the pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient discontinued from the study. Abortions (elective or spontaneous) occurring from the time the patient signs the ICF until 90 days after the last dose of study drug must be reported as an SAE.

Any SAE occurring in association with a pregnancy that is brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study drug must be promptly reported in the same manner.

Once pregnancy is confirmed in a study participant, study drug will be discontinued, see [Section 8.3.6](#) for additional information.

8.2.7 Overdose

An overdose of the study drug will be considered an AE if the dose administered to the patient exceeds the maximum dose described in the protocol by 15% or more. If such an overdose occurs during the study, with or without any signs or symptoms, it must be reported to the Sponsor using the SAE Report Form within 24 hours after the time site personnel first learn about the event.

8.3 Safety Assessments

Safety will be assessed based on the procedures in the subsection below. AEs/SAEs collection and reporting is described in [Section 8.2.2](#).

Unless otherwise specified, all safety assessments on dosing days will be done prior to study drug administration.

8.3.1 Physical Examination

Physical examination will be performed according to institutional standards and will include a whole body skin examination.

8.3.2 ECOG Performance Status

ECOG performance status grades are presented in [Appendix 1](#) and will be captured as per SoE ([Table 1](#)).

8.3.3 Height and Weight

Height and weight will be measured as per SoE ([Table 1](#)).

Additional measurements will be performed if clinically indicated.

Patients should monitor their weight at home to mitigate the risks for edema/effusions. Refer to [Section 6.6.2](#) for further details.

8.3.4 Vital Signs

Vital signs include the measurements of arterial blood pressure (systolic and diastolic), heart rate, respiratory rate, and body temperature and will be performed according to the institutional standards. For Day 1 of each cycle, vital signs are to be measured before the start of the loncastuximab tesirine infusion and at the end of infusion.

8.3.5 Laboratory Tests

Samples will be collected at the time points specified as per SoE ([Table 1](#)).

Any clinically significant abnormal laboratory test results will be recorded as AEs or SAEs.

Hematology: white blood cells (WBC) with 5-part differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), platelet count, hemoglobin, and hematocrit.

Chemistry: ALT, AST, GGT, alkaline phosphatase (ALP), amylase, lipase, total bilirubin (conjugated and unconjugated bilirubin only when total bilirubin is abnormal), sodium, potassium, chloride, phosphate, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, creatinine, creatine phosphokinase, total protein, albumin, glucose, and lactate dehydrogenase.

Coagulation: partial thromboplastin time (PTT) and International Normalized Ratio (INR).

Urinalysis: pH, specific gravity, protein, WBC, red blood cell (RBC), ketones, glucose, and bilirubin.

Urinalysis may be performed by dipstick. Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation consists at a minimum of WBC and RBC quantitation per high power field, as well as semi-quantitative assessment of other cells and substances, if present, such as epithelial cells, bacteria, and crystals (“few,” “moderate,” “many”). Other evaluations depending on microscopic findings may be added.

8.3.6 Pregnancy Test

A highly sensitive β -HCG test in urine or blood β -HCG test will be performed in woman of childbearing potential for eligibility (see [Section 5.1](#) Inclusion criterion 10) and throughout the study as per SoE.

The C1D1 pre-dose pregnancy test can be waived if the test for eligibility was done within 3 days of C1D1. After starting the study drug, all efforts should be made to keep the interval between 2 consecutive pregnancy tests no more than 6 weeks.

If a pregnancy test is positive, the study drug must be held pending confirmation. If the pregnancy is confirmed, treatment will be discontinued permanently for the patient. Refer to [Section 8.2.6](#) for the handling of the patient and reporting the event.

8.3.7 ECG

Three consecutive (also called triplicate) 12-lead ECGs will be performed at defined timepoints throughout the study as per SoE ([Table 1](#)). Refer to [Table 4](#) for the detailed schedule of ECGs.

ECGs will be performed after the patient is resting for at least 5 minutes.

