Protocol Number: ADCT-402-103

Official Title: A Phase 1/2 Open-Label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine and Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma (LOTIS-3)

NCT Number: NCT03684694

Document Date: 31 August 2021

CLINICAL STUDY PROTOCOL

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A Phase 1/2 Open-Label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine and Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma (LOTIS-3)

PROTOCOL NO.: ADCT-402-103

Sponsor: **ADC Therapeutics SA**
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Protocol Amendment 5: 31 August 2021

Confidentiality Statement

PROTOCOL APPROVAL – SPONSOR SIGNATORY

Study Title:	"A Phase 1/2 Open-Label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine and Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma (LOTIS-3)"
Protocol Number:	ADCT-402-103
Protocol Amendment 5:	31 August 2021

Protocol accepted and approved by:

[redacted]
Head of Early Clinical Development
ADC Therapeutics America Inc.
Phone: [redacted]
e-mail: [redacted]

[redacted] _____ 31 August 2021

Signature Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled: "A Phase 1/2 Open-Label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine and Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma (LOTIS-3)" 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 Amendment 5, dated 31 August 2021, 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 SA or implement protocol changes without Independent Ethics Committee approval except to eliminate an immediate risk to patients. I agree to administer the study drugs only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the study drugs 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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ABW	adjusted body weight
ADA	anti-drug antibody
ADC	antibody drug conjugate
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AI	accumulation index
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AlloSCT	allogeneic stem cell transplant
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration-time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration-time curve from time zero to the end of the dosing interval
BID	twice a day
BMI	body mass index
B-NHL	B-cell NHL
BOR	best overall response
BP	blood pressure
BTK	Bruton's tyrosine kinase
C	cycle
C1D1	Cycle 1 Day 1
CAR-T	chimeric antigen receptor T-cell
CD19	cluster of differentiation
CFR	Code of Federal Regulations
cfDNA	circulating free DNA
CI	confidence interval
CL	apparent systemic clearance
C_{max}	maximum concentration
CNS	central nervous system
[redacted]	
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
D	day
DESC	Dose Escalation Steering Committee
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity

Abbreviation	Definition
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion
EORTC	The European Organization for Research and Treatment of Cancer
EOT	end of treatment
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCB	germinal center B-cell
GCP	Good Clinical Practice
gDNA	genomic DNA
GGT	gamma glutamyl transferase
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
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	intravenous(ly)
LymS	lymphoma subscale
MedDRA	Medical Dictionary for Regulatory Activities
MCL	mantle cell lymphoma
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	pyrrolobenzodiazepine
PD	progressive disease
PET	positron emission tomography

Abbreviation	Definition
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
po	orally/per os
PR	partial response
PRO	patient-reported outcome
PTT	partial thromboplastin time
QLQ	quality of life questionnaire
QoL	quality of life
QT	measure between Q wave and T wave in the electrocardiogram
QTcF	Fredericia correction of the QT measure
Q3W	every 3 weeks
RBC	red blood cell
RFS	relapse-free survival
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	standard of care
SoE	Schedule of Events
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	treatment-emergent adverse event
T_{half}	apparent terminal half-life
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
µL	microliter
ULN	upper limit of normal
US	United States
Val	valine
V_{ss}	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

SUMMARY OF CHANGES AND RATIONALE

Protocol Amendment 5

The primary reason for this global Protocol Amendment 5 was to amend the study design for the Phase 2 by enrolling approximately 100 patients with relapsed or refractory Diffuse Large B-Cell Lymphoma (DLBCL) to a new treatment cohort in which loncastuximab tesirine will be given every cycle (rather than intermittently) in combination with ibrutinib. This is to explore if the intensified regimen improves treatment response and durability in patients with advanced DLBCL. The RP2D for loncastuximab tesirine which has been determined as 60 µg/kg will be re-determined after the testing of 75 µg/kg dose has been completed in the Phase 1 portion of the study. In this new treatment cohort loncastuximab tesirine will be given at re-determined RP2D. Ibrutinib will be given orally at 560 mg daily on Cycle 1 (C1) and C2, and subsequent doses of ibrutinib will be given at 420 mg daily to mitigate potential additive adverse events.

The summary of changes and the rationale in Protocol Amendment 5 is as follows:

- Section 3 Study Objectives and Endpoints:
  - The primary objective for Phase 2 study was modified to evaluate the efficacy of loncastuximab tesirine given at every cycle in combination with ibrutinib in patients with relapsed or refractory DLBCL.
  - The primary endpoint for Phase 2 study was changed to Complete Response Rate (CRR) according to the 2014 Lugano classification as determined by independent review committee (IRC) in all DLBCL patients given loncastuximab tesirine at every cycle in combination with ibrutinib, instead of the non-GCB DLBCL cohort only receiving intermittent dosing of loncastuximab tesirine. The latter has been moved to a secondary endpoint.
  - [redacted]

- Section 4.1 Study Design Overview:
  - Updated the study design by introducing a new treatment cohort for DLBCL patients in which loncastuximab tesirine is given at every cycle in combination with ibrutinib to potentially improve response rate and durability in Phase 2 once a re-determined MTD/PR2D has been defined. Ibrutinib will be given at 560 mg po daily for first 2 cycles, then 420 mg po daily for subsequent cycles starting at C3 for this new treatment. The dose selection rationale for this new DLBCL treatment cohort was added in Section 2.2. Also, a two-stage design with futility monitoring was added for the new treatment cohort. The new treatment cohort was added in Section 4.3 Treatment Period and Section 6.3 Dosing of Study Drug. A table of two treatment cohorts for Phase 2 was generated for easy reference in Section 6.3.

- Closed the patient enrollment to non-GCB DLBCL cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib in Phase 2.
- Updated the study sample size from 161 to 243 taking into account 100 DLBCL patients in the new treatment cohort and the early enrollment closure of the non-GCB DLBCL cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib in Phase 2. Section 9.1 Sample Size was amended for the same reasons.

- Section 5.1 Inclusion Criteria:
  - Clarified criterion 3 to allow patients not considered by the investigator to be a candidate for stem cell transplantation to participate in the study.
  - For inclusion criterion 11 added a barrier method to hormonal contraceptives (oral, injectable, patch, intrauterine devices) as one of highly effective forms of birth control to follow contraception recommendation for ibrutinib.

- Section 6.5.2 Dose Delays and Modifications_Ibrutinib:
  - Updated the dose modification of ibrutinib in case of toxicity when given at a dose of 420 mg daily.
  - Updated the ibrutinib dose modification recommendations during coadministration of a strong or moderate CYP3A inhibitor in reference to ibrutinib Investigator Brochure (IB). Section 6.8.2 was updated as well.
  - Updated to allow ibrutinib dose re-escalation during the study treatment.

- Section 6.7.3 Treatment and Prophylaxis of Infusion-Related Hypersensitivity Reactions: Removed the protocol specified guidance for prophylaxis of infusion-related hypersensitivity reaction as ranitidine is not available in some countries, and institutional standard of care is a good alternative.

- Section 7.1 Discontinuation from Study Treatment: Added transplant therapy as one of reasons for end of study treatment to document the events.

- Section 8.3.7 ECG: Table 10 of ECG collection schedule for Phase 2 patients in loncastuximab tesirine given at every cycle in combination with ibrutinib was added to clearly indicate the monitoring of cardiac safety for patients in newly added cohort.

- Section 8.4.2 Immunogenicity: Updated Table 12: For Phase 2 study removed ADA collections at C6 and C10 for all patients and added ADA collection to C13 for patients receiving loncastuximab tesirine given at every cycle in combination with ibrutinib to monitor ADA titer. A footnote was added to clarify the applicable protocol version for the removal of C6 and C10 collection.

- [redacted]

- [redacted]

- Section 9.3.2 Cohort Given Loncastuximab Tesirine at Every Cycle in Combination with Ibrutinib: This new subsection was added under Section 9.3 Phase 2 Interim Analysis for Futility per new study design. The interim analysis for futility when Lonca was given intermittently is now located in section 9.3.1.

- Section 9.4 Final Analysis: Deleted the exact binomial test for final analysis of Phase 2 primary endpoint as it does not apply in the new study design.

In addition, non-substantial clarifications/corrections for inconsistencies, as well as administrative and editorial changes were included; revisions to the protocol text have also been applied to the synopsis section and Schedule of Events (SoE), Table 2 for Phase 2 study.

Protocol Amendment 4

The primary reasons for Protocol Amendment 4 were to extend the contraception duration for applicable subjects to align with the current regulatory guidance; to update guidance to investigators regarding loncastuximab tesirine dose delays and modifications as well as prohibited medication for concurrent use with loncastuximab tesirine; and to remove the loncastuximab tesirine dose adjustment for patients with a body mass index (BMI) ≥35kg/m^2. This amendment also provided two clarifications: one regarding patient reported outcome (PRO) collection time points during the study follow-up and the other notifying that mantle cell lymphoma (MCL) patients enrolled into the Phase 2 part of the study will have central reviews of their scans. Lastly, this amendment incorporated all country specific amendments from the country specific protocols to this global protocol to eliminate country specific protocols going forward.

The summary of changes and the rationale in Protocol Amendment 4 is as follows:

- To align with the current regulatory guidance (United States [US] Federal Drug Administration, "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations", May 2019 and Clinical Trials Facilitation and Coordination Group, "Recommendations related to contraception and pregnancy testing in clinical trials", 21 Sep 2020), the contraception duration required for women of childbearing potential (WOCBP) and for men with female partners of childbearing potential were extended to the time from signing informed consent form to at least 9 months and 6 months post last loncastuximab tesirine treatment, respectively, when applicable. The sections below in the protocol were revised to comply with the change.
    - Section 5.1 Inclusion Criteria: Revised Inclusion Criterion #11 to: Women of childbearing potential must agree to use a highly effective method of contraception from the time of giving informed consent until at least 9 months after the last dose of loncastuximab tesirine or 1 month after last dose of ibrutinib, whichever comes last. 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 6 months after the patient receives his last dose of loncastuximab tesirine or 3 months after last dose of ibrutinib, whichever comes last.
    - Section 8.2.6 Pregnancy Reporting: Updated the duration of reporting pregnancy to align with the contraception duration.
    - Section 8.3.6 Pregnancy Test: Added a final pregnancy test for female patients at ≥9 months post last dose of loncastuximab tesirine during the study follow-up, if applicable. Specified to allow a remote pregnancy test during follow-up. Clarified that additional tests may be obtained, if needed. The Schedule of Events (SoE) Tables (Table 1 and Table 2) were updated accordingly.

- Schedule of Events Table 2 for Phase 2 Study:
  - Updated PRO collection time point, footnote 13 (and delete footnote 14) to read: "Collect EQ-5D-5L only, via phone or at the study site every 12 weeks after the end of treatment for 1 year." This was to ensure that PRO is collected uniformly for all patients and to minimize protocol deviations that can occur when trying to collect data from patients who progress after discontinuing study treatment.
  - Updated pregnancy test and provided specifications in the footnote 14.
- Section 5.1 Inclusion Criteria: Added a note to Inclusion Criteria #2 & #4 to exclude MCL patients in Italy to incorporate the country specific requirement.
- Section 6.2.2 Study Treatment Preparation and Administration: A clarification was made for the loncastuximab tesirine dose adjustment when subject weight change is 10% or more at subsequent dosing from the baseline to align with the instructions from the pharmacy manual.
- Section 6.3.1 Loncastuximab Tesirine Dosing: Removed dosing adjustment for patients with a BMI $\geq 35 kg/m^2$ as recent population pharmacokinetics analysis revealed the dose adjustment is not needed.
- Section 6.5.1 Dose Delays and Modifications/Loncastuximab Tesirine:
  - Modified dose holding for liver function test abnormalities to ≥Grade 3 only, based on the updated safety profile.
  - Added dose discontinuation criteria: Grade 4 infusion related reactions and Hy's law liver injury to provide the standard criteria across the study for study drug discontinuation due to severity of both events and to align with other Loncastuximab Tesirine studies.
- Section 6.8.2 Prohibited During Study:
  - Made a correction for inconsistency on strong CYP3A inducers.
  - Removed P-glycoprotein (P-gp) inhibitors as prohibited medications for concurrent use with loncastuximab tesirine as the IC_{50} values for the inhibition are considerably in excess of the likely clinical exposure to SG3199, and deleted Appendix 4.
- Section 8.1 Efficacy Assessments: Modified to include images from MCL patients treated in the Phase 2 study to be submitted for central review to ensure that all patients enrolled in the Phase 2 study undergo central review of their radiographic scans.
- Section 9.10 Immunogenicity Analyses: Updated to follow FDA Immunogenicity Testing Guidance 2019.
- Section 11.1 Regulatory and Ethical Conduct of the Study: Added a note to exclude the patient's legally authorized representative/legal guardian in France to incorporate a country specific requirement.

In addition, non-substantial clarifications/corrections for inconsistencies, as well as administrative and editorial changes were included; revisions to the protocol text have also been applied to the synopsis section.

Protocol Amendment 3

In order to potentially increase the duration of response in patients enrolled and treated with loncastuximab tesirine and ibrutinib, this study has been amended to allow for additional doses of loncastuximab tesirine to be administered on Day 1 of Cycles 5, 6, 9 and 10 in the Phase 2 portion of the study.

In addition, the Sponsor on a case-by-case review will allow patients benefitting clinically at 1 year to receive additional doses of study drug(s).

The following changes have occurred:

- Study Title was updated with program number – LOTIS-3
- Table 1, Schedule of Events was modified to remove coagulation and urinalysis collection during the study and to include assessments only relevant to the Phase 1 portion of the study.
- Table 2, Schedule of Events: a new table was added for Phase 2 only and includes additional doses of loncastuximab tesirine administration and updates to the collection times for coagulation and urinalysis, electrocardiogram (ECG), pharmacokinetics (PK), anti-drug antibody (ADA), and patient-reported outcomes (PROs).
- Section 1.2.1, Loncastuximab Tesirine Description shows an updated loncastuximab tesirine compound figure (Figure 1).
- Section 2.2, Rationale for Dose Selection was modified to include additional doses of loncastuximab tesirine in Phase 2.
- Section 4.3, Treatment Period was updated to include additional doses of loncastuximab tesirine in Phase 2 and to allow for additional dosing of study drugs for patients benefitting clinically at 1 year.
- Section 6.1.1, Loncastuximab Tesirine was modified to include frozen liquid formulation of loncastuximab tesirine in Phase 2.
- Section 6.3.1, Loncastuximab Tesirine Dosing was updated to include administration of loncastuximab tesirine for patients with complete response (CR), partial response (PR) and stable disease (SD) on Day 1 of Cycles 5, 6, 9, and 10 in Phase 2 of the study.
- Section 6.3.2, Ibrutinib Dosing was updated to specify that ibrutinib dosing will begin simultaneously with loncastuximab tesirine dosing (concomitant treatment).
- Section 6.5.1, Loncastuximab Tesirine was updated to allow continued dosing with ibrutinib if loncastuximab tesirine is delayed or discontinued due to related toxicity.
- Section 6.5.2, Ibrutinib was updated to include guidance for Grade 2 adverse events (AEs). Additional update to allow continued dosing with loncastuximab tesirine if ibrutinib is delayed or discontinued due to related toxicity was provided.
- Section 8.1, Efficacy Assessment was updated to include that Week 14 imaging should be performed prior to C5D1
- Section 8.3.7, ECG: a new table (Table 8) was added for triplicate ECG collection in Phase 2.

