Title: A Phase 2 Randomized Study of Loncastuximab Tesirine Versus Idelalisib in Patients with Relapsed or Refractory Follicular Lymphoma (LOTIS 6)

Protocol Number: ADCT-402-202

NCT Number: NCT04699461

Protocol Version & Date: Version 3.0
7th April 2021

CLINICAL STUDY PROTOCOL

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A Phase 2 Randomized Study of Loncastuximab Tesirine Versus Idelalisib in Patients with Relapsed or Refractory Follicular Lymphoma (LOTIS 6)

PROTOCOL ADCT-402-202

PHASE 2

ADC Therapeutics SA

[redacted]

Protocol Amendment 3.0 07 April 2021

Confidentiality Statement

Protocol Approval – Sponsor Signatory

Study Title	A Phase 2 Randomized Study of Loncastuximab Tesirine Versus Idelalisib in Patients with Relapsed or Refractory Follicular Lymphoma (LOTIS 6)
Protocol Number	ADCT-402-202
Protocol Amendment 3.0	**07 April 2021**

Protocol accepted and approved by:

[redacted]

[redacted]

07-Apr-2021
Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled: "A Phase 2 Randomized Study of Loncastuximab Tesirine Versus Idelalisib in Patients with Relapsed or Refractory Follicular Lymphoma (LOTIS 6)" 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 Protocol Amendment 3.0, dated 07 Apr 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 or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer the study treatment only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the study treatment 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

Summary of Changes for Protocol Amendment 3.0

The primary reason for Protocol Amendment 3 is to align the frequency of laboratory evaluations for patients treated with idelalisib with the idelalisib Summary of Product Characteristics (SmPC); to exclude patients with history of hypersensitivity to any of the excipients of study drugs; to align contraception guidance for women of childbearing potential (WOCBP) receiving idelalisib treatment with the idelalisib SmPC; and to extend SAE reporting duration to at least 5 half-lives after the last loncastuximab tesirine dose based on regulatory authority request.

The summary of changes and the rationale in Protocol Amendment 3.0 is as follows:

- Changed treatment cycle length for the idelalisib arm from 3 weeks to 4 weeks and added hematology tests every 2 weeks (Q2W) for the initial 6 months (cycles 1 to 7) and ALT/AST/total bilirubin tests Q2W for the initial 3 months (cycles 1 to 4) of idelalisib treatment.
    - Section 4.1 Overview & Section 4.2.3 Treatment Period: Amended the idelalisib treatment cycle length from 3 weeks to 4 weeks.
    - Schedule of Events: Split Schedule of Events (SoE) table (Table 1) to Table 1 Schedule of Events for Loncastuximab Tesirine Arm and Table 2 Schedule of Events for Idelalisib Arm for a better clarity.
    - Added hematology tests on day 15 for cycles 1 to 7 and AST/ALT /total bilirubin tests on day 15 for cycles 1 to 4 for patients in idelalisib arm in Table 2.
    - PRO-CTCAE questionnaire for patients in the idelalisib arm ends in cycle 7 to correspond to 6-month treatment duration compared to loncastuximab tesirine. Updated the schedule for PRO-CTCAE questionnaire in SoE (Table 2).
    - Section 7 Study Assessments and Procedures was revised to reference Table 1 and Table 2 for the study events, where applicable.
- Section 5.2 Exclusion Criteria: Added an exclusion criterion: History of hypersensitivity to any of the excipients of loncastuximab tesirine or idelalisib.
- Section 6.8.4 Contraceptive Guidance: Added “If WOCBP use hormonal contraceptives such as birth control pills, a second barrier method of contraception (e.g., condoms) must be used during idelalisib treatment until 1 month after last dose of idelalisib.”
- Section 8.2 Eliciting and Reporting Adverse Events/Serious Adverse Events: Amended to extend collection of SAEs to at least 76 days after the last dose of loncastuximab tesirine or until initiation of new anticancer treatment, whichever is earlier, to ensure appropriate surveillance of any late onset events while eliminating the confounding influence of other anti-cancer therapies based on updated conjugated loncastuximab tesirine Ab half-life (15.2 days). As idelalisib is a comparator, SAE follow-up duration for idelalisib was also updated to align with loncastuximab tesirine. Table 1 and Table 2 were updated to reflect the change.

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.

List of Prior Protocol Versions

Document	Version Date	Rationale for Changes
Protocol Amendment 2.0	19 Feb 2021	The primary reason for Protocol Amendment 2 was to extend the contraception duration post loncastuximab tesirine for female participants with childbearing potential from 6 to 9 months to align with current regulatory guidance.
Protocol Amendment 1.0	25 Nov 2020	The primary reason for Protocol Amendment 1 was to incorporate the changes in response to the US FDA feedback. This amendment combines changes regarding safety monitoring, study stratification, and statistical analysis. In addition, updates include removal of QTcF eligibility criteria and dexamethasone equivalent as premedication, assigning ORR as key secondary endpoint, as well as modifications on PRO schedules.
Protocol Original	26 Aug 2020	