At timepoints coinciding with blood sample collection including PK, ECGs should be taken prior to blood collection.

If a patient experiences Torsade de Pointes, additional concomitant PK samples (i.e., unscheduled) should be collected.

Table 4. Schedule for Triplicate ECG Collection

Cycle	Day	ECG timepoint (window)
Screening	-	Any time within 28 days prior to C1D1
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI) Post-dose* 4 h (\pm 15 min)
	D8	Post-dose* 168 h (\pm 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (\pm 48 h; but within 30 min prior to PK sample)
C2	D1	Pre-dose (within 30 min prior to PK sample) EOI (within 10 min prior to EOI) Post-dose* 4 h (\pm 15 min)
	D8	Post-dose* 168 h (\pm 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (\pm 48 h; but within 30 min prior to PK sample)
C3	D1	Pre-dose (within 30 min prior to PK sample) EOI (within 10 min prior to EOI)
C5, C7 ... every other cycle	D1	Pre-dose (within 30 min prior to PK sample)
EOT		Any time (but within 30 min prior to PK sample)
Unscheduled		Any time

Abbreviations: ECG, electrocardiogram; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.

*Post-dose timepoint is counted from start of infusion.

ECGs will be submitted for a central review. Submission instructions for the central review will be provided in a separate manual. Assessments will include determination of heart rate and rhythm and the PR, QRS, QT, QTcF, and QTcB intervals.

8.4 Pharmacokinetics, Pharmacodynamics, and Immunogenicity

PK, ADA, [REDACTED] will be collected as per SoE (Table 1). Additional biological samples may be collected by the Investigator when clinically indicated (e.g., at the time of significant AEs that are at least possibly related to the study drug) and may be used for PK, pharmacodynamics, [REDACTED]

When multiple samples are required at the same timepoint, collection of safety samples should be first followed by PK, then ADA, [REDACTED]

In order to better understand the disease, metabolic disposition, and pharmacologic behavior of loncastuximab tesirine in humans, samples remaining after primary analyses may be utilized for further analysis.

Biological samples may be retained for up to 10 years to further address scientific questions as new information in regards to the disease or the study drug becomes available.

For detailed instructions related to central laboratory sample collection, labeling, processing, storage, or shipment refer to the appropriate laboratory manual(s).

8.4.1 Pharmacokinetics

The concentration in serum of loncastuximab tesirine (total antibody), PBD-conjugated antibody, and unconjugated warhead SG3199 will be assessed by a central laboratory designated by the Sponsor using validated bioanalytical methods.

Approximately 6 mL of whole blood will be collected as per Table 1 and Table 5. Blood should be drawn from a vein away from the one used for study drug infusion.

PK samples must be stored at -70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

At timepoints coinciding with ECG collection, PK blood collection should occur immediately after the end of the ECG recording and, when applicable, after vital signs. If a patient experiences Torsade de Pointes, additional PK samples (e.g., unscheduled) should be collected.

Table 5. Sampling Schedule for PK and ADA

Cycle	Day	PK timepoint (window)	ADA timepoint (window)
C1	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (preferably within 2 h prior to start of infusion)
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	Post-dose* 336 h (± 48 h)
C2	D1	Pre-dose (within 2h prior to start of infusion) EOI (-5 to +10 min) Post-dose* 4 h (± 10 min)	Pre-dose (within 2 h prior to start of infusion)
	D8	Post-dose* 168 h (± 48 h)	-
	D15	Post-dose* 336 h (± 48 h)	-
C3	D1	Pre-dose (within 2 h prior to start of infusion) EOI (-5 to +10 min)	Pre-dose (within 2 h prior to start of infusion)
C5, C7, ... every other cycle	D1	Pre-dose (within 2 h prior to start of infusion)	Pre-dose (within 2 h prior to start of infusion)
EOT		At any time during visit day	At any time during visit day
Unscheduled		Any time	Any time (if applicable, close to PK sample)

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.

*Post-dose timepoint is counted from start of infusion.