- Section 8.4.1, Pharmacokinetics: Table 9 (formerly Table 7) was modified to remove ADA collection in C5 and subsequent odd cycles in Phase 1.
- Section 8.4.1, Pharmacokinetics: a new table (Table 10) for PK and ADA collection was added for Phase 2.
- Section 8.5, Patient-Reported Outcomes Questionnaires was updated with a summary statement and PRO collection guidance.
- Sections 13.5, 13.6, and 13.7, sample PRO questionnaires, EORTC QLQ-C30 (Appendix 5), LymS of FACT-Lym (Appendix 6) and EQ-5D-5L (Appendix 7) were added.
- Protocol synopsis was revised to align with the changes in the protocol.
- Editorial corrections and clarifications were applied throughout.

Protocol Amendment 2

Based on the observed complete response (CR) rate in patients who were enrolled and treated with loncastuximab tesirine and ibrutinib in part 1, this trial has been amended to a Phase 1/2 protocol. There were two dose-limiting toxicities (DLTs) during the DLT period at 90 µg/kg of loncastuximab tesirine in a concomitant therapy with ibrutinib. Since the two DLTs would require the maximum tolerated dose (MTD) to be at a lower than anticipated dose of loncastuximab tesirine, the Sponsor may consider exploring and evaluating a new dose level of 75 µg/kg loncastuximab tesirine in concomitant therapy with ibrutinib in the dose escalation of Phase 1.

Patients with the germinal center B-cell-like (GCB) subtype of diffuse large B-cell lymphoma (DLBCL) account for a significant portion of patients with DLBCL. Considering that the Sponsor has seen encouraging results in the current non-GCB DLBCL patient subgroup, this trial will expand enrollment to allow GCB DLBCL patients on study treatment.

The trial sample size has been increased to approximately 161 patients, and its Phase 2 will evaluate efficacy in non-GCB DLBCL patients as its primary endpoint.
Supplementary secondary endpoints are added in Section 3.

The following changes have occurred:

- Table 1, Schedule of Events was modified to add genomic deoxyribonucleic acid (gDNA), circulating free DNA (cfDNA) samples, and patient-reported outcomes (PROs) questionnaire collection for Phase 2.
- Section 1.2.1, Loncastuximab Tesirine Description section shows an updated loncastuximab tesirine compound figure.
- Section 1.2.2, Safety and Efficacy of Loncastuximab Tesirine was updated to show new data from ADCT-402-101 study.
- Section 2, Study Rationale was updated to support the changed study design.
- Section 2.1, Rationale for Study Design was modified to include potential expansion in Phase 2.
- Section 2.2, Rationale for Dose Selection was modified to include language on Phase 2 and the verbiage of sequential therapy was removed.
- Patients tolerated concomitant therapy of loncastuximab tesirine with ibrutinib very well during Part 1; therefore, sequential dosing was no longer needed.
- Table 3, Study Objectives and Endpoints was revised to show updated objectives and endpoints for both phases.
- Section 4.1, Overview was modified to remove sequential therapy language and to allow GCB DLBCL patients on trial.
- Section 5.1, Inclusion Criteria: To further evaluate efficacy and safety in the DLBCL treatment group, Inclusion Criterion #2 was modified to allow all patients with pathologic diagnosis of DLBCL on trial.

- Section 5.1, Inclusion Criteria: To adhere to Clinical Trial Facilitation Group guidance, Inclusion Criterion #11 was modified to show that men with female partners of childbearing potential must agree to use highly effective contraception from the time of consent until 20 weeks after last treatment.
- Section 6.1.1, Loncastuximab Tesirine was updated to show loncastuximab tesirine's new drug formulation that will be used on trial for both phases.
- Section 6.2.1, Packaging and Storage was updated to match packaging and storage instructions for the loncastuximab tesirine's new formulation.
- Section 6.3.1, Loncastuximab Tesirine Dosing shows the addition of a third dose level for the escalation portion of Phase 1 and the removal of sequential therapy, as sequential dosing will no longer need to be conducted.
- Table 4, Concomitant Treatment with Loncastuximab Tesirine and ibrutinib was updated to remove the two loncastuximab tesirine doses of 120 µg/kg and 150 µg/kg as a concomitant therapy.
- Section 6.5.1, Loncastuximab Tesirine: dose modification guidelines are now shown in a tabular format and specific skin toxicity dose modification guidelines have been added to help investigators manage skin related incidences for patients during study treatment.
- Section 6.7.4, Skin Toxicity was modified to include recommendation on the avoidance of sun exposure and treatment measures.
- Section 6.8.2, Prohibited During Study shows an addition of P-glycoprotein (P-gp) inhibitors that should be avoided in concomitant use with loncastuximab tesirine.
- Section 8.1, Efficacy Assessments were modified to include central imaging reviews. Additionally, to better understand concomitant therapy response, this trial will collect response data during Follow up Period for patients who receive chimeric antigen receptor T-cell (CAR-T) therapy after treatment with the combination of loncastuximab tesirine and ibrutinib.
- Section 8.2.2, Eliciting and Reporting Adverse Events/Serious Adverse Events was modified to add adverse event (AE)/serious adverse event (SAE) reporting requirements for patients who receive CAR-T therapy after study drug discontinuation.
- [redacted]
- Section 8.5, Patient-Reported Outcomes Questionnaires were added.
- Section 9.1, Sample Size was changed to approximately 161 patients.
- Section 9.1.1, Phase 2 Sample Size Calculation for non-GCB DLBCL Cohort was added.
- Section 9.3, Phase 2 Interim Analysis for Futility has been revised to show that this trial will have a single interim analysis using Simon's 2 stage design in the non-GCB DLBCL cohort.
- Section 9.4, Final Analysis was changed to add language on the analysis needed for the Phase 2 portion of this trial.
- Section 9.8, Safety and Subgrouping Analyses was changed to add language in regards to Phase 2 analyses.

- Section 9.9, Pharmacokinetic Analyses was updated to enrich the pharmacokinetic (PK) profile by adding apparent systemic clearance (CL), apparent volume of distribution, and apparent terminal half-life to its determination.
- Section 13.4, Appendix 4: P-gp Inhibitors was added to the study protocol.
- Protocol Synopsis was revised to align with the changes in the protocol.
- Editorial corrections and clarifications were applied throughout.

Protocol Amendment 1

- Table 1, Schedule of Events was revised to include HBV, HCV, and HIV tests at screening for patients who have unknown status to allow for data to be available for all patients to determine whether they meet Exclusion Criterion 10.
- Section 5.2, Exclusion Criteria was modified to remove the notation from Exclusion Criterion 10 that testing for HIV, HBV, and HCV is not mandatory to allow for data to be available for all patients to determine whether they meet this exclusion criterion.
- Section 5.2, Exclusion Criteria, Criterion 15 was modified to add the exclusion of patients with tuberculosis infection.
- Section 6.2.1, Packaging and Storage was updated to match the ibrutinib Investigator's Brochure (IB).
- Section 6.2.2, Preparation and Administration was updated to include precautions concerning extravasation of loncastuximab tesirine based on updated safety information.
- Section 6.3.1, Loncastuximab Tesirine Dosing was revised to clarify the criteria for using sequential dosing.
- Section 6.4.1, Dose Escalation Design was revised to specify a minimum of 5 days between dosing the first and second patient at each dose level during dose escalation (Part 1) to align with the dose escalation procedure being used, and was also revised to allow enrollment of additional patients during the dose escalation phase at the discretion of the Dose Escalation Steering Committee (DESC) to accommodate the potential need for additional safety information.
- Section 6.4.3, Dose-Limiting Toxicity Definition was modified to clarify the non-hematologic DLT definition.
- Section 6.5.1, Loncastuximab Tesirine was revised to clarify criteria for dose hold and resumption for non-hematologic and hematologic toxicity.
- Section 6.7.1, Premedication for Loncastuximab Tesirine and Section 6.7.3, Treatment and Prophylaxis of Infusion-Related to Hypersensitivity Reactions were modified to allow the use of intravenous (IV) dexamethasone.
- Section 8.2.2.1, Adverse Events of Special Interest (AESIs) was added to provide information regarding reporting the AESI of major hemorrhage.
- Section 8.3.5, Laboratory Tests added HBV, HCV, and HIV testing.
- Table 9 was revised to show updated PK time points for C5 and C6; this change has also been reflected in the Schedule of Events (Table 1).
- Section 9.8.1, Adverse Events was revised to clarify which treatment-emergent adverse events (TEAEs) will be included in the statistical analysis.
- Protocol Synopsis was revised to align with the changes in the protocol.
- Editorial corrections and clarifications were applied throughout.

LIST OF PRIOR PROTOCOL VERSIONS

Document	Version Date
Protocol Amendment 4.0	26 March 2021
Protocol Amendment 3.0	14 May 2020
Protocol Amendment 2.0	9 January 2020
Protocol Amendment 1.0	8 July 2019
Protocol Original	21 June 2018

PROTOCOL SYNOPSIS

Protocol Number:	ADCT-402-103
Title:	A Phase 1/2 Open-Label Study to Evaluate the Safety and Efficacy of Loncastuximab Tesirine and Ibrutinib in Patients with Advanced Diffuse Large B-Cell Lymphoma or Mantle Cell Lymphoma
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 1/2
Indication:	Diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL)
Rationale:	Non-Hodgkin Lymphoma (NHL) is the 7th most common type of cancer in the United States (US) and accounted for an estimated 4.3% of new cancer cases in 2017. It is most commonly a disease of older individuals with approximately 75% of new cases diagnosed in individuals 55 years of age or older (median age at diagnosis= 66 years). Response to initial treatment generally exceeds 50% and the overall 5-year survival rate in the US is 70%. However, a significant proportion of patients will relapse. 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 autologous stem cell transplant (HD-ASCT), highlights the need for new forms of treatment for NHL. Loncastuximab tesirine (ADCT-402) is an antibody drug conjugate (ADC) that has been designed to target and kill cluster of differentiation 19 (CD19)-expressing malignant B-cells. Loncastuximab tesirine (is approved in the United States for the treatment of adults with relapsed or refractory (R/R) large B-cell lymphoma after two or more lines of systemic therapy. Preliminary data from a Phase 1 study also showed activity of loncastuximab tesirine in patients with R/R MCL. Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK), a mediator of the B-cell-receptor signaling pathway implicated in the pathogenesis of B-cell cancers. Ibrutinib is approved for use in patients with R/R MCL. It has also shown some activity in R/R DLBCL. While both compounds have shown activity as a single agent, a substantial proportion of patients will not have a complete response (CR) to either agent, and most patients will progress at some point. Combining two agents with different mechanisms of action has the potential to have increased activity compared to either agent alone. Thus, combining an ADC such as loncastuximab tesirine with a BTK inhibitor such as ibrutinib represents a rational approach for study in the clinic. The primary purpose of this study is to explore whether loncastuximab tesirine and ibrutinib can be safely combined, and if so, identify the dose(s) and regimens appropriate for further study. In addition, the study

can generate preliminary evidence as to whether loncastuximab tesirine and ibrutinib may increase the response rate and durability of response compared to previous results with either compound as a single agent.

Due to preliminary antitumor activity in Phase 1/2, the study will be expanded into a new treatment cohort in Phase 2 in order to explore and confirm the safety and efficacy of the combination.

Objectives:

Primary Objective

Phase 1:

- To characterize the safety and tolerability of loncastuximab tesirine in combination with ibrutinib, and to identify the MTD/recommended dose and schedule for future studies

Phase 2:

To evaluate the efficacy of loncastuximab tesirine given at every cycle in combination with ibrutinib in patients with relapsed or refractory DLBCL

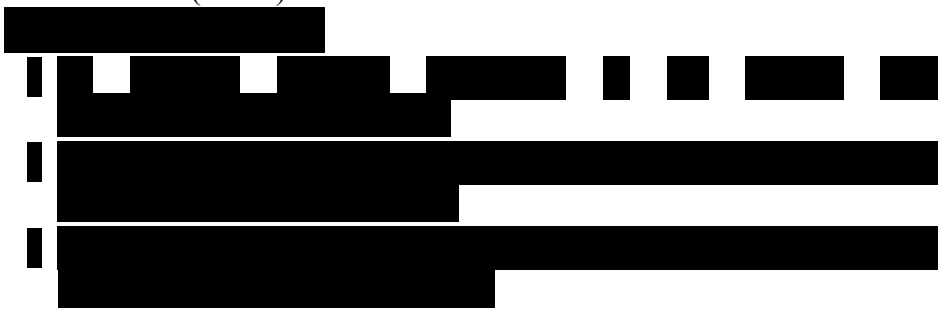
Secondary Objectives

Phase 1:

- To evaluate the antitumor effect of the combination of loncastuximab tesirine with ibrutinib
- To characterize the pharmacokinetic (PK) profile of loncastuximab tesirine when given in combination with ibrutinib
- To evaluate the immunogenicity of loncastuximab tesirine when given in combination with ibrutinib

Phase 2:

- To further evaluate the safety and efficacy of loncastuximab tesirine in combination with ibrutinib in non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients
- To further evaluate the PK profile and immunogenicity of loncastuximab tesirine when given in combination with ibrutinib
- To evaluate the impact of the combination on patient-reported outcomes (PROs)



Endpoints:

Primary Endpoints

Phase 1:

- Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
- Incidence of dose-limiting toxicities (DLTs) (dose escalation only)
- Frequency of dose interruptions and dose reductions
- Changes from baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs)

Phase 2:

- Complete response rate (CRR) according to the 2014 Lugano classification (Cheson et al., 2014) as determined by Independent Review Committee (IRC) in all DLBCL patients given loncastuximab tesirine at every cycle in combination with ibrutinib; CRR defined as the proportion of patients with a best overall response (BOR) of CR.

Secondary Endpoints

Phase 1:

- Overall response rate (ORR) according to the 2014 Lugano classification as determined by Investigator. ORR defined as the proportion of patients with a BOR of CR or partial response (PR)

Phase 1 and Phase 2:

- Duration of response (DOR) defined as the time from the documentation of first tumor response to disease progression or death, in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients
- Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients
- Progression-free survival (PFS) defined as the time between start of treatment and the first documentation of progression, or death in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients
- Overall survival (OS) defined as the time between the start of treatment and death from any cause, in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients
- Concentrations and PK parameters of loncastuximab tesirine (total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated cytotoxin SG3199) in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients
- Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine, in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients

Phase 2:

- ORR according to the 2014 Lugano classification in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients. ORR as determined by Investigator and/or IRC.
- CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by Investigator and/or IRC in non-GCB DLBCL, GCB DLBCL, and MCL patients
- CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by Investigator and/or IRC in all DLBCL patients in the cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib.
- CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by Investigator in all DLBCL patients in the cohort where loncastuximab tesirine is given at every cycle in combination with ibrutinib.
- Frequency and severity of AEs and SAEs, in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients
- Changes from baseline of safety laboratory values, vital signs, ECOG performance status, and 12-lead ECGs in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients
- Change from baseline in symptoms, functions and overall health status as measured by The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30, LymS of FACT-Lym, and EQ-5D-5L in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients

Study Design:

This is a Phase 1/2 open-label single-arm combination study, with a dose escalation Phase 1 followed by Phase 2. The study will enroll approximately 243 patients.

Phase 1:

A standard 3+3 dose escalation design will be used. The DLT Period will be the 21 days following the first dose of ibrutinib. The dose escalation cohort will receive loncastuximab tesirine for 2 cycles with concurrent ibrutinib (concomitant therapy) and may then continue ibrutinib therapy

up to 1 year. An additional dose level of 75 µg/kg loncastuximab tesirine may be explored and evaluated during this phase of the study.