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List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AIDS	Acquired Immuno-deficiency Syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BID	twice daily
β-HCG	human chorionic gonadotropin
BOR	best overall response
C1D1	Cycle 1 Day 1
CAR-T	chimeric antigen receptor T-cell
CD	cluster of differentiation
[redacted]	[redacted]
CMH	Cochran–Mantel–Haenszel test
CI	confidence interval
CMV	cytomegalovirus
CR	complete response
CRO	contract research organization
CRR	Complete Response Rate
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOI	end of infusion
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQoL–5 Dimensions–5 Levels
EWB	emotional well-being
EZH2	enhancer of zeste homolog 2
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FL	follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index

Abbreviation	Definition
FSH	follicle stimulating hormone
FWB	functional well-being
GCP	Good Clinical Practice
[redacted]	[redacted]
GGT	gamma glutamyl transferase
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IV	Intravenous
ITT	intent-to-treat
MRI	magnetic resonance imaging
NHL	non-Hodgkin's lymphoma
ORR	overall response rate
OS	overall survival
PBD	pyrrolobenzodiazepine
PCR	polymerase chain reaction
PD	progressive disease
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PJP	Pneumocystis jirovecii pneumonia
PK	pharmacokinetic(s)
PR	partial response
PWB	physical well-being
R/R	relapsed or refractory
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
QT	measure between Q wave and T wave in the electrocardiogram
QTcF	Fridericia correction of the QT measure
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	standard of care
SoE	schedule of events
SJS	Stevens-Johnson syndrome
SmPC	Summary of Product Characteristics

Abbreviation	Definition
SWB	social/family well-being
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WBC	white blood cell
WOCBP	women of childbearing potential

Protocol Synopsis

Protocol Number:	ADCT-402-202
Title:	A Phase 2 Randomized Study of Loncastuximab Tesirine Versus Idelalisib in Patients with Relapsed or Refractory Follicular Lymphoma (LOTIS 6)
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 2
Indication:	Follicular lymphoma (FL)
Rationale:	Non-Hodgkin Lymphoma (NHL) is ranked as the 5th to 9th most common cancer in most countries worldwide, with almost 510,000 new cases estimated in 2018. Follicular lymphoma represents the 2nd most common subtype of NHL and ~20–25% of all new NHL diagnoses in western countries. While the majority of patients with FL will respond to initial therapy, almost all of them will relapse; thus, FL is considered incurable and is an area of significant unmet medical need. Loncastuximab tesirine (ADCT-402) is an antibody-drug conjugate (ADC) that has been designed to target and kill cluster of differentiation (CD)19-expressing malignant B-cells. CD19 is highly expressed in B-cell NHL, including FL. Data from a Phase 1 study of loncastuximab tesirine in relapsed or refractory (R/R) B-cell NHL shows significant activity of loncastuximab tesirine in heavily pretreated patients with R/R FL, with an overall response rate (ORR) of 78.6% and a complete response rate (CRR) of 64.3%. Median duration of response and median progression free survival were both not reached. Idelalisib is an inhibitor of phosphatidylinositol 3-kinase (PI3K). There are several PI3K inhibitors which are used in later-line treatment of R/R FL. The approved PI3K inhibitors have ORRs ranging from 42% to 59%, with substantially lower CRRs of 1% to 14%. Idelalisib was chosen as the comparator for this study as it is the PI3K inhibitor with the widest range of use.
Objectives:	**Primary Objective** To evaluate the efficacy of single agent loncastuximab tesirine compared to idelalisib in patients with relapsed or refractory follicular lymphoma. **Secondary Objectives** • To further evaluate the additional efficacy of single agent loncastuximab tesirine compared to idelalisib in patients with relapsed or refractory follicular lymphoma.

- To assess the safety profile of loncastuximab tesirine in patients with relapsed or refractory follicular lymphoma.
- To characterize the pharmacokinetics (PK) profile of loncastuximab tesirine.
- To evaluate the immunogenicity of loncastuximab tesirine.
- To evaluate the impact of loncastuximab tesirine treatment compared to idelalisib on patients-reported outcomes (PROs) (e.g., symptoms, functions, and overall health status).

Endpoints:

Primary Endpoint

Complete response rate according to the 2014 Lugano classification as determined by central review in patients with follicular lymphoma. Complete response rate is the proportion of patients with a best overall response (BOR) of complete response (CR) assessed prior to any subsequent anticancer treatment.

Secondary Endpoints

Key Secondary Endpoint

- Overall response rate (ORR) defined as the percentage of patients with a BOR of CR or partial response (PR) by central review assessed prior to any subsequent anticancer treatment.

Other Secondary Endpoints

- Progression free survival (PFS) defined as the time between the randomization date and the first documentation of recurrence, progression, or death.
- Overall survival (OS) defined as the time between the randomization date and death from any cause.
- Duration of response (DOR) defined as the time from the documentation of tumor response to disease progression or death.
- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs).
- Changes from baseline of safety laboratory values, vital signs, 12-lead electrocardiogram (ECG), and Eastern Cooperative Oncology Group (ECOG) performance status.

- Concentrations and PK parameters of loncastuximab tesirine total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated warhead SG3199.
- Anti-drug antibody (ADA) titers
- Change from baseline in PROs as measured by EuroQol–5 Dimensions–5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym).
- The occurrence, severity, and interference of specific symptomatic adverse events selected from Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

Study Design:

This is a prospective, randomized, 2-arm, multi-center, and open-label Phase 2 study in patients with R/R FL. The study will enroll approximately 150 patients. Eligible patients will be randomly assigned to treatment with loncastuximab tesirine or idelalisib in a 2:1 ratio. The randomization will be stratified based on time since last systemic therapy (≤2 years vs >2 years). Block randomization with size of 3 will be used to generate the randomization list. The study will include a screening period (up to 28 days), a treatment period (cycles of 3 weeks for loncastuximab tesirine treatment and cycles of 4 weeks for idelalisib treatment) until disease progression/discontinuation of study treatment), and a follow-up period (for up to 3 years from end of treatment).