To understand the metabolic disposition of loncastuximab tesirine in humans, samples remaining after PK analysis is complete may be pooled among patients for potential metabolite identification.

8.4.2 Immunogenicity

Detection of ADAs will be performed by using a screening assay for identification of antibody positive samples/patients, a confirmation assay, and titer assessment, and will be performed using the Meso-Scale Discovery Electrochemiluminescence platform (MSD-ECL). If an ADA is confirmed, a functional assay for the assessment of the neutralizing capacity of the ADA will be performed.

Approximately 6 mL of whole blood will be collected as per [Table 1](#) and [Table 5](#). Blood should be drawn from a vein away from the one used for study drug infusion.

For patients who test positive for ADAs, an additional ADA sample will be requested for testing every 12 weeks following the EOT visit until the ADA titer falls to a background level.

ADA samples must be stored at -70°C. Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.



8.5 Health-Related Quality of Life (HRQoL) Questionnaires

8.5.1 EuroQol-5 Dimensions-5 Levels (EQ-5D-5L)

EQ-5D-5L is designed as an international, standardized, generic instrument for describing and evaluating QoL (EuroQol Group, 1990). The EQ-5D-5L consists of two parts:

- The descriptive system: QoL is classified according to five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises five levels of perceived problems (e.g., none, slight, moderate, severe, extreme).
- The visual analog scale (VAS): patients are asked to indicate their health state today on a VAS with the endpoints labeled ‘the best health you can imagine’ (score 100) and ‘the worst health you can imagine’ (score 0). Patients are asked to mark an “X” on the VAS to indicate their own health and then to report the score in a text box. If there is a discrepancy between where the patient has placed the X and the number he/she has written in the box, the number in the box is to be entered in the CRF together with a comment indicating the discrepancy.

8.5.2 Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

FACT-Lym is a lymphoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT) questionnaire (Hlubocky FJ et al, 2013). It consists of 15 specific items that are used together with the core 27-item questionnaire FACT-G. The patient is asked to respond to each item with a score of 0–4, where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. A higher score indicates a worse level of QoL.

9 Statistical Considerations

Full details of the analysis plan, including a more technical and detailed elaboration of the statistical analyses, will be provided in the statistical analysis plan (SAP). [REDACTED]

9.1 Sample Size Calculation

Patients with DLBCL who have failed second line therapy have a very poor prognosis, with response to second-line salvage therapy ranging from 14-26%, with a median survival of 6.1 months (Seshadri et al., 2008; Crump et al., 2017). A treatment with a response rate of 20% would be a clinically meaningful option for this patient population.

The primary hypothesis is that the ORR based on central review for patients treated with loncastuximab tesirine is significantly greater than 20% (i.e., $H_0: p \leq 0.2$ vs. $H_a: p > 0.2$). This hypothesis will be tested at type I error of 0.05 (two sided).

Using nQuery exact test for single proportion, a sample size of 140 patients has >99% power to achieve a 1-sided significance level of 0.025 (2-sided significance level of 0.05). This sample size will provide adequate precision for observed ORR in the expected range. A 2-stage design will be used, with an interim analysis for futility on the first 52 patients. If ≥ 10 patients respond, the study will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment will be halted if futility is confirmed to minimize exposure of patients in the study. With the null hypothesis that the true response rate is 0.2, and the alternative hypothesis that the true response rate is significantly greater than 20%, (40% is used for calculation), the design controls the type I error rate at 0.025 and yields a power of >99%.

9.2 Analysis Populations

- All Treated Population: All patients who receive at least 1 dose of loncastuximab tesirine. This population will be used in the primary analyses of efficacy and safety.
- Per-Protocol Population: All patients in the all-treated population without major protocol deviations, which will be further described in detail in the SAP.
- PK Population: All patients in the per-protocol population with at least 1 pre- (C1D1) and 1 post-dose valid assessment.
- Pharmacodynamics Population: All patients in the per-protocol population with at least 1 valid pharmacodynamics/ [REDACTED]

9.3 Interim Analysis for Futility

A single interim analysis is planned using Simon's 2-stage procedure. The purpose of this interim analysis is solely to determine if there is a sufficient ORR observed early in the study to warrant continuing study enrollment to completion. The interim analysis constitutes a futility analysis; it will not be used to stop the trial early for positive efficacy.