A DESC composed of study investigators and ADC Therapeutics personnel will be responsible for decisions concerning dose escalation. When the maximum tolerated dose (MTD) or Recommended Phase 2 Dose (RP2D) is defined there will be an efficacy and safety evaluation made by the Sponsor in consultation with investigators to determine benefit risk of the combination therapy.

Once MTD or RP2D is determined and if there is a ≥10% improvement observed in CRR or ORR in any of the treatment cohorts in all DLBCL, non-GCB, GCB, or MCL when compared to the loncastuximab tesirine monotherapy, along with an acceptable safety profile, then Phase 2 of the study will commence.

Phase 2:

Once the dose level of loncastuximab tesirine has been defined, the Phase 2 portion of the study planned to enroll in 3 separate cohorts: non-GCB DLBCL, GCB DLBCL, and MCL.

In the non-GCB DLBCL cohort, a Simon's 2-stage design will be used with an interim analysis for futility on the first 22 patients. If ≥6 patients achieve CR, this cohort will proceed to complete full enrollment. Enrollment will continue during the interim analysis; however, further enrollment in this cohort will be halted if futility is confirmed.

As of the data cutoff April 21, 2021, the interim analysis for Non-GCB and GCB DLBCL cohorts was performed and the futility on non-GCB DLBCL was not met.

Subsequent to the interim analysis showing the potential of every cycle dosing of loncastuximab tesirine (see Section 2.2), the following will be performed:

- RP2D will be re-determined by DESC
- Enrollment of the non-GCB DLBCL cohort treated with the combination of loncastuximab tesirine administered at an intermittent dose schedule and daily ibrutinib will be closed. GCB and MCL will complete the enrollment target set forth in the initial phase 2 design and remain under the initial treatment schedule.
- A new Phase 2 cohort of approximately 100 R/R DLBCL patients (with at least 40 patients each of GCB and non-GCB) will be introduced at the re-determined RP2D of loncastuximab tesirine administered in every cycle in combination with ibrutinib po daily given.

A two-stage design with futility monitoring will be used for this new Phase 2 cohort. In the first stage, 60 patients will be accrued. If there are 20 or fewer CRs in these 60 patients, this cohort will be stopped. Otherwise, 40 additional patients will be accrued for a total of 100.

Patient Selection:

Inclusion Criteria:

1. Male or female patient aged 18 years or older
2. Pathologic diagnosis of DLBCL; or MCL (**For Italy Sites Only:** MCL patients are excluded.)
3. Patients with DLBCL must have relapsed or refractory disease and have failed or been intolerant to available standard therapy **(including stem cell transplant if patient was eligible)**
4. Patients with MCL must have relapsed or refractory disease and have received at least one prior line of therapy (**For Italy Sites Only:** This exclusion criterion is not applicable)
5. Patients who have received previous CD19-directed therapy must have a biopsy which shows CD19 expression after completion of the CD19-directed therapy
6. Measurable disease as defined by the 2014 Lugano Classification
7. 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.

8. ECOG performance status 0 to 2
9. Screening laboratory values within the following parameters:
   a) Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3$/ microliter (µL) (off growth factors at least 72 hours)
   b) Platelet count $\geq 75 \times 10^3$/µL without transfusion in the past 7 days
   c) Hemoglobin ≥8 g/dL (4.96 mmol/L), transfusion allowed
   d) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) ≤2.5 × the upper limit of normal (ULN)
   e) Total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 × ULN)
   f) Blood creatinine ≤1.5 × 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.

10. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to start of study drugs on C1D1 (cycle 1 day 1) for women of childbearing potential

11. Women of childbearing potential must agree to use a highly effective method of contraception from the time of giving informed consent until at least 9 months after the last dose of loncastuximab tesirine or 1 month after last dose of ibrutinib, whichever comes last. 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 6 months after the patient receives his last dose of loncastuximab tesirine or 3 months after last dose of ibrutinib, whichever comes last

    * 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. In addition, a barrier method along with hormonal contraceptive is required as per manufacturer's recommendation for ibrutinib use.

    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

Exclusion Criteria:

1. Known history of hypersensitivity to or positive serum human ADA to a CD19 antibody
2. Known history of hypersensitivity to ibrutinib
3. Previous therapy with ibrutinib or other BTK inhibitors
4. Previous therapy with loncastuximab tesirine
5. Requires treatment or prophylaxis with a moderate or strong cytochrome P450 (CYP) 3A inhibitor
6. Allogenic or autologous transplant within 60 days prior to start of study drugs (C1D1)
7. Active graft-versus-host disease
8. Post-transplantation lymphoproliferative disorder

9. Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other central nervous system (CNS) autoimmune disease
10. Known seropositive and requiring anti-viral therapy for human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV).
11. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
12. Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease
13. 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)
14. Breastfeeding or pregnant
15. Significant medical comorbidities, including but not limited to, uncontrolled hypertension (blood pressure [BP] ≥160/100 millimeters of mercury (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 mellitus, severe chronic pulmonary disease, or tuberculosis infection (tuberculosis screening based on local standards)
16. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drugs (C1D1), except shorter if approved by the Sponsor
17. Use of any other experimental medication within 14 days prior to start of study drugs (C1D1)
18. Planned live vaccine administration after starting study drugs (C1D1)
19. Any condition that could interfere with the absorption or metabolism of ibrutinib including malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel
20. Inherited or acquired bleeding disorders
21. Ongoing anticoagulation treatment, except for low-dose heparinisation or equivalent
22. 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

	23. Congenital long QT syndrome or a corrected QTcF interval of >480 ms at screening (unless secondary to pacemaker or bundle branch block) 24. 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 25. 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
Estimated Duration of Patient Participation and Study Duration:	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 to 4 weeks), and a Follow-up Period (approximately every 12 weeks for up to 2 years after treatment discontinuation). Patients may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria. The end of study will occur at the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by Sponsor.
Efficacy Assessments:	• Disease assessments: Positron emission tomography-computed tomography (PET-CT) Note: If tumor is not PET-avid at baseline, CT with contrast or magnetic resonance imaging (MRI) must 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.
Safety Assessments:	• Physical examinations • ECOG Performance status • Height and weight • Vital signs • Safety laboratories (hematology, chemistry, coagulation, urinalysis) • Pregnancy test, if applicable • 12-lead ECGs (triplicate) • AEs/SAEs, graded according to CTCAE version 4.0.
Other Assessments:	• Blood sampling for PK, ADA [redacted] • PROs: EORTC QLC-C30, LymS of FACT-Lym and EQ-5D-5L

Study Drugs, Dosage, and Mode of Administration:

Phase 1:

All dose levels will have ibrutinib dosing beginning simultaneously with loncastuximab tesirine dosing (concomitant treatment). During this phase, the study may explore and evaluate a new dose level of 75 µg/kg loncastuximab tesirine in combination with ibrutinib as a concomitant therapy after the first interim data analysis in Phase 2.

Concomitant Treatment with Loncastuximab Tesirine and Ibrutinib

Dose Level	Loncastuximab Tesirine	Ibrutinib
1	60 µg/kg IV Q3W × 2	560 mg/day po continuous beginning C1D1
2	90 µg/kg IV Q3W × 2	560 mg/day po continuous beginning C1D1
3	75 µg/kg IV Q3W × 2	560 mg/day po continuous beginning C1D1

Note: Dose Levels 1 and 2 have completed enrollment, the subsequent Dose Level 3 has been added to further explore the combination.

The DLT Period will be the first 21 days of ibrutinib treatment for all patients in Phase 1 dose escalation.

At the discretion of the DESC, enrollment may be expanded to further evaluate safety and efficacy at any dose level that has completed the 3+3 dose escalation cohort with no more than 1 DLT in 6 patients. Additional patients may be added only if there is at least 1 patient with documented PR or CR.

No more than 10 patients each in the 2 treatment cohorts (GCB DLBCL and MCL) can be treated at the expanded enrollment portion of Phase 1, and up to 20 patients may be treated at the non-GCB DLBCL cohort. This will allow the trial to enroll up to 40 patients among the 3 cohorts, in the expansion portion of Phase 1.

Patients who have a response of PR or stable disease (SD) at the 14-week disease assessment may receive 2 additional doses of loncastuximab tesirine given 4 weeks apart at C5 and C6.

Phase 2:

Two treatment cohorts will be tested:

- Patients assigned to a cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib will receive loncastuximab tesirine at the initial recommended dose (60 µg/kg) determined in the Phase 1 portion of the study. Loncastuximab tesirine will be administered to the patients Q3W for 2 cycles (C1D1 and C2D1). Patients who have a response of CR, PR, and SD at later disease assessments (Week 14 and Week 30) will receive additional doses of loncastuximab tesirine on C5D1, C6D1, C9D1, and C10D1. Ibrutinib dosing at 560 mg/day po daily will begin simultaneously with loncastuximab tesirine dosing and continue throughout the treatment.

- Patients assigned to a cohort where loncastuximab tesirine is given at every cycle in combination with ibrutinib will receive loncastuximab tesirine at re-determined RP2D at every treatment cycles. Loncastuximab tesirine will be infused through IV Q3W for first 2 cycles and followed by Q4W for all subsequent treatment cycles. Ibrutinib dosing will begin simultaneously with loncastuximab tesirine dosing. Ibrutinib 560 mg/day po daily will be taken in C1 and C2 only. Ibrutinib dose will be reduced to 420 mg/day po daily at C3 and for all subsequent treatment cycles.

Concomitant Treatment with Loncastuximab Tesirine and Ibrutinib

Treatment Cohort	Loncastuximab Tesirine	Ibrutinib	Targeted Enrollment
Loncastuximab Tesirine Given Intermittently in Combination with Ibrutinib	Initial RP2D (60 µg/kg) IV Q3W for C1 and C2, then Q4W at C5, C6 and C9, C10 when a response of CR, PR or SD is observed.	560 mg/day po daily beginning C1D1	Non-GCB DLBCL (n=66. Enrollment will be closed at n=48) GCB DLBCL (n=30) MCL (n=10)
Loncastuximab Tesirine Given at Every Cycle in Combination with Ibrutinib	Re-determined RP2D IV Q3W for C1 and C2, followed by Q4W at all subsequent cycles.	560 mg/day po daily beginning C1D1 for C1 and C2, then reduced to 420 mg/day daily for all subsequent cycles.	All DLBCL (n=100 with ≥40 patients each from GCB and Non-GCB)

Sample Size:

Approximately 243 patients for the entire study.

Phase 1:

Up to 55 patients will be treated with the combination of loncastuximab tesirine and ibrutinib.

Phase 2:

Approximately 188 patients will be enrolled to Phase 2 study.

Approximately 88 patients will be treated with the combination of loncastuximab tesirine given intermittently with ibrutinib daily in three different disease cohorts:

- Non-GCB DLBCL cohort was to enroll approximately 66 patients. Enrollment was paused in this cohort after interim data analysis for futility. The study will close with approximately 48 patients.
- GCB DLBCL cohort will enroll approximately 30 patients, and
- MCL cohort will enroll approximately 10 patients.

Approximately 100 R/R DLBCL patients with at least 40 patients each for GCB and non-GCB will be accrued to the new treatment cohort where loncastuximab tesirine is given at every cycle with ibrutinib po daily.

Statistical Considerations:	**Statistical Analysis:** ORR, CR rate with 95% confidence interval (CI) will be presented. DOR, PFS, RFS, and OS will be analyzed using the Kaplan-Meier approach. Safety analyses will be presented descriptively. **Phase 2 Sample Size Justification for the non-GCB DLBCL Cohort Where Loncastuximab Tesirine is Given Intermittently in Combination with Ibrutinib** Simon's 2-stage design (Simon, 1989) will be used. The null hypothesis that the true CRR is 0.2 will be tested against a one-sided alternative. In the first stage, 22 patients will be accrued. If there are 5 or fewer CRs in these 22 patients, this cohort will be stopped. Otherwise, 44 additional patients will be accrued for a total of 66. The null hypothesis will be rejected if 20 or more CRs are observed in 66 patients. This design yields a type I error rate of 0.05 and power of 90% when the true CRR is 0.4. **Phase 2 Sample Size Justification for the Cohort Where Loncastuximab Tesirine is Given at Every Cycle in Combination with Ibrutinib** Two-stage design with futility monitoring (Zeng et al., 2015) will be used. The null hypothesis that the true CRR is 0.3 will be tested against a one-sided alternative. In the first stage, 60 patients will be accrued. If there are 20 or fewer CRs in these 60 patients, this cohort will be stopped. Otherwise, 40 additional patients will be accrued for a total of 100. The null hypothesis will be rejected if 40 or more CRs are observed in 100 patients. This design yields a type I error rate of 0.05 and power of 85% when the true CRR is 0.45. Enrollment will continue during the interim analysis.

SCHEDULE OF EVENTS

Table 1 Schedule of Events: Phase 1

	Protocol Section	Screening	Treatment Period					Follow-up Period (up to 2 years from EOT)
			Cycle 1 and Cycle 2 (C1 and C2) (3-week cycles)			C3 and beyond (up to 1 year after C1D1) (4-week cycles)	EOT	Every 12 weeks
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						
[redacted]								
Physical examination	8.3.1	X	X	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 14 weeks after C1D1, then every 8 weeks				X[3]	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	X	
Coagulation and urinalysis	8.3.5	X						
HIV, HCV, HBV[5]	8.3.5	X						
Pregnancy test, if applicable	8.3.6	X	X[4]			X	X	X[6]
12-lead ECG[7]	8.3.7 Table 8	X	X (pre-dose, EOI-, and 4 h post-dose)	X	X	X[8]	X	

Table continued on next page.

	Protocol Section	Screening	Treatment Period					Follow-up Period (up to 2 years from EOT)
			Cycle 1 and Cycle 2 (C1 and C2) (3-week cycles)			C3 and beyond (up to 1 year after C1D1) (4-week cycles)	EOT	Every 12 weeks
Day (D)		**-28 to –1**	**1**	**8**	**15**	**1**		
Premedication	6.7		D-1 to D2			X[9]		
Loncastuximab tesirine administration[7]	6.3.1		X			X (C5 and C6 for patients who are SD or PR at Week 14 evaluation)		
Ibrutinib administration	6.3.2		Daily × 21 days (concomitant administration only)			Daily × 28 days[10]		
Loncastuximab tesirine PK sample	8.4.1 Table 11		X[7] (pre-dose, EOI, and 4 h post-dose)	X	X	X (C3 for all patients; C5 and C6 pre-dose for patients receiving loncastuximab tesirine, C7 for patients receiving loncastuximab tesirine during C5 and C6)	X	
Loncastuximab tesirine ADA sample[7]	8.4.2 Table 11		X[7] (pre-dose)		X (C1 only)	X[11]	X[12]	
Concomitant medications	6.8	From ICF signature date or D -14, whichever is earlier, until 30 days after last dose of study drug(s)						
Adverse events	8.2	AE/SAEs from ICF signature date until 30 days after last dose of study drug(s); thereafter, related SAEs only						
1st new anticancer treatment	4.4						X	X
Survival	7.1						X	X

Abbreviations: ADA: anti-drug antibody; AE: adverse event; BP: blood pressure; C: Cycle; [redacted]; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOT: end of treatment; [redacted]; h: hour; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HR: heart rate; ICF: informed consent form; PK: pharmacokinetics; PR: partial response; RR: respiratory rate; SAE: serious AE; SD: stable disease; Temp: temperature

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(s) but preferably within 30 days after last dose of study drug(s) unless a new anticancer treatment is planned to be administered before the 30 days, in which case EOT should be conducted before initiation of the new anticancer treatment.
- Follow-up Period: Visit Day ± 14 days.
- Physical examination, ECOG, hematology, and chemistry can be performed within 24 hours prior to administration of study drug(s).