A non-binding futility analysis on the primary endpoint of CRR will be performed for the first 60 patients around 12 weeks after the 60th patient is randomized (enough time for 2 disease assessments).

Patient Selection:

Inclusion Criteria:

1. Written informed consent must be obtained prior to any study procedures.
2. Male or female patients aged 18 years or older, with pathologic diagnosis of follicular lymphoma (Grade 1, 2, 3A) in the most recent tumor biopsy.

3. Relapsed or refractory disease following two or more treatment regimens, at least one of which must have contained an anti-CD20 therapy.
4. Patients who have received previous CD19-directed therapy must have a biopsy which shows CD19 expression after completion of the CD19-directed therapy.
5. Measurable disease as defined by the 2014 Lugano Classification as assessed by positron emission tomography-computed tomography (PET-CT) or, if not FDG-avid, CT or magnetic resonance imaging (MRI).
6. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block (or minimum 10 freshly cut unstained slides if block is not available).

   Note: Any biopsy since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred.
7. ECOG performance status 0 to 2.
8. Adequate organ function as defined by screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$ (off growth factors at least 72 hours),
   b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 2 weeks,
   c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) $\leq 2.5 \times$ the upper limit of normal (ULN),
   d. Total bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's syndrome may have a total bilirubin up to $\leq 3 \times$ ULN).
   e. Calculated creatinine clearance ≥ 30 mL/min by the Cockcroft and Gault equation.

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

9. 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 study treatment. Men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of giving informed consent until at least 6 months after the patient receives his last dose of study treatment.

Exclusion Criteria:

1. Previous treatment with loncastuximab tesirine.
2. Previous treatment with idelalisib.
3. History of hypersensitivity to any of the excipients of loncastuximab tesirine or idelalisib.
4. Follicular lymphoma which has transformed to diffuse large B-cell lymphoma (DLBCL) or other aggressive lymphoma.
5. Requires treatment or prophylaxis with a strong cytochrome P450 (CYP) 3A inhibitor, inducer, or sensitive substrate.
6. History of or ongoing drug-induced pneumonitis.
7. History of or ongoing inflammatory bowel disease.
8. Any condition that could interfere with the absorption or metabolism of idelalisib including malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel.
9. 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.
10. Autologous transplant within 30 days prior to start of study treatment (C1D1).
11. Allogenic transplant within 60 days prior to start of study treatment (C1D1).
12. Active graft-versus-host disease.
13. Post-transplantation lymphoproliferative disorders.
14. Human immunodeficiency virus (HIV) seropositive with any of the following:
    a. CD4+ T-cell counts <350 cells/μL.

b. Acquired immuno-deficiency syndrome (AIDS)-defining opportunistic infection within 12 months prior to screening.

c. Not on anti-retroviral therapy, or on anti-retroviral therapy for <4 weeks at the time of screening.

d. HIV viral load ≥400 copies/mL.

15. Serologic evidence of chronic hepatitis B infection and unable or unwilling to receive standard prophylactic anti-viral therapy or with detectable hepatitis B virus (HBV) viral load.
16. Serologic evidence of hepatitis C infection without completion of curative treatment or with detectable hepatitis C virus (HCV) viral load.
17. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.
18. Lymphoma with active central nervous system involvement, including leptomeningeal disease.
19. 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).
20. Breastfeeding or pregnant.
21. Significant medical comorbidities, including but not limited to, uncontrolled hypertension (BP ≥160/100 mm Hg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease.
22. Any Grade ≥3 active infection which requires IV antibiotics, IV antiviral, or IV antifungal treatment.
23. Major surgery, radiotherapy, chemotherapy or other anti-neoplastic therapy within 14 days prior to start of study treatment (C1D1), except shorter if approved by the Sponsor.
24. Use of any other experimental medication within 30 days prior to start of study treatment (C1D1).
25. Live vaccine administration within 4 weeks prior to Cycle 1 Day 1.

26. Failure to recover to ≤ Grade 1 (Common Terminology Criteria for Adverse Events [CTCAE] v5.0) from acute non-hematologic toxicity (except ≤ Grade 2 neuropathy or alopecia) due to previous therapy prior to screening.
27. 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 (up to 28 days), a treatment period (cycles of 3 weeks for loncastuximab treatment arm and cycles of 4 weeks for idelalisib treatment arm), and a follow-up period (for up to 3 years after the end of treatment).

Patients may continue treatment until disease progression, unacceptable toxicity, or other discontinuation criteria, whichever occurs first.

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

Efficacy Assessments:

Disease assessments will be performed using PET-CT, as per Schedule of Events (SoE) until tumor progression. Additional disease assessments may be obtained, if clinically indicated.

Note: If disease is not FDG-avid at baseline, CT or MRI may be used for disease assessments. The assessment method determined to identify sites of disease at baseline should be used for all subsequent assessments.