In the first stage of the study, an interim analysis will be performed at the time when the 52nd patient has two tumor assessments (approximately 12 weeks after start of study drug). Enrollment will continue during the interim analysis. If ≥ 10 patients respond, the study will proceed to the second stage. If < 10 patients respond, study enrollment will be halted.

Patients already enrolled may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria (Section 7), whichever occurs first. Additionally, patients benefitting clinically at 1 year may continue treatment after a case by case review with the Sponsor.

9.4 Final Analysis

For primary and key secondary endpoints analyses, a database snapshot will be taken when all patients have a minimum of 6 months follow up after initial documented response. All efficacy, safety, and PK endpoints will be analyzed and reported in the clinical study report (CSR). Results of the population PK analysis will be reported separately.

The exact binomial test will be used in the final analyses for the primary endpoint because of the practical consideration that accrual cannot be limited to exactly 140 patients and because patients included in the interim analysis as non-responding may be included in the final analysis as responding if they experience a late response.

Follow-up analyses will be performed when all the patients complete the study per protocol. The results will be reported in a CSR addendum.

9.5 Demographics and Baseline Characteristics

The analyses include:

- Demographic information such as age, gender, ethnicity, and race (to the extent allowed by local regulations).
- Cancer medical history, which includes a complete history of all surgeries and significant diagnoses, and all cancer treatment, including surgery, radiation therapy, chemotherapy, etc.
- Any other relevant medical history.

9.6 Efficacy Analyses

Primary efficacy analyses will be based on response as determined by central review. Response reported by investigators will be used for sensitivity analyses.

9.6.1 Overall Response Rate

The ORR will be defined as the proportion of patients with a BOR of CR or PR. The overall response category will be derived based on response assessment performed on or before the start of subsequent anti-cancer therapy. For the primary ORR analysis in the all treated population, patients with a CR or PR will be counted as successes and all other patients (including those with missing response information) will be counted as failures.

The percentage of ORR with its 95% confidence interval (CI) will be presented. In contrast to CR, PR, or PD, a BOR of SD can only be made after the patient is on-study for a minimum of 35 days after the first dose of study drug. Any tumor assessment indicating SD before this time period will be considered as a non-evaluable for BOR if no assessment after this time period is available.

9.6.2 Duration of Response

DOR will be defined among responders (CR or PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression based on central review. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method. The median duration of response and 95% CI will be presented. DOR will be analyzed by response subgroup (CR, PR). Further details will be outlined in the SAP.

9.6.3 Complete Response Rate

Complete Response Rate (CRR) will be defined as the proportion of patients with a best overall response of CR. The percentage of CRR with its 95% CI will be presented.

9.6.4 Relapse-free Survival

RFS will be defined among CR patients as the time from the earliest date of first complete response until the first date of either disease relapse or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression based on central review. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method. The median duration of response and 95% CI will be presented. Further details will be outlined in the SAP.

9.6.5 Progression-Free Survival

PFS will be defined among all treated patients as the time from first dose of study drug until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression based on central review. For patients whose disease has not progressed at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by the Kaplan-Meier method. The median PFS time and 95% CI will be presented. Further details will be outlined in the SAP.

9.6.6 Overall Survival

Median OS will be defined as the time from the beginning of study drug treatment until death due to any cause. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. The data will be analyzed by the Kaplan-Meier method. The median OS and 95% CI will be presented. Further details will be outlined in the SAP.

9.6.7 Subgroup analysis

Subgroup analyses will be performed for ORR, DOR, CR, RFS, PFS, and OS using the following variables if appropriate

- Demographic variables: age group, gender, race, and country
- Baseline disease characteristics: tumor staging, and subtype
- Number of prior systemic therapies and response to prior systemic therapies

Other subgroup analysis factors may be evaluated as appropriate and the details will be provided in SAP.