[redacted]

[2] Screening imaging (PET-CT, positron emission tomography) 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 prior to C3D1 and Week 14 imaging should be performed prior to C5D1. All other imaging for disease assessment for patients on study drug(s) should be performed within ± 2 weeks of the scheduled time point. Disease assessments should be performed at the time points 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(s) for reasons other than disease progression.

[4] Not needed if screening assessment was performed within 3 days prior to C1D1.

[5] Only for patients whose status is unknown.

[6] A final pregnancy test is to be performed at ≥9 months post last loncastuximab tesirine dose if applicable. A remote pregnancy test is acceptable during study follow-up. The pregnancy test can be performed if clinical indicated during the study.

[7] On days when loncastuximab tesirine is administered, ECG, PK, and ADA time points are in relation to start of loncastuximab tesirine infusion.

[8] Cycle 3 only.

[9] For patients dosed with loncastuximab tesirine on C5 and C6 only.

[10] Ibrutinib will be dosed at 560 mg po daily in all cycles for all patients.

[11] C3 for all patients; C5 and C6 pre-dose for patients receiving loncastuximab tesirine, C7 for patients receiving loncastuximab tesirine during C5 and C6, see Table 11.

[12] Patients who test positive for ADAs will be requested to supply additional ADA samples as specified in the protocol, Section 8.4.2.

Table 2 Schedule of Events: Phase 2

	Protocol Section	Screening	Treatment Period					Follow-up Period (up to 2 years from EOT)
			Cycle 1 and Cycle 2 (C1 and C2) (3-week cycles)			C3 and beyond (up to 1 year after C1D1) (4-week cycles)	EOT	Every 12 weeks
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						
[redacted]								
Physical examination	8.3.1	X	X	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 14 weeks after C1D1, then every 8 weeks				X[3]	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	X	
Coagulation and urinalysis	8.3.5	X						
HIV, HCV, HBV[5]	8.3.5	X						
Pregnancy test, if applicable	8.3.6	X	X[4]			X	X	X[6]
[redacted]								
12-lead ECG	8.3.7 Table 9& Table 10	X	X (pre-dose, EOI-, and 4 h post-dose)	X	X	X[8]	X	

Table continued on next page.

	Protocol Section	Screening	Treatment Period					Follow-up Period (up to 2 years from EOT)
			Cycle 1 and Cycle 2 (C1 and C2) (3-week cycles)			C3 and beyond (up to 1 year after C1D1) (4-week cycles)	EOT	Every 12 weeks
Premedication	6.7		D-1 to D2			X[9]		
Loncastuximab tesirine administration[10]	6.3.1		X			X[11]		
Ibrutinib administration	6.3.2		Daily × 21 days (concomitant administration only)			Daily × 28 days[12]		
Loncastuximab tesirine PK sample	8.4.1 Table 12		X[10] (pre-dose, EOI, and 4 h post-dose)	X	X	X (C3, C5, C6, C7, C9, C10, and C11 pre-dose)	X	
Loncastuximab tesirine ADA sample[7]	8.4.2 Table 12		X[10] (pre-dose)		X (C1 Only)	X[13]	X[14]	
[redacted]								
PROs[15]	8.5		X (pre-dose)			X (pre-dose)	X	X[16]
Concomitant medications	6.8	From ICF signature date or D -14, whichever is earlier, until 30 days after last dose of study drug(s)						
Adverse events	8.2	AE/SAEs from ICF signature date until 30 days after last dose of study drug(s); thereafter, related SAEs only						
1st new anticancer treatment	4.4						X	X
Survival	7.1						X	X

Abbreviations: ADA: anti-drug antibody; AE: adverse event; BP: blood pressure; C: Cycle; [redacted]; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOT: end of treatment; [redacted]; h: hour; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HR: heart rate; ICF: informed consent form; PK: pharmacokinetics; PR: partial response; PRO: patient-reported outcome; RR: respiratory rate; SAE: serious AE; SD: stable disease; Temp: temperature

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(s) but preferably within 30 days after last dose of study drug(s) unless a new anticancer treatment is planned to be administered before the 30 days, in which case EOT should be conducted before initiation of the new anticancer treatment.

- Follow-up Period: Visit Day ± 14 days.
- Physical examination, ECOG, hematology, and chemistry can be performed within 24 hours prior to administration of study drug(s).

[redacted]

2. Screening imaging (PET-CT, positron emission tomography) 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 prior to C3D1 and Week 14 imaging should be performed prior to C5D1. All other imaging for disease assessment for patients on study drug(s) should be performed within ± 2 weeks of the scheduled time point. Disease assessments should be performed at the time points 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(s) for reasons other than disease progression.
4 Not needed if screening assessment was performed within 3 days prior to C1D1.
5 Only for patients whose status is unknown.
6 A final pregnancy test is to be performed at ≥9 months post last dose of loncastuximab tesirine, if applicable. A remote pregnancy test is acceptable during study follow-up. The pregnancy test can be performed if clinical indicated during the study.

[redacted]

8 C 3 (pre-dose), C5 (pre-dose), C6 (pre-dose and EOI), C9 (pre-dose), and C10 (pre-dose and EOI) for patients with loncastuximab tesirine given intermittently in combination with ibrutinib; and C3 and beyond pre-dose only for patients with loncastuximab tesirine given at every cycle in combination with ibrutinib; see Table 9 and Table 10.
9 For all patients when dosed with loncastuximab tesirine.
10 Loncastuximab tesirine is dosed at 60 µg/kg for patients with loncastuximab tesirine given intermittently in combination with ibrutinib; Loncastuximab tesirine is dosed at re-determined RP2D for patients with loncastuximab tesirine given at every cycle in combination with ibrutinib. On days when loncastuximab tesirine is administered, ECG, PK, and ADA time points are in relation to loncastuximab tesirine infusion.
11 Loncastuximab tesirine will be administered at C5, C6, C9, and C10 for patients assigned to loncastuximab tesirine given intermittently in combination with ibrutinib who have a response of CR, PR, and SD at later disease assessments. Loncastuximab tesirine will be administered at every cycle for patients assigned to loncastuximab tesirine given at every cycle in combination with ibrutinib.
12 For patients in the cohort given loncastuximab tesirine intermittently in combination with ibrutinib, ibrutinib will be taken at 560 mg po daily in all cycles.
For patients in the cohort given loncastuximab tesirine at every cycle in combination with ibrutinib, ibrutinib will be taken at 560 mg po daily in C1 & C2 only, then a dose reduction to 420 mg daily po at C3 and all subsequent cycles
13 For treatment cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib ADA sample will be collected pre-dose on C3 C5, C7, C9, C11.
For Treatment cohort where loncastuximab tesirine is given at every cycle in combination with ibrutinib ADA sample will be collected pre-dose on C3 C5, C7, C9, C11, C13. Please refer to Table 12 for further details.
14 Patients who test positive for ADAs will be requested to supply additional ADA samples as specified in the protocol, Section 8.4.2.
15 Should be collected prior to clinical assessments and treatment.
16 Collect EQ-5D-5L only, via phone or at the study site every 12 weeks after the end of treatment for 1 year.

1 INTRODUCTION AND BACKGROUND

1.1 Non-Hodgkin Lymphoma and CD19

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 United States (US) and will account for an estimated 4.3% (n=72,240) of new cancer cases in 2017 (Siegel et al., 2017). In the US, tumors of B-cell origin make up 85% to 90% of NHL.

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 diffuse large B-cell lymphoma (DLBCL).

1.1.1 Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma accounts for an estimated 32.5% of NHL (Al-Hamadani et al., 2015). Standard first-line therapy uses immuno-chemotherapy such as R-CHOP. The response rate to front-line R-CHOP is >80% but 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 overall 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. Additional immuno-chemotherapy following a second HD-ASCT or allogeneic stem cell transplant (AlloSCT) produces responses in only a small proportion of patients with substantial toxicity.

Recently, autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (axicabtagene ciloleucel [Yescarta®] and tisagenlecleucel [Kymriah®]) has been shown to produce responses in ~50% to 70% of patients with relapsed or refractory (R\R) DLBCL, with ~30% to 50% achieving CR. Durable responses have been achieved in patients who achieve a CR, but the duration of response (DOR) in patients with a partial response (PR) is short (2.1 months for axicabtagene ciloleucel). Moreover, there is significant toxicity, particularly cytokine release syndrome and neurologic events, including encephalopathy. 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.

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 medical need for more effective salvage treatments for patients with R/R DLBCL (Coiffier et al., 2016; Epperla et al., 2017)

1.1.2 Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare and aggressive form of NHL that predominantly affects older individuals. Standard first-line therapy uses immuno-chemotherapy. Patients who are eligible for consolidation with HD-ASCT are typically treated with cytarabine-based regimens. Patients who are not eligible for treatment with HD-ASCT receive regimens such as R-CHOP or R-bendamustine. Most patients (80% to 90%) respond to front-line therapy, but many will relapse. There are a number of agents available for second-line therapy, including bortezomib, lenalidomide, and ibrutinib. However, the response rates are low for bortezomib and lenalidomide, at 33% and 28% respectively. The response to ibrutinib is higher at 65%, but only 17% of these are CR. Thus, there remains unmet medical need for additional salvage treatments for patients with R/R MCL (Campo et al., 2015).

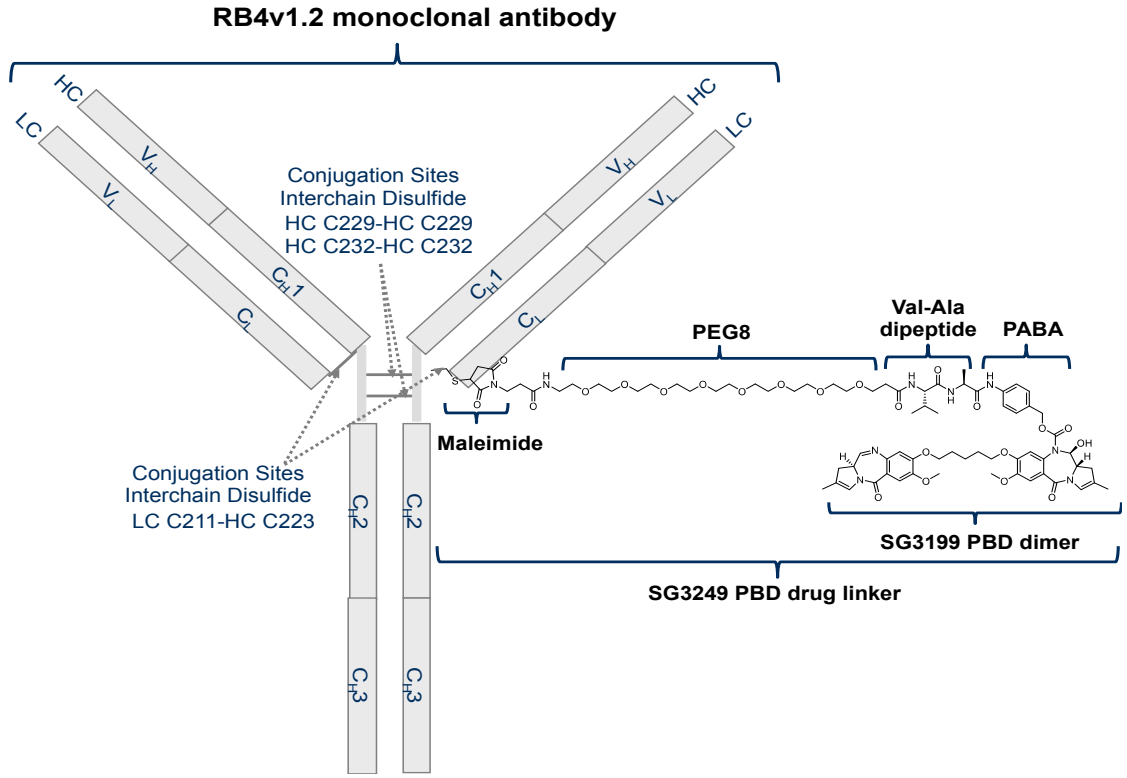
1.2 Loncastuximab Tesirine and Ibrutinib

1.2.1 Loncastuximab Tesirine Description

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; PBD, pyrrolobenzodiazepine; PEG, polyethylene glycol; RB4v1.2, humanized monoclonal antibody directed against CD19 antigen; Val, valine.

Loncastuximab tesirine binds with picomolar affinity to human CD19. After binding and internalization, loncastuximab tesirine trafficks 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 deoxyribonucleic acid (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).

Loncastuximab tesirine (Zynlonta™) was approved in the United States in April 2021 for the treatment of adults with R/R large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy. (Zynlonta FDA-US PI)

1.2.2 Safety and Efficacy of Loncastuximab Tesirine

1.2.2.1 Phase 1 Study, ADCT-402-101

ADCT-402-101 (NCT02669017) is a first-in-human Phase 1 study of loncastuximab tesirine in patients with R/R B-cell lineage NHL (B-NHL). Eligible patients are ≥18 years of age and 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 are 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 is to evaluate the safety and tolerability of the dose(s) determined in Part 1. Efficacy (ORR, DOR, progression-free survival [PFS], and overall survival [OS]), pharmacokinetics (PK), [redacted] and immunogenicity are also being assessed in both parts of the study.

A total of 183 patients with R/R B-NHL received at least 1 infusion of loncastuximab tesirine, at dose levels from 15 to 200 µg/kg. The protocol defined MTD was not reached in Part 1 of the study. Doses of 120 and 150 µg/kg every 3 weeks (Q3W) were chosen to be further evaluated in Part 2 of the study based on antitumor activity and tolerability seen during the dose escalation part. The study was completed on 24-Jun-2019.

The median age was 63 years (range: 20 to 87). The median number of previous chemotherapy regimens was 3 (range: 1 to 13) with 23% of patients having prior stem cell transplant.

The most common non-hematologic TEAEs (observed in at least 15% of patients), regardless of relationship to study treatment, were fatigue (42.6%); nausea (32.2%); edema peripheral (31.7%); GGT increased (31.1%); rash (24.6%); dyspnea (22.4%); constipation (21.9%); pleural effusion (21.3%); blood alkaline phosphatase increased (20.2%); cough, decreased appetite, and AST increased (18.6%, each); pyrexia (18.0%); vomiting (17.5%); ALT increased (17.5%); abdominal pain (15.8%); and diarrhea (15.3%).

The most common non-hematologic Grade ≥3 TEAEs (observed in at least 5% of patients) were GGT increased (21.3%), blood alkaline phosphatase increased (6.6%), febrile neutropenia (5.5%), and hypokalemia (5.5%). TEAEs in 16 (11.1%) patients led to treatment discontinuation.

TEAEs in 35 (19.1%) patients led to treatment discontinuation. Dose-limiting toxicity (DLT) was reported in 4 patients (3 thrombocytopenia and 1 febrile neutropenia).

There were 152 serious adverse event (SAE) reports (197 events) from 96 (52.5%) patients. Of these, 47 reports in 34 patients were considered at least possibly related to study drug. Of these 47 SAE reports (60 events), only 10 events were seen in multiple patients: pleural effusion (8), febrile neutropenia (7), lung infection (3), pericardial effusion (3), sepsis (3), dyspnea (2), fluid overload (2), generalized edema (2), injection site extravasation (2), and pyrexia (2).

Based on the Phase 1 experience, edema and effusion related reactions, abnormal liver function tests (particularly GGT), and skin-related toxicities are considered important potential risks for loncastuximab tesirine. These events have also been observed with other compounds containing

the same warhead. The events of febrile neutropenia and pleural effusion are likely related to loncastuximab tesirine and are, therefore, considered adverse drug reactions (ADRs).