Safety Assessments:

- Physical examination
- ECOG Performance status
- Height and weight
- Vital signs
- Safety laboratories (hematology, chemistry, coagulation, CMV tests, urinalysis)
- Pregnancy test, if applicable
- 12-Lead ECG (triplicate)
- AEs/SAEs, graded according to CTCAE version 5.0

Other Assessments:	• [redacted] • [redacted] • PROs: EQ-5D-5L, FACT-LYM, and specific symptomatic AEs selected from PRO CTCAE
Study Treatment, Dosage, and Mode of Administration:	**Loncastuximab Tesirine Treatment Arm:** Loncastuximab tesirine will be administered to patients assigned to loncastuximab tesirine arm as an IV infusion of 150 µg/kg every 3 weeks (Q3W) for 2 cycles, then 75 µg/kg Q3W for subsequent cycles. **Idelalisib Treatment Arm:** Patients assigned to idelalisib arm will take 150 mg idelalisib orally twice daily.
Statistical Considerations:	**Study Hypotheses:** Null hypothesis is that 1) there is no difference in CRR between the treatment arms. The alternative hypothesis is that loncastuximab tesirine improves CRR. 2) there is no difference in ORR between the treatment arms. The alternative hypothesis is that loncastuximab tesirine improves ORR. **Sample Size Justification:** Approximately 150 patients will be enrolled and randomly assigned to treatment with loncastuximab tesirine or idelalisib in a 2:1 ratio. The study is over-powered for primary efficacy endpoint, when a 55% of CRR in loncastuximab tesirine, (compared to observed 64.3% CRR in phase 1 trial), and 15% from idelalisib (Salles G, 2017) are assumed. The purpose of a larger sample size and 2:1 randomization ration is to provide safety evaluation on ~100 FL patients treated with loncastuximab tesirine per a regulatory agency request. **Statistical analysis:** The CR rate will be tested in the intent-to-treat population by using CMH method adjusting for stratification factor from randomization list. The point estimates for odds ratio and difference in CRR with 95% confidence interval (CI) will be presented. A non-binding futility analysis on the primary endpoint of CRR will be performed for the first 60 patients around 12 weeks after the 60th patient is randomized (enough time for 2 disease assessments).

O'Brien-Fleming spending function as the non-binding lower bound (futility) will be used.

Final analysis of the primary endpoint will take place 12 months after the last patient is randomized. The same method will be used.

If CRR is significantly different between two arms, the key secondary endpoint ORR will be tested sequentially using the same approach as CRR.

PFS, OS analysis will be performed using PROC LIFETEST, adjusting for stratification factor. Kaplan-Meier plot for PFS, OS, and DOR will be presented by treatment.

Subgroup analyses with age, gender, region, and other important baseline characteristics will be conducted for efficacy endpoint if proper.

Schedule of Events

Table 1. Schedule of Events for Loncastuximab Tesirine Arm

	Protocol Section	Screening	Treatment Period			EOT	Follow-up Period (up to 3 years from EOT) Every 12 weeks
(1 Cycle = 3 weeks)			**Cycle 1**	**Cycle 2**	**Cycle 3 & Beyond**		
Day (D)		**-28 to -1**	**1**	**1**	**1**		
Informed consent	7.1	X					
Randomization	4.2.2		X (D-1)				
Eligibility criteria	5	X					
Demography	7.2	X					
Medical/Cancer history	7.2	X					
[redacted]							
Physical examination	7.4.1	X	X	X	X	X	
ECOG performance status	7.4.2	X	X	X	X	X	
Height	7.4.3	X					
Weight	7.4.3	X	X	X	X	X	
Vital signs[2] (BP, HR, RR, Temp)	7.4.4	X	X	X	X	X	
Disease assessment[3,4]	7.3	Screening, 6 weeks and 12 weeks after C1D1, then every 12 weeks until 2 years from C1D1, then every 6 months.					
Hematology and Chemistry[5]	7.4.5	X	X	X	X	X	
Coagulation and Urinalysis	7.4.5	X					
HBV, HCV tests	7.4.5	X					
CMV IgG, Antigen or PCR test (all patients)[6]	7.4.5	X					
HIV tests	7.4.5	X					
Pregnancy test[7], if applicable	7.4.6	X	X	X	X	X	X[7] at ≥ 9 months post last loncastuximab tesirine dose
12-lead ECG (Triplicate)	7.4.7	X	X (Pre-dose)	X (Pre-dose), EOI-only for loncastuximab tesirine arm		X	
Pre-medication	6.4		D-1 to D2	D-1 to D2	D-1 to D2		

	Protocol Section	Screening	Treatment Period			EOT	Follow-up Period (up to 3 years from EOT) Every 12 weeks
(1 Cycle = 3 weeks)			**Cycle 1**	**Cycle 2**	**Cycle 3 & Beyond**		
Day (D)		**-28 to -1**	**1**	**1**	**1**		
Loncastuximab tesirine Administration (IV infusion)	6.2.2		X	X	X		
PK sample	7.5.1		X (Pre-dose and EOI)	X (Pre-dose and EOI)	X (C3-C6: Pre-dose and EOI; C7, then every other cycle: Pre-dose)	X	
ADA sample	7.5.2		X (Pre-dose)		X (C3, then every other cycle: Pre-dose)	X	X[8]
[redacted]							
Patient Reported Outcomes (EQ-5D-5L)	7.6.1		X	X	X	X	X[10] Up to 1 year from EOT