9.7 Safety Analyses

Safety analyses will be presented descriptively.

9.7.1 Adverse Events

The focus of AE summarization will be on TEAEs. A TEAE is defined as an AE that occurs or worsens in the period extending from the first dose of study drug to 30 days after the last dose of study drug or start of new anti-cancer therapy, whichever is earlier.

TEAEs will be summarized. Summary tables will be presented to show the number of patients reporting TEAEs by severity grade and corresponding percentages. A patient who reports multiple TEAEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade.

Separate summaries will be prepared for TEAEs classified as severe or life-threatening (Grade 3 or higher); study drug-related AEs; AEs leading to treatment interruption, modification, or discontinuation; serious AEs; and death. Dose interruptions, reductions, and relative dose intensity will also be summarized.

9.7.2 Clinical Laboratory Results

Clinical hematology, coagulation panel, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Shifts for clinical laboratory results that can be graded according to CTCAE v4.0 (or more recent) will be summarized by CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in “worst-case post-Baseline” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. Further details will be provided in the SAP.

9.7.3 Additional Safety Assessments

The results of scheduled assessments of vital signs, physical examinations, ECOG performance status, and 12-lead ECGs will be summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in “worst case” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study drug. All data will be listed. Further details will be provided in the SAP.

9.8 Pharmacokinetic Analyses

The PK profile may include, but is not limited to, determination of: maximum concentration (C_{max}), area under the concentration-time curve from time zero to the end of the dosing interval ($AUC_{0-\tau}$), area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), clearance (CL), and accumulation index (AI).

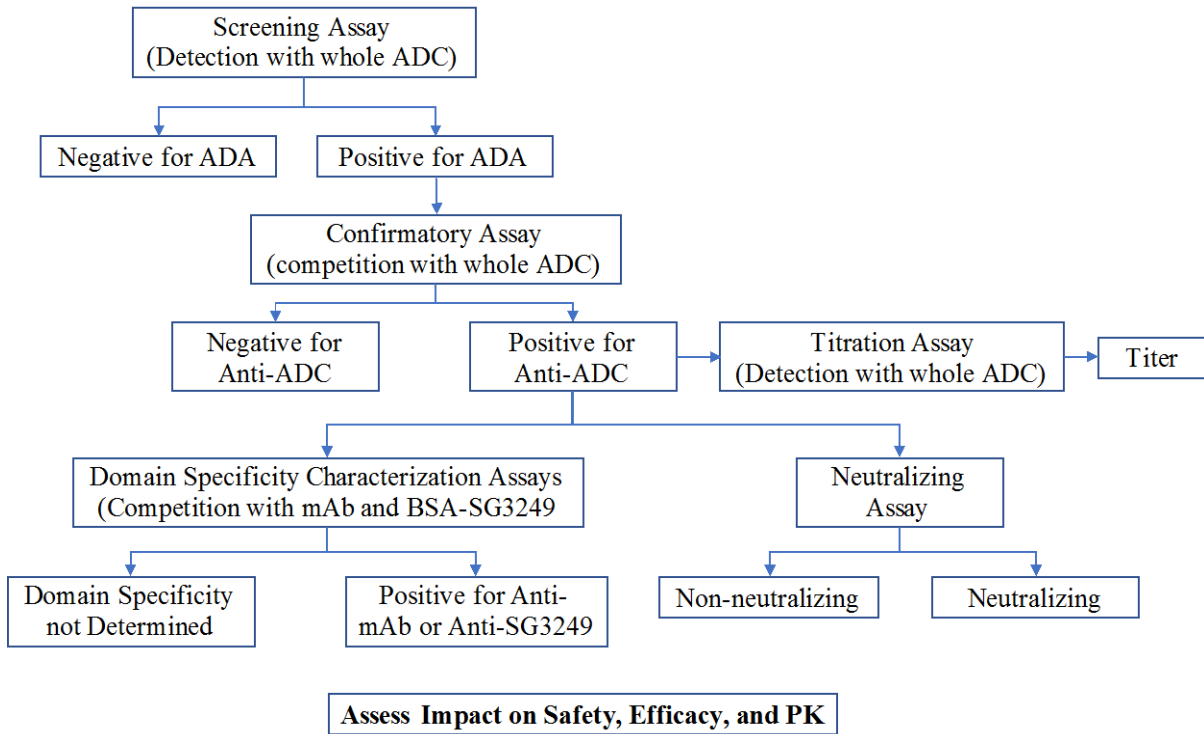
PK parameters will be determined for all PK-evaluable patients using a non-compartmental method with Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ, US) or other appropriate software. Supplemental population PK analyses will be undertaken and reported separately to characterize the PK parameters for the typical patient and to identify covariate factors which influence drug disposition.