Out of 180 evaluable patients with B-NHL, 48 (26.7%) achieved CR and 34 (18.9%) achieved PR, for an ORR of 82/180 (45.6%). Median PFS was 3.09 months and median DOR was 5.36 months.

Out of 137 evaluable patients with DLBCL, 32 (23.4%) achieved CR and 26 (19%) achieved PR, for ORR of 58/137 (42.3%). Median PFS was 2.83 months and median DOR was 4.47 months.

Out of 15 evaluable patients with MCL, 5 (33.3%) achieved CR and 2 (13.3%) achieved PR, for ORR of 7/15 (46.7%). Median DOR was not reached, and median PFS was 4.8 months.

Out of 14 evaluable patients with follicular lymphoma, 9 (64.3%) achieved CR and 2 (14.3%) achieved PR, for ORR of 11/14 (78.6%). Median DOR and median PFS were not reached.

1.2.2.2 Phase 2 Study, ADCT-402-201

Study ADCT-402-201 is a Phase 2 study to evaluate the efficacy of loncastuximab tesirine used as monotherapy in patients with R/R DLBCL. The study determines the ORR according to the 2014 Lugano classification, as well as evaluate the duration of response (DOR), CR, survival, safety, pharmacokinetics (PK), and health-related quality of life.

As of the data cut-off date on 06 April 2020, the enrollment was completed and a total of 145 patients with R/R DLBCL received at least one dose of loncastuximab tesirine. The median age was 66.0 years (range: 23-94). The median number of previous chemotherapy regimens was 3 (range: 2-7) with 16.6% of patients having prior stem cell transplantation.

Loncastuximab tesirine was effective, producing durable responses in heavily pretreated patients with DLBCL. The ORR was 48.3% by independent central review, with a complete response rate (CRR) of 24.1%, and responses were rapid with median time to first response of 41.0 days. Responses were durable, with a median DOR of 10.25 months. The probability to maintain a response for at least nine months was 63.8%. The median PFS was 4.93 months, and the median OS was 9.92 months.

In addition, Loncastuximab tesirine was effective in patients with high-risk disease, producing durable responses in patients with double hit/triple hit disease, advanced stage disease (Stage III/IV), transformed disease, primary refractory disease, and disease which was refractory to all prior systemic therapies; and was also effective in elderly patients and in patients who had failed previous aggressive salvage therapy, including CD19-directed CAR-T therapy.

Loncastuximab tesirine was well-tolerated when administered in repeated 3-week cycles at 150 µg/kg for two cycles and 75 µg/kg for subsequent cycles. Toxicities were generally reversible and manageable in most patients with dose delays/reductions and standard supportive care. Overall, 105 (72.4%) patients had grade ≥3 TEAEs. The most common (≥10%) grade ≥3 TEAEs were neutropenia (25.5%), thrombocytopenia (17.9%), GGT increased (16.6%), and anemia (10.3%). Treatment-related TEAEs leading to treatment discontinuation occurred in 24 patients (16.6%), most commonly GGT increased (14 patients; 9.7%). No increase in toxicity was seen in patients aged ≥65 years compared with younger patients.

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

1.2.3 Ibrutinib Description

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK), a mediator of the B-cell-receptor signaling pathway implicated in the pathogenesis of B-cell cancers. BTK's role in signaling results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro. Ibrutinib is indicated for the treatment of a variety of B-cell malignancies, including MCL, chronic lymphocytic leukemia/small lymphocytic leukemia, Waldenström's macroglobulinemia, and marginal zone lymphoma. Specifically, it is indicated for the treatment of patients with MCL who have received at least one prior line of therapy.

1.2.4 Safety and Efficacy of Ibrutinib

The safety and efficacy of ibrutinib in patients with MCL who have received at least one prior therapy were evaluated in an open-label, multi-center, single-arm trial of 111 previously treated patients (Imbruvica® PI). The median age was 68 years (range, 40 to 84 years), 77% were male, and 92% were Caucasian. At baseline, 89% of patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The median time since diagnosis was 42 months, and median number of prior treatments was 3 (range, 1 to 5 treatments), including 11% with prior stem cell transplant. At baseline, 39% of subjects had at least one tumor ≥ 5 cm, 49% had bone marrow involvement, and 54% had extranodal involvement at screening.

Ibrutinib was administered orally at 560 mg once daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the revised International Working Group for NHL criteria. The primary endpoint in this study was investigator-assessed ORR.

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite. The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections. Fatal and serious cases of renal failure have occurred with ibrutinib therapy. Increases in creatinine 1.5 to 3 times the upper limit of normal (ULN) occurred in 9% of patients. Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (1.8%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Out of 111 evaluable patients with MCL, 17.1% achieved a CR and 48.6% achieved a PR, for an ORR of 65.8%. The median DOR was 17.5 months.

Ibrutinib has also shown activity in DLBCL at the dose planned for this study, although this appears to be limited to the activated B-cell (ABC) subtype. A Phase 1/2 clinical trial involving

80 subjects showed an ORR of 37% (14/38) for patients with the ABC subtype, but only 5% (1/20) for patients with the germinal center B-cell (GCB) subtype (Wilson et al., 2015).

Additional details may be found in the current ibrutinib IB.

2 STUDY RATIONALE

While both loncastuximab tesirine and ibrutinib have shown activity as single agents, a substantial proportion of patients will not have a CR to either agent, and most patients will progress at some point.

Combining two agents with different mechanisms of action has the potential to increase activity compared to either agent alone. Thus, combining an ADC such as loncastuximab tesirine with a BTK inhibitor such as ibrutinib represents a rational approach for study in the clinic.

The activity of combining loncastuximab tesirine with ibrutinib has been observed, and further exploration is needed to establish efficacy and safety of the combination therapy taken in a concomitant regimen.

2.1 Rationale for Study Design

This is a Phase 1/2, multi-center study to assess the safety and efficacy of loncastuximab tesirine in combination with ibrutinib for patients with R/R DLBCL and MCL.

Phase 1:

As this is the first study combining the two agents, a standard 3+3 dose escalation design will be used. At the discretion of the DESC, enrollment may be expanded to further evaluate safety and efficacy at any dose level that has completed the 3+3 dose escalation cohort with no more than 1 DLT of 6 patients. Additional patients may be added only if there is at least 1 patient with documented PR or CR. No more than 10 patients in each of the two treatment cohorts (GCB DLBCL and MCL) can be treated at the expanded enrollment portion of Phase 1, and up to 20 patients may be treated in the non-GCB DLBCL cohort. This expansion will allow the trial to enroll approximately 40 patients among the 3 cohorts.

Phase 2:

A Dose Escalation Steering Committee (DESC) composed of study investigators and ADC Therapeutics personnel will be responsible for decisions concerning dose escalation. When the MTD or Recommended Phase 2 Dose (RP2D) is defined, there will be an efficacy and safety evaluation made by the Sponsor in consultation with investigators to determine benefit risk of the combination therapy.

Once MTD or RP2D is determined and if there is a ≥10% improvement observed in complete response rate (CRR) or ORR in any of the treatment cohorts in all DLBCL, non-GCB, GCB, or MCL when compared to the loncastuximab tesirine monotherapy, along with an acceptable safety profile, then Phase 2 will commence.

MCL patients must have had at least one prior therapy, in line with the approved indication for ibrutinib. DLBCL patients will be required to have failed or been intolerant to available standard therapies.

2.2 Rationale for Dose Selection

Ibrutinib will be given at the approved dose of 560 mg po (per os) daily. As this is a novel combination, loncastuximab tesirine administration will start at 60 µg/kg intravenously (IV) Q3W, which is 40% of the RP2D of 150 µg/kg. An additional dose level of 75 µg/kg has been added and may be explored and evaluated during dose escalation portion of Phase 1. Because of the potential for extended toxicity with prolonged administration, loncastuximab tesirine will be limited to 2 doses initially.

Phase 2 will use the RP2D decided by the DESC or the MTD of loncastuximab tesirine explored and evaluated in Phase 1. Loncastuximab tesirine will be administered on C1D1 and C2D1. Patients who have a response of CR, PR, or SD at later disease assessments (Week 14 and Week 30) will receive additional doses of loncastuximab tesirine on C5D1, C6D1, C9D1, and C10D1. The additional doses of loncastuximab tesirine are anticipated to further increase the duration of response while maintaining an acceptable toxicity profile as observed in the Phase 1 portion of the study. The ibrutinib dose will be at 560 mg po daily for this combination.

Two treatment cohorts (60 µg/kg or 90 µg/kg of loncastuximab tesirine Q3W x 2 in combination with ibrutinib at 560 mg PO daily) were initially tested in Phase 1 dose escalation portion, the RP2D was determined to be 60 µg/kg loncastuximab tesirine plus ibrutinib by DESC.

As of the data cutoff April 21, 2021, the interim data analysis of Phase 2 non-GCB and GCB DLBCL cohorts with intermittent doses of 60 µg/kg loncastuximab tesirine at Q3W at C1, C2, and Q4W at C5, C6, C9, and C10 in combination with ibrutinib was completed, and the futility on non-GCB DLBCL was not met. Six out of 22 non-GCB DLBCL patients achieved complete response. CRR for non-GCB DLBCL, GCB DLCBL and all DLBCL were 27.3%, 46.2% and 34.2% respectively. ORR for non-GCB DLBCL, GCB DLCBL and all DLBCL were 45.5%, 76.9% and 57.1% respectively. Based on the interim data analysis, the RP2D is being re-determined by testing loncastuximab tesirine dose at 75 µg/kg in combination with ibrutinib in Phase 1dose escalation to maximize ORR and DOR. Meanwhile the enrollment to non-GCB DLBCL cohort with the combination regimen of intermittent dosing of loncastuximab tesirine at 60 µg/kg and daily ibrutinib was paused (N=approximately 48 of a planned 66 patients). GCB and MCL will complete the enrollment target set forth in the initial phase 2 design. All patients treated with loncastuximab tesirine intermittently in combination with ibrutinib will remain in the same dose and schedule until the end of treatment.

Rationale for exploring the 75 µg/kg dose level in Phase 1 is based on using PK/Exposure-response modeling of loncastuximab tesirine as a monotherapy. Predictions of average PBD-conjugated antibody concentration (Cavg) were shown to increase substantially from 0.271 µg/kg anticipated with the current intermittent cycle regimen (60 µg/kg Q3W in Cycles 1 and 2, then Q4W during Cycles 5 and 6) to values of 0.658 µg/mL and 0.526 µg/mL for the 75 µg/kg and 60 µg/kg doses, respectively, for the every cycle treatment regimens (Appendix 7). Probabilities of ORR anticipated with the every cycle treatment regimens are predicted to increase commensurately with values of 0.727 (75 µg/kg) and 0.677 (60 µg/kg), relative to a reference response rate of 0.57 for the intermittent cycle regimen. At the discretion of the DESC, loncastuximab tesirine will be administered at every cycle in combination with ibrutinib in Phase 2.

Once the re-determined RP2D will be defined, the new Phase 2 cohort will commence: loncastuximab tesirine will be infused at re-determined RP2D on Day 1 of every treatment cycle; and ibrutinib dose at 560 mg po daily will be given only at Cycles 1 and 2, followed by a dose reduction to 420 mg daily at Cycle 3 and for subsequent cycles. This dose regimen employing loncastuximab tesirine in every treatment cycle is designed to expose the tumor with the maximum antitumor activity in a tolerable dose combination at the first two cycles to maximize dose intensity and is anticipated to further improve the tumor response and/or extend the duration of response by giving loncastuximab tesirine infusion on Day 1 of every treatment cycle as compared to the intermittent loncastuximab tesirine dosing regimen. To reduce potential additive adverse events such as bone marrow suppression from the combination regimen, ibrutinib dose will be reduced to 420 mg daily from Cycle 3 and beyond. This is supported by the observation from the data collected in this trial: as of the data cutoff on April 21, 2021, 6 of 8 AEs leading to ibrutinib dose reduction occurred after Cycle 2.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3 Study Objectives and Endpoints

Primary	
Objectives	**Endpoints**
Phase 1: • To characterize the safety and tolerability of loncastuximab tesirine in combination with ibrutinib, and to identify the MTD/recommended dose and schedule for future studies	**Phase 1:** • Frequency and severity of adverse events (AEs) and serious adverse events (SAEs) • Incidence of dose-limiting toxicities (DLTs) (dose escalation only) • Frequency of dose interruptions and dose reductions • Changes from baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs)
Phase 2: • To evaluate the efficacy of loncastuximab tesirine given at every cycle in combination with ibrutinib in patients with relapsed or refractory DLBCL	**Phase 2:** • CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by independent review committee (IRC) in all DLBCL patients given loncastuximab tesirine at every cycle in combination with ibrutinib; CRR defined as the proportion of patients with a best overall response (BOR) of complete response (CR)

Table continued on next page.

Secondary	
Objectives	**Endpoints**
Phase 1: • To evaluate the antitumor effect of the combination of loncastuximab tesirine with ibrutinib • To characterize the PK profile of loncastuximab tesirine when given in combination with ibrutinib • To evaluate the immunogenicity of loncastuximab tesirine when given in combination with ibrutinib	**Phase 1:** • Overall response rate (ORR) according to the 2014 Lugano classification as determined by Investigator. ORR defined as the proportion of patients with a BOR of CR or partial response (PR) **Phase 1 and Phase 2:** • Duration of response (DOR) defined as the time from the documentation of first tumor response to disease progression or death, in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients • Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients • Progression-free survival (PFS) defined as the time between start of treatment and the first documentation of progression, or death in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients • Overall survival (OS) defined as the time between the start of treatment and death from any cause in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients • Concentrations and PK parameters of loncastuximab tesirine (total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated cytotoxin SG3199) in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients
Phase 2: • To further evaluate the safety and efficacy of loncastuximab tesirine in combination with ibrutinib in non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients • To further evaluate the PK profile and immunogenicity of loncastuximab tesirine when given in combination with ibrutinib • To evaluate the impact of the combination on patient-reported outcomes (PROs)	**Phase 2:** • ORR according to the 2014 Lugano classification in the non-GCB DLBCL, GCB DLBCL, all DLBCL, and MCL patients. ORR defined as the proportion of patients with a BOR of CR or PR for all treated patients. ORR as determined by IRC and/or Investigator. • CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by Investigator and/or IRC in Non-GCB DLBCL, GCB DLBCL, and MCL patients • CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by Investigator and/or IRC in all DLBCL patients in the cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib • CRR according to the 2014 Lugano classification (Cheson et al., 2014) as determined by Investigator in all DLBCL patients in the cohort where loncastuximab tesirine is given at every cycle in combination with ibrutinib. • Frequency and severity of AEs and SAEs in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients • Changes from baseline of safety laboratory values, vital signs, ECOG performance status, and 12-lead ECGs in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients • Change from baseline in PROs as measured by The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, LymS of FACT-Lym, and EQ-5D-5L in the non-GCB DLBCL, GCB DLBCL, all DLBCL and MCL patients

Table continued on next page.

4 STUDY DESIGN

4.1 Overview

This is a Phase 1/2, open-label, single-arm combination study to assess the safety and efficacy of loncastuximab tesirine in combination with ibrutinib in patients with R/R DLBCL (non-GCB, GCB) and MCL. Phase 1 will cover the dose escalation portion of the study, which will then be followed by Phase 2.

The study will enroll approximately 243 patients.

Phase 1 will enroll up to 55 patients who will be treated with the combination of loncastuximab tesirine and ibrutinib.