	Protocol Section	Screening	Treatment Period			EOT	Follow-up Period (up to 3 years from EOT) Every 12 weeks
(1 Cycle = 3 weeks)			**Cycle 1**	**Cycle 2**	**Cycle 3 & Beyond**		
Day (D)		**-28 to -1**	**1**	**1**	**1**		
Patient Reported Outcomes (FACT-Lym)	7.6.2		X	X	X C3-C18 only	X (only if EOT occurs prior to C19)	
PROs (GP-5 and items selected from PRO-CTCAE) **(Complete at home except C1D1)**	7.6.3 7.6.4		X[9] **Day 1 & Day 10**	X[9] **Day 10**	X[9] C3 – C9 only **Day 10**		
Concomitant medications	6.9	From ICF signature date or Day -14 whichever is earlier, until at least 30 days after last dose of study treatment					
Adverse events	8	AEs from ICF signature date until at least 30 days after last dose of study treatment; SAEs from ICF signature date until at least 76 days after last dose of study treatment or initiation of new anticancer therapy, whichever is earlier; thereafter only related SAEs					
1st new anticancer treatment							X
Survival							X

Abbreviations: ADA: anti-drug antibody; AE: adverse events; BP: blood pressure; β-HCG: β subunit of Human chorionic gonadotropin; C: cycle; C1D1: cycle 1 day 1; [redacted] CMV: cytomegalovirus; CT: computerized tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOT: end of treatment; FACT-Lym: The Functional Assessment of Cancer Treatment-Lymphoma questionnaire; FDG: (18)F-fluorodeoxyglucose; [redacted]; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HR: heart rate; ICF: informed consent form; IV: Intravenous; MRI: Magnetic resonance imaging; PCR: polymerase chain reaction; PK: pharmacokinetics; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RR: respiratory rate; SAE: serious AEs; Temp: temperature;.

Visit Scheduling Windows:

- Treatment Period: Visit day ± 3 days (excluding C1D1 which is the reference day).
- EOT: As soon as possible after decision to discontinue the study treatment but preferably at least 30 days after last dose of study treatment 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.

[redacted]

[2] Vitals should be taken at pre-dose and EOI for every loncastuximab tesirine dosing visit.

[3] Positron-emission tomography-computed tomography will be used to perform imaging study. If disease is not FDG-avid at baseline, CT or MRI may be used. Screening imaging must be performed within 4 weeks prior to C1D1 and the same assessment method must be used throughout the study. Week 6 and Week 12 imaging should be performed within ±5 days of the scheduled timepoint. All other imaging for disease assessment should be performed within ±2 weeks of the

scheduled time point. Imaging for disease assessment should be performed at the scheduled timepoint even if drug dosing is delayed. Additional disease assessments may be obtained, if clinically indicated.

[4] During follow-up period disease assessments to be performed in patients who discontinued study treatment for reasons other than disease progression or initiation of other anti-cancer therapy (except for hematopoietic stem cell transplant).

[5] ≤3days prior to administration of study treatment for loncastuximab tesirine arm patients.

[6] CMV tests include CMV IgG and CMV antigen or PCR test at screening visit for all patients.

[7] Serum or urine β-HCG test to be done on every visit at local lab if applicable. If the urine pregnancy test is positive, a serum β-HCG test is required for confirmation. Remote pregnancy test is acceptable when patient has no required site visit planned during follow-up period. Additional tests may be obtained, if needed.

[8] Only patients who test positive for ADAs may be asked to provide additional ADA samples every 12 weeks until the ADA titer falls to the baseline level.

[9] Patients will complete PRO-CTCAE items and GP-5 at study site on C1D1; at home on Day 10 (± 2 day) of each cycle for up to Cycle 9.

[10] In the event that patients complete follow up visit at home instead of being on site, EQ-5D-5L will be completed on Visit day (+2 days).

Table 2. Schedule of Events for Idelalisib Arm

	Protocol Section	Screening	Treatment Period			EOT	Follow-up Period (up to 3 years from EOT) Every 12 weeks
(1 Cycle = 4 weeks)			**Cycle 1 to Cycle 7**		**Cycle 8 & Beyond**		
Day (D)		**-28 to -1**	**1**	**15**	**1**		
Informed consent	7.1	X					
Randomization	4.2.2		X C1 only (D-1)				
Eligibility criteria	5	X					
Demography	7.2	X					
Medical/Cancer history	7.2	X					
[redacted]							
Physical examination	7.4.1	X	X		X	X	
ECOG performance status	7.4.2	X	X		X	X	
Height	7.4.3	X					
Weight	7.4.3	X	X		X	X	
Vital signs[2] (BP, HR, RR, Temp)	7.4.4	X	X		X	X	
Disease assessment[3,4]	7.3	Screening, 6 weeks and 12 weeks after C1D1, then every 12 weeks until 2 years from C1D1, then every 6 months.					
Hematology[5]	7.4.5	X	X	X	X	X	
Chemistry[5]	7.4.5	X	X	AST/ALT/total bilirubin - C1 to C4 only	X	X	
Coagulation and Urinalysis	7.4.5	X					
HBV, HCV tests	7.4.5	X					
CMV IgG, Antigen or PCR test (all patients)[6]	7.4.5	X					
CMV Antigen or PCR test (for patients with positive CMV tests or history of CMV infection)[7]	7.4.5		X		X	X	
HIV tests	7.4.5	X					
Pregnancy test[8], if applicable	7.4.6	X	X		X	X	