Demographic data for the PK population will be summarized. Potential correlations of PK parameters to baseline characteristics and safety observations will be assessed but may be reported separately. In addition, the influence of loncastuximab tesirine PBD-conjugated antibody and unconjugated warhead SG3199 concentrations on the QTc interval will be assessed but reported separately.

9.9 Immunogenicity Analyses

A tiered immunogenicity strategy (Figure 2) will be undertaken to evaluate ADAs by screening and confirmatory assays with titer evaluation, followed by characterization and evaluation of neutralizing capacity as needed. ADA sample collection, banking, and testing in validated and to be validated assays will be according to the new FDA Draft Guidance for Industry (April 2016): ‘Assay Development and Validation for Immunogenicity testing of Therapeutic Protein Products’.

Figure 2. Anti-drug Antibody Tiered Immunogenicity Testing Strategy



Abbreviations: ADA, anti-drug antibody; ADC, antibody-drug conjugate; BSA, bovine serum albumin; mAb, monoclonal antibody; PK, pharmacokinetics.

Results from ADA testing will include tabular summarization for number/proportion of patients with positive pre-dose ADA response, number of patients with post-dose ADA response only, and number of patients with positive ADA response at any time. The denominator will be the total number of patients tested for ADAs in the study.



10 Data Management and Quality Assurance

The Investigator will maintain accurate source documentation including patient medical records, laboratory reports, ECG strips, and patient diaries.

Investigative site qualified personnel will enter patient data into an EDC system. The analysis data sets will be a combination of these data and data from other sources.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the world health organization (WHO) Drug Dictionary.

After database lock, each study site will receive information about all of their site-specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a copy of study data from all sites will be created and sent to the Sponsor for storage. The CRO will maintain a duplicate copy for its records. In all cases, patient initials will not be collected or transmitted to the Sponsor.

For detailed instruction on data entry procedures and timelines, please refer to the eCRF Completion Guidelines.

11 Ethical, Regulatory, and Study Management Considerations

11.1 Regulatory and Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and all applicable regulations.

11.2 Independent Ethics Committee or Institutional Review Board

Federal regulations and ICH guidelines require that approval be obtained from an institutional review board (IRB)/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study intended to be provided to the patient or the patient's legally authorized representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for obtaining continued review of the clinical research as specified by the IRB/IEC, at intervals not exceeding 1 year. The Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

11.3 Patient Information and Consent

Informed consent in compliance with IRB/IEC and local regulations shall be obtained from each patient or their legally authorized representative before performing any study procedures and will be documented with a signed IRB/IEC approved ICF. Before enrollment, each prospective patient or his or her legally authorized representative will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legally authorized representative understands the implications of participating in the study, the patient/legally authorized representative will be asked to give consent to participate in the study and sign the ICF. The process for obtaining consent has to be documented at the institution.

If the ICF is revised during the course of the study, all patients on-study, including those in follow-up, must sign the revised form, unless otherwise indicated by the IRB/IEC (local or global, as applicable). In such case, the reason for not re-consenting the patient should be documented.