A standard 3+3 dose escalation design will be used in Phase 1. The DLT Period will be the first 21 days of ibrutinib treatment. The dose escalation cohort will receive loncastuximab tesirine for 2 cycles with concurrent ibrutinib (concomitant therapy) and may then continue ibrutinib therapy up to 1 year. An additional dose level of 75 μg/kg has been added and may be explored and evaluated.

At the discretion of the DESC, enrollment may be expanded to further evaluate safety and efficacy at any dose level that has completed the 3+3 dose escalation cohort with no more than 1 DLT in 6 patients. Additional patients may be added only if there is at least 1 patient with documented PR or CR.

No more than 10 patients in each of the 2 treatment cohorts (GCB DLBCL and MCL) can be treated at the expanded enrollment portion of Phase 1, and up to 20 patients will be treated in the non-GCB DLBCL cohort. This will allow the trial to enroll up to 40 patients among the 3 expanded cohorts.

When the MTD or RP2D is defined, there will be an efficacy and safety evaluation made by the Sponsor in consultation with investigators to determine benefit risk of the combination therapy.

Once MTD or RP2D is determined and if there is a ≥10% improvement observed in CRR or ORR in any of the treatment cohorts in all DLBCL, non-GCB DLBCL, GCB DLBCL, or MCL when compared to the loncastuximab tesirine monotherapy, along with an acceptable safety profile, then the Phase 2 portion of the study will commence.

Patients who have a response of PR or SD at the 14-week assessment may receive two additional doses of loncastuximab tesirine given 4 weeks apart.

Each of the cohorts will be treated at the RP2D dose of loncastuximab tesirine determined in Phase 1 and ibrutinib. An IRC will be used in all cohorts to evaluate the response to the combination therapy.

Phase 2 planned to enroll approximately 106 patients who were to be treated with the combination of loncastuximab tesirine administered at an intermittent dose schedule and daily ibrutinib in three different disease cohorts:

- Non-GCB DLBCL cohort was to enroll approximately 66 patients. .
- GCB DLBCL cohort will enroll approximately 30 patients, and
- MCL cohort will enroll approximately 10 patients.

In the non-GCB DLBCL cohort, a Simon's 2-stage design (Simon, 1989) will be used with an interim analysis for futility on the first 22 patients (see Section 9.3). If ≥6 patients achieve CR assessed by an IRC, this cohort will proceed to complete full enrollment. Enrollment will continue during the interim analysis. However, further enrollment in this cohort will be halted if futility is confirmed.

Subsequent to the interim analysis with the data cutoff April 21, 2021 showing the potential of every cycle dosing of loncastuximab tesirine (see Section 2.2), the following will be performed:

- RP2D will be re-determined by DESC
- Enrollment of the non-GCB DLBCL cohort treated with the combination of loncastuximab tesirine administered at an intermittent dose schedule and daily ibrutinib will be closed. Approximately 48 patients with non-GCB DLBCL are enrolled to this cohort.
- A new Phase 2 cohort of 100 R/R DLBCL patients (with at least 40 patients each of GCB and non-GCB) will be introduced at the re-determined RP2D of loncastuximab tesirine administered in every cycle in combination with ibrutinib po daily given.

A two-stage design with futility monitoring (Zeng et al., 2015) will be used for this new cohort. In the first stage, 60 patients will be accrued. If there are 20 or fewer CRs in these 60 patients, this cohort will be stopped. Otherwise, 40 additional patients will be accrued for a total of 100. Enrollment will continue during the interim analysis.

Taken together, the Phase 2 will enroll approximately 188 patients.

The study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 3 to 4 weeks), and a Follow-up Period (approximately every 12-week visits for up to 2 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(s). The screening assessments must 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 will start on the date when a patient receives the first dose of study drug(s) and continues until the End of Treatment (EOT) visit.

A treatment cycle is defined as 3 weeks (i.e., 21 days) for Cycles 1 and 2 and 4 weeks (i.e., 28 days) for subsequent cycles. Loncastuximab tesirine will be administered as an IV infusion over 30 minutes on Day 1 of each cycle containing loncastuximab tesirine.

During Phase 1, patients will receive loncastuximab tesirine Q3W for 2 cycles (C1D1 and C2D1). Patients who have a response of PR or SD at the 14-week disease assessment may receive two additional doses of loncastuximab tesirine given 4 weeks apart (C5D1 and C6D1). Ibrutinib will be administered orally once daily continuously during all cycles containing ibrutinib.

During Phase 2, patients on the cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib will receive loncastuximab tesirine Q3W for 2 cycles (C1D1 and C2D1). Patients who have a response of CR, PR, or SD at later disease assessments (Week 14 and Week 30) will receive additional doses of loncastuximab tesirine at C5D1, C6D1, C9D1, and C10D1. Ibrutinib will be administered orally at 560 mg once daily continuously during all cycles. Patients on the cohort where loncastuximab tesirine is given at every cycle in combination with ibrutinib will receive loncastuximab tesirine Q3W on Day 1 of first 2 cycles, followed by Q4W on Day 1 of every subsequent cycles. Ibrutinib will be administered at 560 mg po daily for first two cycles, then a dose reduction to 420 mg po daily for subsequent cycles.

Patients 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 on a case-by-case basis after review and approval by the Sponsor.

4.4 End of Treatment

The EOT visit 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 2 years from EOT, 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 for each patient will be the date of last visit/contact or date of death, whichever occurs last, and the end of study for the study as a whole will be the last visit or last scheduled procedure for the last patient, unless the study is terminated earlier by the 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 or MCL (**For Italy Sites Only:** MCL patients are excluded)
3. Patients with DLBCL must have relapsed or refractory disease and have failed or been intolerant to available standard therapy **(including stem cell transplant if patient was eligible)**
4. Patients with MCL must have relapsed or refractory disease and have received at least one prior line of therapy (**For Italy Sites Only:** This exclusion criterion is not applicable)
5. Patients who have received previous CD19-directed therapy must have a biopsy which shows CD19 expression after completion of the CD19-directed therapy
6. Measurable disease as defined by the 2014 Lugano Classification
7. 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.
8. ECOG performance status 0 to 2
9. Screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$ (off growth factors at least 72 hours)
   b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 7 days
   c. Hemoglobin ≥8 g/dL (4.96 mmol/L), transfusion allowed
   d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) ≤2.5 × the ULN
   e. Total bilirubin ≤1.5 × ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 × ULN)
   f. Blood creatinine ≤1.5 × 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.
10. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to start of study drugs on C1D1 for women of childbearing potential (WOCBP)

11. Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 9 months after the last dose of loncastuximab Tesirine or 1 month after last dose of ibrutinib, whichever comes last. 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 6 months after the patient receives his last dose of or 3 months after last dose of ibrutinib, whichever comes last.

    * 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. In addition, a barrier method along with hormonal contraceptive is required as per manufacturer's recommendation for ibrutinib use.

    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. Known history of hypersensitivity to or positive serum human anti-drug antibody (ADA) to a CD19 antibody
2. Known history of hypersensitivity to ibrutinib
3. Previous therapy with ibrutinib or other BTK inhibitors
4. Previous therapy with loncastuximab tesirine
5. Requires treatment or prophylaxis with a moderate or strong cytochrome P450 (CYP) 3A inhibitor
6. Allogenic or autologous transplant within 60 days prior to start of study drugs (C1D1)
7. Active graft-versus-host disease
8. Post-transplantation lymphoproliferative disorder
9. Active autoimmune disease, including motor neuropathy considered of autoimmune origin and other central nervous system (CNS) autoimmune disease
10. Known seropositive and requiring anti-viral therapy for human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV)
11. History of Stevens-Johnson syndrome or toxic epidermal necrolysis
12. Lymphoma with active CNS involvement at the time of screening, including leptomeningeal disease

13. 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)
14. Breastfeeding or pregnant
15. Significant medical comorbidities, including but not limited to, uncontrolled hypertension (blood pressure [BP] ≥160/100 millimeters of mercury (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 mellitus, severe chronic pulmonary disease, or tuberculosis infection (tuberculosis screening based on local standards)
16. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy within 14 days prior to start of study drugs (C1D1), except shorter if approved by the Sponsor
17. Use of any other experimental medication within 14 days prior to start of study drugs (C1D1)
18. Planned live vaccine administration after starting study drugs (C1D1)
19. Any condition that could interfere with the absorption or metabolism of ibrutinib including malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel
20. Inherited or acquired bleeding disorders
21. Ongoing anticoagulation treatment, except for low-dose heparinisation or equivalent
22. 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
23. Congenital long QT syndrome or a corrected QTcF interval of >480 ms at screening (unless secondary to pacemaker or bundle branch block)
24. 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
25. 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 Screen Failures

Patients who signed the ICF but were found not eligible for the study prior to receiving study drugs, 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
- SAEs and/or death occurring during the Screening Period

6 STUDY TREATMENT

6.1 Study Drugs

6.1.1 Loncastuximab Tesirine

- Loncastuximab tesirine will be provided as a frozen liquid or lyophilized formulation in Phase 1. For Phase 2, frozen liquid or a refrigerated lyophilized formulation of loncastuximab tesirine will be provided. 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.

Patients will receive the same formulation for their entire treatment.

6.1.2 Ibrutinib

Ibrutinib will be provided as 140 mg capsules. Each capsule contains ibrutinib (active ingredient) and the following inactive ingredients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The capsule shell contains gelatin, titanium dioxide, and black ink.

6.2 Management of Clinical Supplies

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

6.2.1 Packaging and Storage

The study drugs will be supplied by the Sponsor through the designated distribution center.

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

All study drugs must be stored according to the pharmacy manual, in a secure area.

- Loncastuximab tesirine liquid formulation: loncastuximab tesirine must be protected from light and stored at -65°C or below. Loncastuximab tesirine must be thawed under ambient conditions.

- Loncastuximab tesirine lyophilized formulation: must be protected from light and stored at 2-8°C.
- Ibrutinib: Packaging and storage information is provided in the ibrutinib IB.

6.2.2 Preparation and Administration

Loncastuximab tesirine 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 prepared will depend on the dose level and the weight of the patient. The weight of the patient at Cycle 1 Day 1 can be used for calculating the dose. If the patient's weight measured on subsequent dosing days has changed by 10% or more compared to the weight used to calculate the previous dose, then the dose should be recalculated based on the new weight. Additional details are included in the pharmacy manual.

Loncastuximab tesirine will be administered as a 30-minute IV infusion. 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 deviations.

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.

Sufficient ibrutinib will be dispensed so each patient can take 560 mg or 420 mg orally once daily until the next visit.

6.2.3 Accountability

The Investigator must maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records must 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 must be reconciled and retained or destroyed according to applicable regulations.

6.3 Dosing of Study Drugs

6.3.1 Loncastuximab Tesirine Dosing

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

During Phase 1, loncastuximab tesirine will be administered on Day 1 of Cycle 1 and Cycle 2 per the dose escalation plan below.

The Sponsor in consultation with the DESC will explore and evaluate a new dose level of 75 µg/kg loncastuximab tesirine in combination with ibrutinib as a concomitant therapy.

Table 4 Phase 1: Concomitant Treatment with Loncastuximab Tesirine and Ibrutinib

Dose Level	Loncastuximab Tesirine	Ibrutinib
1	60 µg/kg IV Q3W × 2	560 mg/day po continuous beginning C1D1
2	90 µg/kg IV Q3W × 2	560 mg/day po continuous beginning C1D1
3	75 µg/kg IV Q3W × 2	560 mg/day po continuous beginning C1D1

Abbreviations: Q3W, every 3 weeks; po, orally; C1D1, Cycle 1 Day 1

Note: Dose Levels 1 and 2 have completed enrollment, the subsequent Dose Level 3 has been added to further explore the combination.

Patients who have a response of PR or SD at the 14-week disease assessment may receive 2 additional doses of loncastuximab tesirine given 4 weeks apart (C5D1 and C6D1).

During Phase 2, two treatment cohorts (Table 5) will be tested:

- Patients assigned to a cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib will receive loncastuximab tesirine at the initial recommended dose (60 µg/kg) determined in the Phase 1 portion of the study. Loncastuximab tesirine will be administered to the patients Q3W for 2 cycles (C1D1 and C2D1). Patients who have a response of CR, PR, and SD at later disease assessments (Week 14 and Week 30) will receive additional doses of loncastuximab tesirine on C5D1, C6D1, C9D1, and C10D1.

- Patients assigned to a cohort where loncastuximab tesirine is given at every cycle in combination with ibrutinib will receive loncastuximab tesirine at re-determined RP2D at every treatment cycles. Loncastuximab tesirine will be infused through IV Q3W for first 2 cycles and followed by Q4W for all subsequent treatment cycles.

Table 5 Phase 2: Concomitant Treatment with Loncastuximab Tesirine and Ibrutinib

Treatment Cohort	Loncastuximab Tesirine	Ibrutinib	Targeted Enrollment
Loncastuximab Tesirine Given Intermittently in Combination with Ibrutinib	Initial RP2D (60 µg/kg) IV Q3W for C1 and C2, then Q4W at C5, C6 and C9, C10 when a response of CR, PR or SD is observed.	560 mg/day po daily beginning C1D1	Non-GCB DLBCL (n=66. Enrollment will be closed at N=48) GCB DLBCL (n=30) MCL (n=10)
Loncastuximab Tesirine Given at Every Cycle in Combination with Ibrutinib	Re-determined RP2D IV Q3W for C1 and C2, followed by Q4W at all subsequent cycles.	560 mg/day po daily beginning C1D1 for C1 and C2, then reduced to 420 mg/day daily at C3D1and for all subsequent cycles.	All DLBCL (n=100 with ≥40 patients each from GCB and Non-GCB)

Refer to Section 6.7 for premedication and supportive care.

6.3.2 Ibrutinib Dosing

Ibrutinib dosing will begin simultaneously with loncastuximab tesirine dosing (concomitant treatment,). Patients will receive ibrutinib orally once daily according to the dose instructions given in the Table 4 and Table 5 at approximately the same time each day.

In Phase 1, ibrutinib administration will begin on Cycle 1 Day 1 for patients receiving concomitant treatment (Table 4).

In Phase 2, ibrutinib will be administered according to the recommended dose and schedule in Table 5.

Home administration of ibrutinib will be documented in a patient diary, which will be reviewed by the Investigator or designee at each study visit.

6.4 Dose Escalation

6.4.1 Dose Escalation Design

The dose escalation of loncastuximab tesirine in Phase 1will follow a standard 3+3 design using the dose levels defined in Section 6.5. The dose one dose level below the dose at which ≥33% of patients experience a DLT will be considered the MTD. Cohorts of 3 patients will be treated, starting at the initial dose level. If 0 of 3 patients in the first cohort at any dose level experience a DLT, then the following cohort will be treated at the next higher dose level. If 2 of 3 patients experience a DLT, then the preceding dose level will be determined as the MTD. If 1 of 3 patients experiences a DLT, then 3 additional patients will be treated at that dose level. If 0 of the 3 additional patients experience a DLT, then the following cohort will be treated at the next higher

dose level. If 1 or more of the 3 additional patients experience a DLT, then the preceding dose level will be determined as the MTD.

There will be a minimum of 5 days between dosing the first and second patient at each dose level during dose escalation.

Patients who discontinue from the study prior to completion of the DLT Period without a DLT will be replaced.

6.4.2 Dose-Limiting Toxicity Period

The first 21 days of ibrutinib administration will be considered the DLT Period for patients in Phase 1 dose escalation who are following the 3+3 study design.