	Protocol Section	Screening	Treatment Period			EOT	Follow-up Period (up to 3 years from EOT) Every 12 weeks
(1 Cycle = 4 weeks)			**Cycle 1 to Cycle 7**		**Cycle 8 & Beyond**		
Day (D)		**-28 to -1**	**1**	**15**	**1**		
12-lead ECG (Triplicate)	7.4.7	X	X C1-C2 only (Pre-dose)			X	
Idelalisib Administration	6.2.2		Twice daily orally				
[redacted]							
Patient Reported Outcomes (EQ-5D-5L)	7.6.1		X		X	X	X[10] Up to 1 year from EOT
Patient Reported Outcomes (FACT-Lym)	7.6.2		X		X C8-C18 only	X (only if EOT occurs prior to C19)	
PROs (GP-5 and items selected from PRO-CTCAE) **(Complete at home except C1D1)**	7.6.3 7.6.4		X[9] **Day 1 & Day 10 for C1, then D10 for C2-C7**				
Concomitant medications	6.9	From ICF signature date or Day -14 whichever is earlier, until at least 30 days after last dose of study treatment					
Adverse events	8	AEs from ICF signature date until at least 30 days after last dose of study treatment; SAEs from ICF signature date until at least 76 days after last dose of study treatment or initiation of new anticancer therapy, whichever is earlier; thereafter only related SAEs					
1st new anticancer treatment							X
Survival							X

Abbreviations: AE: adverse events; BP: blood pressure; β-HCG: β subunit of Human chorionic gonadotropin; C: cycle; C1D1: cycle 1 day 1; [redacted]; CMV: cytomegalovirus; CT: computerized tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOI: end of infusion; EOT: end of treatment; FACT-Lym: The Functional Assessment of Cancer Treatment-Lymphoma questionnaire; FDG: (18)F-fluorodeoxyglucose; [redacted]; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HR: heart rate; ICF: informed consent form; IV: Intravenous; MRI: Magnetic resonance imaging; PCR: polymerase chain reaction; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RR: respiratory rate; SAE: serious AEs; Temp: temperature.

Visit Scheduling Windows:

- Treatment Period: Visit day ± 3 days (excluding C1D1 which is the reference day).
- EOT: As soon as possible after decision to discontinue the study treatment but preferably at least 30 days after last dose of study treatment 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.

[redacted]

[2] Vitals could be taken regardless of dosing time on the visit day.

[3] Positron-emission tomography-computed tomography will be used to perform imaging study. If disease is not FDG-avid at baseline, CT or MRI may be used. Screening imaging must be performed within 4 weeks prior to C1D1 and the same assessment method must be used throughout the study. Week 6 and Week 12 imaging should be performed within ±5 days of the scheduled timepoint. All other imaging for disease assessment should be performed within ±2 weeks of the scheduled time point. Imaging for disease assessment should be performed at the scheduled timepoint even if drug dosing is delayed. Additional disease assessments may be obtained, if clinically indicated.

[4] During follow-up period disease assessments to be performed in patients who discontinued study treatment for reasons other than disease progression or initiation of other anti-cancer therapy (except for hematopoietic stem cell transplant).

[5] Safety lab sample collection on visit days may occur at any time during the visit.

[6] CMV tests include CMV IgG and CMV antigen or PCR test at screening visit for all patients.

[7] CMV antigen or PCR test for patients with positive CMV serology or history of CMV infection who are receiving treatment with idelalisib.

[8] Serum or urine β-HCG test to be done on every visit at local lab if applicable. If the urine pregnancy test is positive, a serum β-HCG test is required for confirmation. Additional tests may be obtained, if needed.

[9] Patients will complete PRO-CTCAE items and GP-5 at study site on C1D1; at home on Day 10 (± 2 day) of each cycle for up to Cycle 7.

[10] In the event that patients complete follow up visit at home instead of being on site, EQ-5D-5 will be completed on Visit day (+2 days).

1 Introduction and Background

1.1 Disease Background

Non-Hodgkin Lymphoma (NHL) is ranked as the 5th to 9th most common cancer in most countries worldwide, with almost 510,000 new cases estimated in 2018 (Miranda-Filho, 2019). Follicular lymphoma (FL) represents the 2nd most common subtype of NHL and ~20–25% of all new NHL diagnoses in western countries (Carbone, 2019). In the United States (US), the annual incidence of FL was 2.7 per 100,000 on 2017 (Howlader N, 2020). In Western Europe, the annual incidence of FL has rapidly increased during recent decades and has risen from 2–3/100,000 during the 1950s to 5/100,000 recently (Mounier M, 2015). While the majority of patients with FL will respond to initial therapy, almost all of them will relapse; thus, FL is considered incurable (Hiddeman, 2014) and is an area of significant unmet medical need.