11.4 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, regulatory authorities, or the IRB/IEC.

The Investigator and other study staff may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements as required under 21 CFR 54 and local regulations. In addition, the Investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

11.6 Serious Adverse Events Report Requirements

The Sponsor will ensure that all relevant safety information (SAEs and SUSARs) is reported to the FDA and competent authorities of European Member States, and to the IRB/IEC, in accordance with current legislation.

11.7 Study Conduct

The Investigator will conduct all aspects of this study in accordance with the principles of the current version of ICH E6 as well as all national, state, and local laws and regulations. Study personnel involved in conducting this study will be qualified by education training and experience to perform their respective tasks. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

11.8 Protocol Amendments

Any change in the study plan requires a protocol amendment. All amendments to the protocol must be reviewed and approved following the same process as the original protocol before the amended protocol can be implemented. The Investigator will inform the governing IRB/IEC of all protocol amendments issued by the Sponsor in accordance with established IRB/IEC procedure. Only protocol amendments intended to eliminate an apparent immediate hazard to patient(s) may be implemented immediately, i.e., without IRB/IEC approval, but the circumstances of the change must be documented and submitted to the IRB/IEC.

11.9 Monitoring of the Study

All aspects of the study will be carefully monitored by the Sponsor or designee for compliance with GCP and applicable government regulations.

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency access to all study records.

The Investigator should promptly notify the Sponsor and the CRO of any inspections scheduled by any regulatory authorities and promptly forward copies of any inspection reports received to the Sponsor.

11.10 Records Retention

Essential documents should be retained for at least 15 years from the completion of the study (last patient last visit) and 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 study drug. However, 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 as to when these documents no longer need to be retained.

11.11 Publications

Following completion of the study, the results from the study may be reported publicly by making any oral public presentation and/or submitting or presenting a manuscript, abstract, or other materials relating to the Study at scientific meetings and/or to a publisher, reviewer, or other outside person in scientific journals (“Publication”), provided; however, that Publication of the results from an individual site shall not be made before the first multi-site Publication by Sponsor. The Sponsor shall coordinate the drafting, editing, authorship, and other activities related to study Publication and shall mutually agree with the Investigator(s) on the number, medium, forum, and timing for Publication. The Sponsor shall solicit input regarding contents of the Publication from all Investigators and in consultation with all sites. The Sponsor acknowledges the right of the Investigator(s) to publish the results of this study after the entire study has completed, but also reserves the right to a window to review the Publication for regulatory compliance as well as for protection of its intellectual property. In particular, the Sponsor may request to remove the Sponsor’s confidential information and suspend Publication for a certain period of time to protect the Sponsor’s intellectual property interest, as further set forth in the Clinical Trial Agreement with the clinical study site(s) and Investigator(s).

12 Reference List

- Adair JR, Howard PW, Hartley JA, et al. Antibody-drug conjugates - a perfect synergy. *Expert Opin Biol Ther* 2012;12(9):1191-1206.
- Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National Cancer Data Base from 1998 to 2011. *Am J Hematol* 2015;90(9):790-795.
- Beck A, Goetsch L, Dumontet C, et al. Strategies and challenges for the next generation of antibody-drug conjugates. *Nat Rev Drug Discov* 2017;16(5):315-337.
- Cairo MS, Coiffier B, Reiter A, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: An expert TLS panel consensus. *Br J Haematol* 2010;149(4):578-586.
- Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. *J Clin Oncol* 2014;32(27):3059-3067.
- Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? *Hematology Am Soc Hematol Educ Program* 2016(1):366-378.
- Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood* 2017;130(16):1800-1808.
- Epperla N, Hamadani M. Hematopoietic cell transplantation for diffuse large B-cell and follicular lymphoma: Current controversies and advances. *Hematol Oncol Stem Cell Ther* 2017;10(4):277-284.
- Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol* 2010;28(27):4184-4190.
- Hartley JA. The development of pyrrolobenzodiazepines as antitumour agents. *Expert Opin Investig Drugs* 2011;20(6):733-744.
- Hlubocky FJ, Webster K, Cashy J, et al. The development and validation of a measure of health-related Quality of Life for Non-Hodgkin's Lymphoma: The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym). *Lymphoma* 2013:1-9
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5(6):649-655.
- Rudin CM, Pietanza MC, Bauer TM, et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol* 2017;18(1):42-51.
- Scheuermann RH, Racila E. CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. *Leuk Lymphoma* 1995;18(5-6):385-397.
- Seshadri T, Stakiw J, Pintilie M, et al. Utility of subsequent conventional dose chemotherapy in relapsed/refractory transplant-eligible patients with diffuse large B-cell lymphoma failing platinum-based salvage chemotherapy. *Hematology* 2008;13(5):261-266.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67(1):7-30.