6.4.3 Dose-Limiting Toxicity Definition

A DLT is defined as any of the following events which occur during the DLT Period, except those that are clearly due to underlying disease or extraneous causes:

A **hematologic** DLT is defined as:

- Grade 4 anemia
- Grade 3 anemia requiring transfusion
- Grade 4 neutropenia lasting > 7 days
- Febrile neutropenia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia which results in clinically significant bleeding or requires a transfusion

A **non-hematologic** DLT is defined as:

- Hy's law case: AST and/or ALT > 3 × ULN and bilirubin > 2 × ULN, and without initial findings of cholestasis (serum alkaline phosphatase [ALP] activity < 2 × ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin
- Any other non-hematologic toxicities ≥ Grade 3, with the exception of the following conditions:
  - Grade 3 fatigue for ≤ 7 days.
  - Grade 3 nausea, vomiting, or diarrhea in the absence of premedication that responds to therapy and improves by at least 1 grade within 3 days or to ≤ Grade 1 within 7 days.
  - Grade 3 elevations of ALP and GGT elevations, unless considered clinically relevant by the Investigator.
  - Grade 3 elevation of serum lipase or serum amylase for ≤ 7 days if without clinical signs or symptoms of pancreatitis.

- Grade 3 electrolyte abnormalities which normalize within 48 hours (with or without medical intervention) and which do not manifest themselves clinically; in such instance, a follow-up sample MUST be taken within 48 hours to check whether such normalization has occurred.

Patients who experience a DLT that resolves or stabilizes with appropriate medical management may continue treatment at the discretion of the Investigator in consultation with the Sponsor.

6.4.4 Dose Escalation Steering Committee

A DESC will oversee dose escalation and general safety of the study.

Membership of the DESC will include:

- Medical and/or pharmacovigilance representative(s) from the Sponsor and/or designee
- Investigator(s) from each participating site

The DESC will be responsible for:

- Determining dose levels to be administered and the MTD based on assessment of safety findings and DLTs.
- Monitor the safety of the study and review its progress at monthly intervals or more frequently as required.

Decisions made at DESC meetings will be documented in written minutes that will be distributed to DESC members.

6.5 Dose Delays and Modifications

6.5.1 Loncastuximab Tesirine

Table 6 Loncastuximab Tesirine Guidelines for Dose Modifications

Study Drug	Loncastuximab Tesirine
Grade ≥2 edema, effusion All other non-hematologic AEs Grade ≥3	• Loncastuximab tesirine must be held until the toxicity resolves to Grade≤ 1, (Grade 1 or baseline for peripheral neuropathy) • 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% • Investigator may reduce the dose of loncastuximab tesirine by 50% if the toxicity 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 patient
Grade ≥3 neutropenia or thrombocytopenia	• Loncastuximab tesirine must be held until 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% • Investigator may reduce the dose of loncastuximab tesirine by 50% if the toxicity 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 patient
Skin related toxicities including photosensitivity rash Grade ≤2	No dose adjustment is required. Topical treatment to affected areas is indicated: • maculopapular rash, photosensitivity rash: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) • pruritus: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider oral antipruritic • xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID • blistering rash: silvadene 1% cream BID and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus). Periodic reassessment as indicated For Grade 2, the Sponsor recommends dermatological consultation

Table continued on next page.

Study Drug	**Loncastuximab Tesirine**
Skin related toxicities including photosensitivity rash Grade≥3	Hold loncastuximab tesirine until improvement to ≤ Grade 1 and consider dermatological consultation Topical treatment to affected areas is indicated: • maculopapular rash or photosensitivity rash: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider systemic prednisone 0.5 mg/kg for 10 days • pruritus: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider oral antipruritic. • xerosis: consider ammonium lactate 12% or urea 20% BID; and triamcinolone 0.1% cream BID. • blistering rash: silvadene 1% cream BID and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus) and systemic prednisone 0.5 mg/kg for 10 days Periodic reassessment as indicated. 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%. The Investigator may also reduce the dose of loncastuximab tesirine by 50% for any Grade ≥3 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.
Grade 4 infusion related reactions	Permanently discontinue loncastuximab tesirine
Hy's law (AST and/or ALT > 3 × ULN and bilirubin > 2 × ULN)	Permanently discontinue loncastuximab tesirine. Hy's law defined as: AST and/or ALT > 3 × ULN and bilirubin >2 × ULN, and without initial findings of cholestasis (ALP activity <2 × ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury

For ibrutinib dose modification guidance, please see Section 6.5.2.

If loncastuximab tesirine dosing is delayed or discontinued and the toxicity is at least possibly related to locastuximab tesirine, ibrutinib dosing can continue at the discretion of the Investigator and in consultation with the Sponsor.

6.5.2 Ibrutinib

For any Grade 2 AE, a dose reduction can occur at the discretion of the Investigator and in consultation with the Sponsor.

If a patient experiences any Grade ≥3 toxicity, ibrutinib must be held until the toxicity resolves to Grade 1 or baseline. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib therapy may be reinitiated at the original dose.

If toxicity as described above recurs and is considered at least possibly related to ibrutinib, after a dose hold, subsequent doses of ibrutinib will be reduced by 140 mg to 420 mg daily, or to 280 mg daily where applicable.

If toxicity as described above recurs at the reduced dose and is considered at least possibly related to ibrutinib, after a dose hold, subsequent doses of ibrutinib will be reduced by an additional 140 mg to 280 mg daily, or to 140 mg daily where applicable.

If toxicity as described above recurs after a second dose reduction and is considered at least possibly related to ibrutinib, ibrutinib must be discontinued permanently.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation.

Ibrutinib is metabolized primarily by CYP3A4. Avoid concomitant use of systemic strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A. No dose adjustment is required in combination with mild inhibitors.

If the dose of ibrutinib is reduced as per protocol the dose of ibrutinib may be re-escalated, at the investigator's discretion upon discussion with the sponsor, after at least 2 months of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction.

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra doses of ibrutinib should not be taken to make up for the missed dose.

If ibrutinib dosing is delayed or discontinued and the toxicity is at least possibly related to ibrutinib, loncastuximab tesirine dosing can continue at the discretion of the Investigator and in consultation with the Sponsor.

6.6 Overdose Management

An overdose is any dose of study drug(s) given to a patient that exceeds by 15% of the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor. There are no data available to determine what the effects of overdose of loncastuximab tesirine are and whether they can be reversed. There is no specific experience in the management of ibrutinib overdose in patients. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

6.7 Premedication and Supportive Care

6.7.1 Premedication for Loncastuximab Tesirine

Unless contraindicated, administer dexamethasone 4 mg po twice daily:

- the day before each loncastuximab tesirine administration (if possible),
- the day of loncastuximab tesirine administration (first dose 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.

Dexamethasone may be given IV in patients unable to take po.

Patients who experience an infusion-related hypersensitivity reaction will receive the alternative premedication regimen specified in Section 6.7.3.

6.7.2 Treatment of Edema and Pleural Effusion

Peripheral edema and serosal effusions (pleural and pericardial effusions, ascites) have been seen in patients receiving loncastuximab tesirine. Patients should be advised to monitor their weight on a daily basis (preferably each morning around the same time) and notify the study site of weight gain greater than 1 kg from baseline.

Patients with weight gain greater than 1 kg from baseline, new or worsening edema, and/or new or worsening pleural effusion, pericardial effusion, or ascites, should be treated with spironolactone at standard doses. 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 effusion.

6.7.3 Treatment and Prophylaxis of Infusion-Related Hypersensitivity Reactions

The treatment of severe hypersensitivity reactions, including anaphylaxis, should be available for immediate use and may be administered according to institutional SOC.

Any patient who experiences an infusion-related hypersensitivity reaction should receive prophylactic treatment in subsequent cycles according to institutional SOC.

6.7.4 Skin Toxicity

Skin toxicity has been reported in patients receiving loncastuximab tesirine for hematologic malignancies. Often, the toxicities manifested as rash were reported in sun exposed areas; it is therefore recommended that precautions are taken to avoid exposure of skin to sunlight, even through glass (e.g., use of sun protective clothing and sunglasses, sunscreen with a sun protection factor ≥ 30 applied every 2 h, avoidance of being outside with no protection between 10AM and 2PM). Also, fragrance-free detergents and soaps are recommended.

Consideration should be given to corticosteroid therapy in patients who develop clinically significant skin toxicity (see Table 6 for dose modifications and treatment recommendations for skin toxicities).

6.7.5 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.

6.8 Concomitant Medications and Procedures

Medications (except for the study drugs) 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 30 days after last dose of study drug.

6.8.1 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 6.8.2.

Hematopoietic growth factors are permitted as per American Society of Clinical Oncology guidelines (Smith et al., 2006). Patients may not receive prophylactic hematopoietic growth factors during Cycle 1.

6.8.2 Prohibited During Study

- Moderate or strong CYP3A inhibitors and strong CYP3A inducers should be avoided. If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. Information on CYP3A inhibitors and inducers may be found in Section 13.3 (Appendix 3) or at http://medicine.iupui.edu/clinpharm/ddis/main-table/
- Grapefruit and Seville oranges (these contain moderate CYP3A inhibitors)
- Other anticancer therapy with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer
- Other investigational agents
- Live vaccine

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 study treatment for any of the following reasons:

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

IMPORTANT: Study treatment discontinuation is not to be automatically considered as withdrawal from the study. Patients discontinuing study treatment 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 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(s) should have an EOT visit as described in Section 4.4 and Schedule of Events (SoE) (Table 1 and Table 2).

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 the SoE (Table 1 and Table 2) until progression. Disease assessments should take place at the time points specified even if dosing of study drug(s) is delayed. Additional disease assessments may be obtained, if clinically indicated.

Clinical examination for lymphoma will be performed at all disease assessment time points. Positron emission tomography-computed tomography (PET-CT) of the neck/chest/abdomen/ pelvis and other areas of known disease or newly suspected disease, will be 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) with contrast or magnetic resonance imaging (MRI) must be used for subsequent disease assessments.

Images for all patients treated during the Phase 2 portion of the study 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.

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

During the Treatment Period, imaging will be performed 6 weeks and 14 weeks after C1D1, then every 8 weeks until EOT. Week 6 imaging should be performed prior to C3D1 and Week 14 imaging should be performed prior to C5D1. All other imaging should be performed within ± 2 weeks of the scheduled time point. Disease assessments should be performed at the time points 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.

During the Follow-up Period, patients who discontinued study drug(s) 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 2 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 in Section 13.2 (Appendix 2) as CR, PR, SD, or progressive disease (PD). Images will be obtained according to local site imaging protocols.

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 examinations, 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.

Adverse events (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 the start of a new anti-cancer therapy, whichever occurs earlier; thereafter, only related SAEs will be reported with two 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:
    a. 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
    b. SAEs
    c. 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:
    a. Grade ≥3 AEs of cytokine release syndrome, encephalopathy, edema or effusion, rash, hepatic toxicity
    b. SAEs
    c. 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(s) (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.

8.2.2.1 Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) are AEs of clinical importance that may require safety evaluation. For this study, events of major hemorrhage, as defined below, will be considered AESIs and must be reported to the pharmacovigilance department of the Sponsor or delegate (e.g., CRO) within 24 hours after site personnel first learn about the event. Reporting will occur through the EDC system.

Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AE of Grade 3 or higher*
- Any treatment-emergent SAE of bleeding of any grade
- Any treatment-emergent CNS hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells (RBC) should be reported as Grade 3 or higher AE per CTCAE v4.03.

8.2.3 Assessment of Severity

Adverse events will be graded according to CTCAE v4.0. For events not included in the CTCAE criteria, the severity of the AE will be graded on a scale of 1 to 5 as shown in Table 7.

Table 7 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(s) is an important part of safety reporting. However, it is not a factor in determining whether or not an AE is reported. An AE will be assessed as related to study drug(s) 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(s) 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, and package insert for ibrutinib. SUSARs will be reported to competent authorities and Independent Ethics Committee (IEC) in accordance with current legislation.

8.2.6 Pregnancy Reporting

Any pregnancy in a patient that occurs from the time the patient signs the ICF up to 9 months after discontinuation of loncastuximab tesirine or up to 1 months after terminating ibrutinib treatment, whichever comes last, during the study must be reported using the Pregnancy Report Form. Any pregnancy in a partner of a male patient that occurs from signing the ICF up to 6 months post last loncastuximab tesirine or up to 3 months post last ibrutinib, whichever comes last, during the study must be reported. 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 during pregnancy reporting period 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(s) must be promptly reported in the same manner.

Once pregnancy is confirmed in a study patient, study drugs will be discontinued, see Section 8.3.6 for additional information.

8.3 Safety Assessments

Safety will be assessed based on the procedures in the subsection below. The AE/SAE collection and reporting are described in Section 8.2.

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

8.3.1 Physical Examination

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

8.3.2 ECOG Performance Status

The ECOG performance status grades are presented in Section 13.1 (Appendix 1) and will be captured as per the SoE (Table 1 and Table 2).

8.3.3 Height and Weight

Height and weight will be measured as per the SoE (Table 1 and Table 2).

Additional measurements should be performed if clinically indicated.

Patients should monitor their weight at home to mitigate the risks for edema/effusions. Refer to Section 6.7.2 for further details.

8.3.4 Vital Signs

Vital signs include the measurements of arterial BP (systolic and diastolic), heart rate, respiratory rate, and body temperature and should be performed according to the institutional standards. Vital signs should be measured before and after each loncastuximab tesirine infusion.

8.3.5 Laboratory Tests

Samples will be collected at the time points specified as per the SoE (Table 1 and Table 2).

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

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

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

Urinalysis: pH, specific gravity, protein, WBC, RBC, ketones, glucose, and bilirubin.

Urinalysis may be performed by dipstick. Abnormal findings should 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.

Other Tests: HBV, HCV, and HIV

8.3.6 Pregnancy Test

A highly sensitive β-HCG test in urine or blood β-HCG test must be performed in WOCBP for eligibility (see Section 5.1, Inclusion Criterion 10) and throughout the study as per the SoE (Table 1 and Table 2) and as needed.

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

two consecutive pregnancy tests no more than 6 weeks. When possible, for WOCBP patients a final pregnancy test should be performed ≥9 months post last dose of loncastuximab tesirine if applicable, however, remote pregnancy test is acceptable.

If a pregnancy test is positive, study drug must be held pending confirmation. If the pregnancy is confirmed, treatment must 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 time points throughout the study as per the SoE (Table 1 and Table 2). Refer to Table 8, Table 9, and Table 10 for the detailed schedule of ECGs.

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

At time points coinciding with blood sample collection including PK, and ECGs should be taken prior to blood collection, and where applicable, before vital sign measurements (refer to Figure 2).

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

Table 8 Schedule for Triplicate ECG Collection: Phase 1

Cycle	Day	ECG Time point (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 (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 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 (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 48 h; but within 30 min prior to PK sample)
C3	D1	Any time (but 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 time point is counted from start of infusion.

Table 9 Schedule for Triplicate ECG Collection: Phase 2 for Cohort Where Loncastuximab Tesirine Is Given Intermittently in Combination with Ibrutinib

Cycle	Day	ECG Time point (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 (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 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 (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 48 h; but within 30 min prior to PK sample)
C3	D1	Any time (but within 30 min prior to PK sample)
C5	D1	Pre-dose (preferably within 2 h prior to start of infusion)
C6	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI)
C9	D1	Pre-dose (preferably within 2 h prior to start of infusion)
C10	D1	Pre-dose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI)
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 time point is counted from start of infusion.