Currently approved therapies for relapsed/refractory (R/R) FL include lenalidomide combined with rituximab and obinutuzumab combined with bendamustine, both of which have full approval in second line, and the phosphatidylinositol 3-kinase (PI3K) inhibitors (idelalisib, copanlisib, and duvelisib), all of which have accelerated approval in third line in US. Idelalisib is only PI3K inhibitor received accelerated approval by Europe Medicines Agency (EMA). In addition, the enhancer of zeste homolog 2 (EZH2) inhibitor tazemetostat received US Food and Drug Administration (FDA) accelerated approval for adult patients with R/R FL whose tumors are positive for an EZH2 mutation and who have received at least 2 prior systemic therapies, and for adult patients with R/R FL who have no satisfactory alternative treatment options. Standard first-line therapy uses immuno-chemotherapy. Although current front-line regimens for Stages III and IV FL such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus obinutuzumab or rituximab, or bendamustine plus obinutuzumab or rituximab are associated with high response rates, most patients still relapse. The approved second line therapies have overall response rates (ORRs) ranging from 59% to 80%, with complete response rates (CRRs) ranging from 16% to 46% (Gazyva® US- Prescribing Information; Revlimid® US-Prescribing Information; Andorsky 2019; Leonard 2019). The approved PI3K inhibitors have ORRs ranging from 42% to 59%, with substantially lower CRRs of 1% to 14% (Zydelig® US- Prescribing Information; Aliqopa™ US- Prescribing Information; Copiktra® US- Prescribing Information). The approved EZH2 inhibitor tazemetostat has ORR 69% with CRR 12% for patients with EZH2 mutant, and ORR 34% with CRR 4% for patients with EZH2 wild-type (TAZVERIK™ US- Prescribing Information). There are a number of agents available for second-line therapy, including cytarabine-containing regimens and idelalisib. It has been reported idelalisib is effective in patients with high-risk FL and early relapse after initial immune-chemotherapy, with 56.8% ORR, 13.5% CRR, and 11.8 months duration of response (DOR) (Gopal et al., 2017).

However, FL is characterized by successive lines of therapy resulting in progressively shorter periods of disease-free survival followed ultimately by the development of either chemotherapy refractoriness, large cell transformation, or death from treatment-related

toxicities (Cheah, 2018). Thus, there remains unmet medical needs for novel drugs for patients with R/R FL.

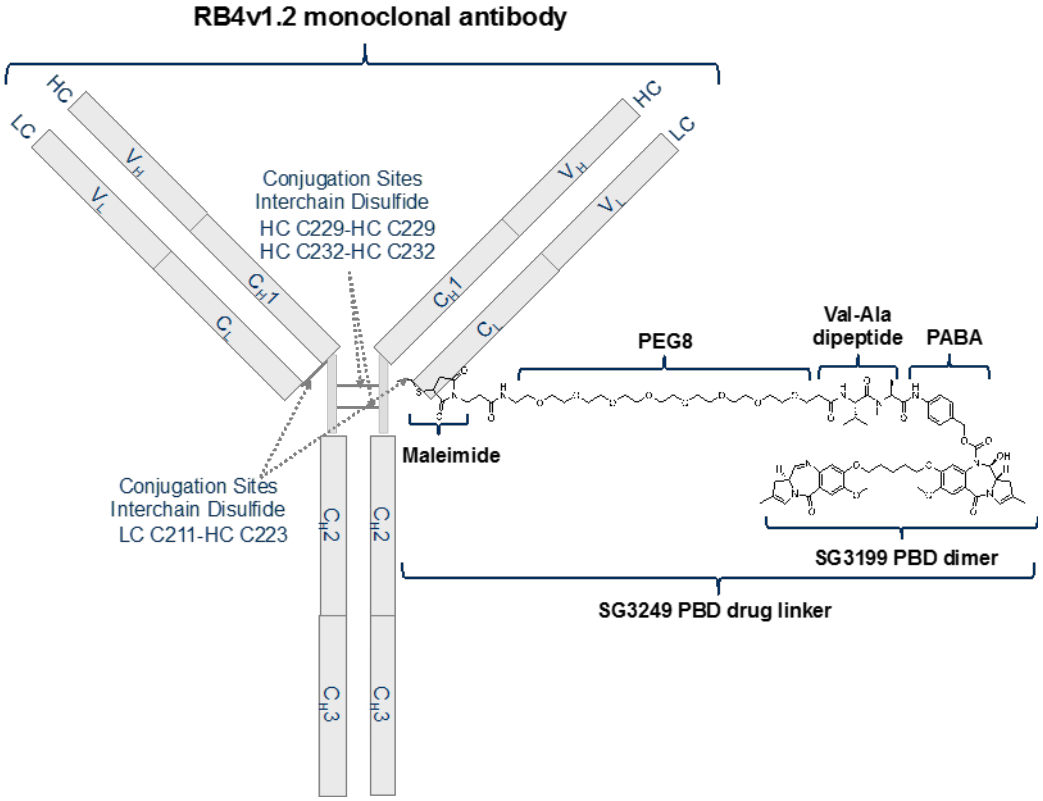
1.2 Description of the Study Drugs

1.2.1 Loncastuximab tesirine (ADCT-402)

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; HC=heavy chain; LC=light chain; PABA=para-aminobenzoic acid; PBD=Pyrrolobenzodiazepine; PEG=polyethylene glycol; RB4v1.2=human monoclonal antibody being studied; Val=valine.