Simon R. Optimal two-stage designs for phase II clinical trials. *Controlled Clinical Trials* 1989;10(1):1-10.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24(19):3187-3205.

13 Appendices

13.1 Appendix 1. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance status grades as indicated below:

Grade	Definition
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, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

[Oken et al., 1982](#)

13.2 Appendix 2. Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Classification)

Response / Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	<ul style="list-style-type: none"> Score 1, 2, or 3* with or without a residual mass on 5PS** <p>Note: Uptake may be greater than normal mediastinum and/or liver in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors). In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake</p>	<ul style="list-style-type: none"> Target nodes/nodal masses must regress to ≤ 1.5 cm in LD No extralymphatic sites of disease
Nonmeasured lesion	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> Absent
Organ enlargement	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> Regress to normal
New lesions	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> None
Bone marrow	<ul style="list-style-type: none"> No evidence of FDG-avid disease in marrow 	<ul style="list-style-type: none"> Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	<ul style="list-style-type: none"> Score 4 or 5** with reduced uptake compared with baseline and residual mass(es) of any size. At interim, these findings suggest responding disease. At end of treatment, these findings indicate residual disease. 	<ul style="list-style-type: none"> $\geq 50\%$ decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm \times 5mm as the default value. When no longer visible, 0 \times 0 mm For a node >5 mm \times 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesion	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> Absent/normal, regressed, but no increase
Organ enlargement	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> Spleen must have regressed by $>50\%$ in length beyond normal
New lesions	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> None
Bone marrow	<ul style="list-style-type: none"> Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan 	<ul style="list-style-type: none"> Not applicable
No response or stable disease	No metabolic response	Stable disease

Response / Site	PET-CT-Based Response	CT-Based Response
Target nodes/nodal masses, extranodal lesions	<ul style="list-style-type: none"> Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment 	<ul style="list-style-type: none"> <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> No increase consistent with progression
Organ enlargement	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> No increase consistent with progression
New lesions	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> None
Bone marrow	<ul style="list-style-type: none"> No change from baseline 	<ul style="list-style-type: none"> Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease (requires at least 1 of the following)
Individual target nodes/nodal masses	<ul style="list-style-type: none"> Score 4 or 5 with an increase in intensity of uptake from baseline and/or 	<ul style="list-style-type: none"> PPD progression
Extranodal lesions	<ul style="list-style-type: none"> New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment 	<p>An individual node/lesion must be abnormal with:</p> <ul style="list-style-type: none"> LDi > 1.5 cm and Increase by $\geq 50\%$ from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by $> 50\%$ of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
Nonmeasured lesions	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> New or recurrent splenomegaly New or clear progression of preexisting nonmeasured lesions
New lesions	<ul style="list-style-type: none"> New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered 	<ul style="list-style-type: none"> Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	<ul style="list-style-type: none"> New or recurrent FDG-avid foci 	<ul style="list-style-type: none"> New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with

measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

** PET 5PS: 1, no uptake above background; 2, uptake \leq mediastinum; 3, uptake $>$ mediastinum but \leq liver; 4, uptake moderately $>$ liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

[Cheson et al., 2014](#)