Table 10 Schedule for Triplicate ECG Collection: Phase 2 for Cohort Where Loncastuximab Tesirine Is Given at Every Cycle in Combination with Ibrutinib

Cycle	Day	ECG Time point (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 (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 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 (± 15 min)
	D8	Post-dose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Post-dose* 336 h (± 48 h; but within 30 min prior to PK sample)
C3 and beyond	D1	Pre-dose (preferably within 2 h prior to start of infusion)
EOT		Any time (but within 30 min prior to PK sample)
Unscheduled		Any time

The 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, [redacted] and Immunogenicity

The PK, ADA[redacted] samples will be collected as per the SoE (Table 1 and Table 2). 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[redacted] testing.

When multiple samples are required at the same time point, 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 regard 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 PK profile 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 2 and Table 11 and Table 12.

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 time points 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 11 Sampling Schedule for PK and ADA: Phase 1

Cycle	Day	PK Time point (window)	ADA Time point (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 2 h 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 (prior to ibrutinib dosing)	Pre-dose (prior to ibrutinib dosing)
C5 and C6 (only for patients receiving loncastuximab tesirine in C5 and C6)	D1	Pre-dose (preferably within 2 h prior to start of infusion)	Pre-dose (preferably within 2 h prior to start of infusion)
C7 (patients receiving loncastuximab tesirine for C5 and C6)	D1	Pre-dose (prior to ibrutinib dosing)	Pre-dose (prior to ibrutinib dosing)
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 time point is counted from start of infusion.

Table 12 Sampling Schedule for PK and ADA: Phase 2

Cycle	Day	PK Time point (window)	ADA Time point (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 2 h 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 if loncastuximab tesirine is dosed (preferably within 2 h prior to start of infusion)	Pre-dose if loncastuximab tesirine is dosed (preferably within 2 h prior to start of infusion)
C5 and C6	D1	Pre-dose (preferably within 2 h prior to start of infusion)	Pre-dose (preferably within 2 h prior to start of infusion) C5 only**
C7	D1	Pre-dose if loncastuximab tesirine is dosed (preferably within 2 h prior to start of infusion)	Pre-dose if loncastuximab tesirine is dosed (preferably within 2 h prior to start of infusion)
C9 and C10	D1	Pre-dose (preferably within 2 h prior to start of infusion)	Pre-dose (preferably within 2 h prior to start of infusion) C9 only **
C11	D1	Pre-dose if loncastuximab tesirine is dosed (preferably within 2 h prior to start of infusion)	Pre-dose if loncastuximab tesirine is dosed (preferably within 2 h prior to start of infusion)
C13	D1	-	Pre-dose (preferably within 2 h prior to start of infusion) for loncastuximab tesirine given at every cycle in combination with ibrutinib only
EOT		At any time during the visit day	At any time during the 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 time point is counted from start of infusion.
**Applicable to protocol amendment version 5 and beyond.

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 2 and Table 11 and Table 12. 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 Patient-Reported Outcomes Questionnaires

The impact of study treatment on disease- and treatment-related symptoms, as well as various aspects of patient's health-related quality of life (HRQoL), will be assessed by three questionnaires:

- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-Core 30 (C30), Section 13.4 (Appendix 4).
- Lymphoma subscale (LymS) of Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym), Section 13.5 (Appendix 5).
- EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L), Section 13.6 (Appendix 6).

Questionnaires will be completed in the respondent's native language, at the scheduled time points prior to the patient's clinical assessment and treatment. Patients will provide responses at the study site or by phone (i.e., the collection of EQ-5D-5L post disease progression). The patient should be given instructions, space, time, and privacy to complete the questionnaires by themselves and without any assistance from anyone else. The study coordinator should encourage the patient to complete the questionnaires without any missing responses.

8.5.1 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – EORTC QLQ-C30

The European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 is a validated and widely used questionnaire to assess quality of life of cancer patients. It is composed of 30 items assessing 15 domains, including five functional scales (physical, role, emotional, cognitive, and social), three multi-item symptoms (fatigue, nausea/vomiting, and pain), six single-item symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and one global health status/ quality of life (QoL) scale. All scales range from 0 to 100 after applying a linear transformation to raw scores. Higher scores in functional scales and global health status/ QoL scales indicate a better HRQoL whereas higher scores in symptom scales indicate more severe symptoms (Aaronson NK et al, 1993). Patients will complete this questionnaire as per the SoE (Table 2).

8.5.2 Lymphoma Subscale (LymS) of FACT-Lym

FACT-Lym is a HRQoL questionnaire validated in patients with NHL. It consists of a general HRQoL assessment (FACT-G) and a disease-specific subscale (LymS). FACT-G (27 items) measures physical well-being, social/family well-being, emotional well-being, and functional well-being. The LymS (15 items) addresses symptoms and functional limitations that are important to patients with NHL, such as lumps and swelling in certain parts of the body, fever, night sweats, itching, and weight loss. Patients are 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. To ease burden on patients, only LymS will be collected and consequently LymS summary score be reported in this trial. The LymS summary score ranges from 0 to 60, with higher scores indicating better HRQoL. (Hlubocky et al, 2013). Patients will complete this questionnaire as per the SoE (Table 2).

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

EQ-5D-5L is designed as an international, standardized, generic instrument for describing and evaluating HRQoL (Herdman et al., 2011). The EQ-5D-5L consists of 2 parts:

a. The descriptive system comprises five dimensions with 1 question for each dimension: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels of perceived problems: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. The descriptive system can be converted into a health utility index for economic evaluation.
b. The visual analog scale (VAS): patients rate their current general health state on a scale ranging from 0 (worst health that can be imagined) to 100 (best health that can be imagined).

Patients will complete this questionnaire as per the SoE (Table 2).

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

The study will enroll approximately 243 patients. Phase 1 will enroll up to 55 patients and Phase 2 will enroll approximately 188 patients.

9.1.1 Phase 2 Sample Size Calculation for non-GCB DLBCL Cohort Where Loncastuximab Tesirine is Given Intermittently in Combination with Ibrutinib

The primary hypothesis is that the CRR based on central review for patients treated with loncastuximab tesirine and ibrutinib is significantly greater than 20% (i.e., H0: $p \leq 0.2$ vs. Ha: $p > 0.2$). This hypothesis will be tested at type I error of 0.05 (two sided).

Simon's 2-stage design (Simon, 1989) will be used. The null hypothesis that the true CRR is 0.2 will be tested against a one-sided alternative. In the first stage, 22 patients will be accrued. If there are 5 or fewer CRs in these 22 patients, this cohort will be stopped. Otherwise, 44 additional patients will be accrued for a total of 66. The null hypothesis will be rejected if 20 or more CRs are observed in 66 patients. This design yields a type I error rate of 0.05 and power of 90% when the true CRR is 0.4.

9.1.2 Phase 2 Sample Size Calculation for the Cohort Where Loncastuximab Tesirine is Given at Every Cycle in Combination with Ibrutinib

The primary hypothesis is that the CRR is based on central review for patients treated with the re-determined RP2D of loncastuximab tesirine and ibrutinib combination is significantly greater than 30% (i.e., H0: $p \leq 0.3$ vs. Ha: $p > 0.3$). This hypothesis will be tested at type I error of 0.05 (two sided).

A Two-stage design with futility monitoring (Zeng et al., 2015) will be used. The null hypothesis that the true CRR is 0.3 will be tested against a one-sided alternative. In the first stage, 60 patients will be accrued. If there are 20 or fewer CRs in these 60 patients, this cohort will be stopped. Otherwise, 40 additional patients will be accrued for a total of 100. The null hypothesis will be rejected if 40 or more CRs are observed in 100 patients. This design yields a type I error rate of 0.05 and power of 85% when the true CRR is 0.45. Enrollment will continue during the interim analysis.

9.2 Analysis Populations

- The Safety population will consist of all patients who receive study drug.
- The DLT-evaluable population will consist of all patients in Phase 1 dose escalation, who receive study drugs, and will exclude patients who discontinue from the study during the DLT Period without experiencing a DLT.
- The Efficacy population will consist of all patients who receive at least 1 dose of study drug, who have valid baseline disease assessment(s), and who have at least one valid post-baseline disease assessment. Patients who do not have a post-baseline assessment due to early clinical progression or death (after receiving study drug) will also be included.
- The PK population will consist of all patients who have at least 1 pre-(C1D1) and 1 post-dose valid PK assessment.
- [redacted]
- Per Protocol population: All patients in the Safety population without major protocol deviations, which will be further described in detail in the SAP.

9.3 Phase 2 Interim Analysis for Futility

9.3.1 Non-GCB Cohort Where Loncastuximab Tesirine is Given Intermittently in Combination with Ibrutinib

A single interim analysis is planned using Simon's 2 stage procedure (Simon, 1989) in the non-GCB DLBCL cohort where loncastuximab tesirine is given intermittently in combination with ibrutinib. The purpose of this interim analysis is solely to determine if there is a sufficient CRR 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 22nd patient has two tumor assessments. Enrollment will continue during the interim analysis. If ≥6 patients achieve CR, the study will proceed to the second stage. If <6 patients achieve CR, enrollment in this cohort will be halted.

9.3.2 Cohort Where Loncastuximab Tesirine is Given at Every Cycle in Combination with Ibrutinib

A two-stage design with futility monitoring (Zeng et al., 2015) is planned in the cohort given loncastuximab tesirine at every cycle in combination with ibrutinib for all DLBCL. The purpose of futility monitoring is solely to determine if there is a sufficient CRR observed early in the study to warrant continuing study enrollment to completion. Futility monitoring 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 60th patient has two tumor assessments. Enrollment will continue during the interim analysis. If ≥21 patients achieve CR, the study will proceed to the second stage. If <21 patients achieve CR, enrollment in this cohort will be halted.

9.4 Final Analysis

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

Follow-up analyses may be performed when all the patients complete the study per protocol.

9.5 Demographics and Baseline Characteristics

Demographics and baseline characteristics, such as medical/medications history and cancer history, will be summarized for the Safety population.

9.6 Exposure to Treatments

Exposure to study drug and prior and concomitant medications will be summarized for the Safety population. Dose interruptions, reductions, and relative dose intensity will also be summarized.

9.7 Efficacy Analyses

In the non-GCB DLBCL cohort, the primary efficacy analyses will be based on response as determined by the IRC.

Responses reported by investigators will be used for sensitivity analyses. Similarly, in other cohorts, responses by the IRC (if available) and by investigators will be summarized separately.

Efficacy analysis will be summarized in the non-GCB DLBCL, GCB DLBCL, and MCL cohort and in the combined DLBCL group (non-GCB plus GCB).

9.7.1 Complete Response Rate

CRR will be defined as the proportion of patients with a best overall response (BOR) of CR, according to the 2014 Lugano classification (Cheson et al., 2014). The BOR will be derived based on response assessment performed on or before the start of subsequent anti-cancer therapy.

The percentage of CRR with its 95% confidence interval (CI) will be presented.

9.7.2 Overall Response Rate

The ORR will be defined as the proportion of patients with a BOR of CR or PR, according to the 2014 Lugano classification. The overall response category will be derived based on response assessment performed on or before the start of subsequent anti-cancer therapy.

The percentage of ORR with its 95% 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.

9.7.3 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. 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 DOR and 95% CI will be presented. Further details will be outlined in the SAP.

9.7.4 Relapse-free Survival

Relapse-free survival (RFS) will be defined among CR patients as the time from the earliest date of first CR until the first date of either disease progression or death due to any cause. 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 RFS and 95% CI will be presented. Further details will be outlined in the SAP.

9.7.5 Progression-free Survival

PFS will be defined as the time from first dose of study drug until the first date of either disease progression or death due to any cause. 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.

9.7.6 Overall Survival

OS will be defined as the time from first dose of study drug 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.

9.8 Safety and Subgroup Analyses

Safety analyses will be presented descriptively

Subgroup analyses may be performed for CRR, ORR, DOR, 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 the SAP.

9.8.1 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 initiation of new anti-cancer therapy (whichever occurs first).

The 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; SAEs; AESIs; and death.

9.8.2 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.

9.8.3 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.

9.9 Pharmacokinetic Analyses

The PK profile will include determination of: maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), area under the concentration-time curve from time zero to the end of the dosing interval (AUC_{tau}), area under the concentration-time curve from time zero to infinity (AUC_{inf}), apparent systemic clearance (CL), apparent volume of distribution (V_{ss}), apparent terminal half-life (T_{half}), and accumulation index (AI).

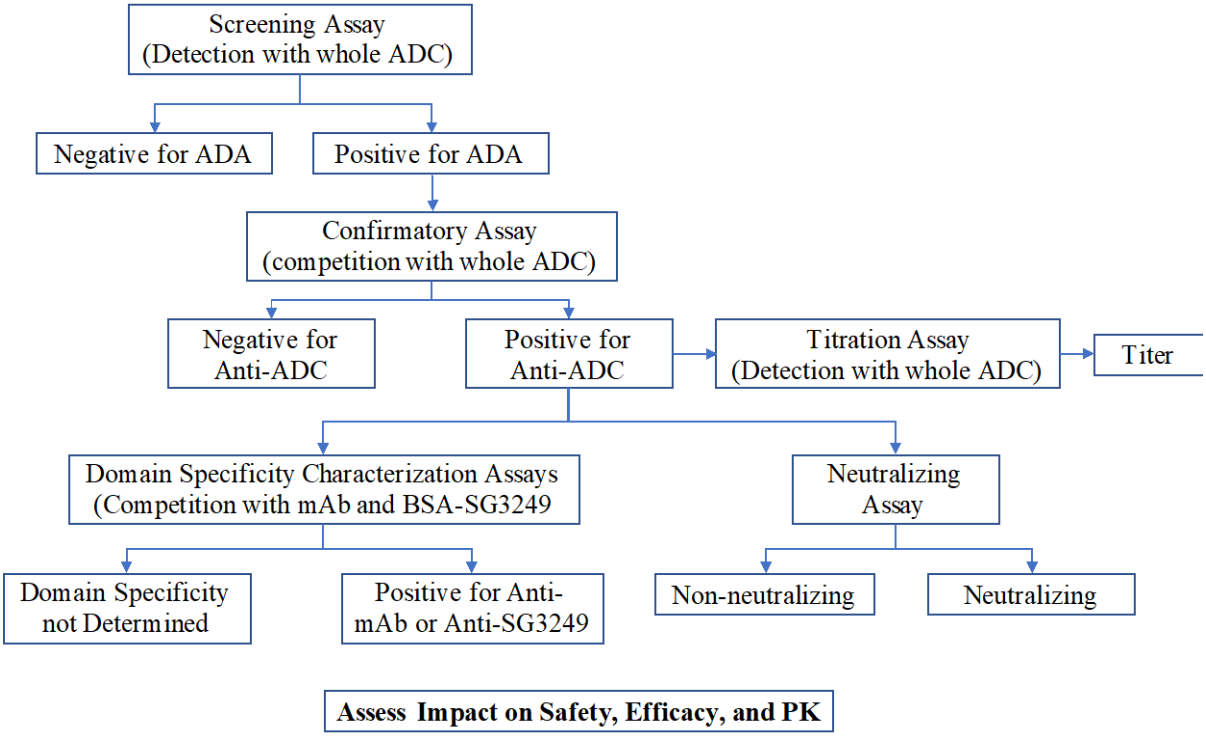
PK parameters will be determined for all PK-evaluable patients using a non-compartmental method with Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ, US) or other appropriate software. Results of the PK analysis may be reported separately.

[redacted]

9.10 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 FDA Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection Guidance for Industry (Jan 2019).

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.

[redacted]

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. **For France sites only:** Any reference to the patient's legally authorized representative/legal guardian in Section 11 is not applicable, as per the request from the French Central Ethics Committee (CEC).

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 cases, 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 Code of Federal Regulations (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/inspection, 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) or until at least 2 years after the last approval of a marketing application in an ICH region or 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

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