Loncastuximab tesirine binds with picomolar affinity to human CD19. After binding and internalization, loncastuximab tesirine traffics to the lysosomes, where the protease-sensitive linker is cleaved and unconjugated PBD dimers (SG3199) are released inside the target cell. The released PBD dimers bind in the minor groove of DNA and form potent cytotoxic DNA

interstream 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, 2017; Beck et al, 2017).

More detailed information about loncastuximab tesirine may be found in the Investigator's brochure (Loncastuximab tesirine IB).

1.2.2 Idelalisib

Idelalisib is a small molecule, an inhibitor of PI3K. Idelalisib induced apoptosis and inhibited proliferation in cell lines derived from malignant B-cells and in primary tumor cells. Idelalisib inhibits several cell signaling pathways, including B-cell receptor signaling and the CXCR4 and CXCR5 signaling, which are involved in trafficking and homing of B-cells to the lymph nodes and bone marrow. Treatment of lymphoma cells with idelalisib resulted in inhibition of chemotaxis and adhesion, and reduced cell viability.

More detailed information about idelalisib may be found in the idelalisib prescribing information or Summary of Product Characteristics (Idelalisib® US- Prescribing Information; Idelalisib-SmPC).

1.2.3 Clinical Study Data for Loncastuximab Tesirine and Idelalisib

Loncastuximab tesirine

ADCT-402-101 (NCT02669017, https://clinicaltrials.gov/ct2/show/NCT02669017), was a first-in-human Phase 1 dose-escalation study of loncastuximab tesirine in R/R B-cell NHL patients. The data from this study showed loncastuximab tesirine exhibits significant anti-tumor activity in heavily pretreated patients with R/R FL, with an ORR of 78.6% and a CRR of 64.3%. Median duration of response and median progression free survival (PFS) were both not reached.

Toxicity was manageable, with the most common Grade ≥3 treatment-emergent adverse events (TEAEs) being Gamma-glutamyl transferase (GGT) increased (21.3%); neutropenia (16.9%); anemia (15.3%); neutrophil count decreased (14.8%); thrombocytopenia (12.0%); platelet count decreased (10.4%); blood alkaline phosphatase (ALP) increased (6.6%); lymphocyte count decreased (6.6%); disease progression (6.0%); febrile neutropenia (5.5%); and hypokalemia (5.5%) (Loncastuximab tesirine IB)

Idelalisib

Idelalisib is the only PI3K inhibitor approved by FDA and EMA as monotherapy for the treatment of adult patients with FL that is R/R to two prior lines of treatment.

In Study 101-09 (NCT01282424, https://clinicaltrials.gov/ct2/show/NCT01282424), 72 patients with FL received 150 mg of idelalisib orally twice (BID) daily until evidence of disease progression or unacceptable toxicity. The ORR was 55.6% and CRR was 16.7%. The median PFS was 11.0 months (range 8.0–14.0), and the median DOR was 11.8 months (range 6.2- 26.9) (Idelalisib -SmPC).

The most common Grade ≥3 TEAEs in 125 adults with indolent non-Hodgkin lymphoma treated with idelalisib 150 mg BID in clinical trials were elevated transaminases (21%), diarrhea (13%), neutropenia (27%), pneumonia (7%), and thrombocytopenia (6%) (Gopal et al, 2014).

1.3 Benefit/Risk Assessment

The primary benefit for this study is that of effective treatment for lymphoma, although this benefit is not guaranteed. The primary risk of this study is the toxicities from the treatment; for loncastuximab tesirine, the most common adverse reactions are gamma-glutamyl transferase increased, neutropenia, thrombocytopenia, fatigue, anemia, nausea, cough, edema, and blood ALP increased, and for idelalisib the most common adverse reactions are diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, and rash and the most common laboratory abnormalities are neutropenia, alanine aminotransferase (ALT) elevations, and aspartate aminotransferase (AST) elevations. It is expected that the potential benefit of effective treatment will outweigh the potential toxicities, providing a positive risk/benefit ratio.

2 Study Rationale

Non-Hodgkin Lymphoma is ranked as the 5th to 9th most common cancer in most countries worldwide, with almost 510,000 new cases estimated in 2018. Follicular lymphoma represents the 2nd most common subtype of NHL and ~20–25% of all new NHL diagnoses in western countries. While the majority of patients with FL will respond to initial therapy, almost all of them will relapse; thus, FL is considered incurable and is an area of significant unmet medical need.

Loncastuximab tesirine (ADCT-402) is an antibody drug conjugate (ADC) that has been designed to target and kill CD19-expressing malignant B-cells. CD19 is highly expressed in B-cell NHL, including follicular lymphoma. Data from a Phase 1 study of loncastuximab tesirine in relapsed or refractory B-cell NHL showed significant activity of loncastuximab tesirine in heavily pretreated patients with relapsed/refractory follicular lymphoma, with an ORR of 78.6% and a CRR of 64.3%. Median DOR and median PFS were both not reached. Data from loncastuximab tesirine studies demonstrated an acceptable safety profile to date and a positive risk-benefit for further evaluation in R/R FL.

2.1 Rationale for Study Design

This is a Phase 2, randomized, 2-arm, and open-label study and will enroll approximately 150 patients. Eligible patients will be randomly assigned to treatment with loncastuximab tesirine or idelalisib in a 2:1 ratio. The randomization will be stratified based on time since last systemic therapy (≤2 years vs >2 years). A randomized trial design was chosen as this is a well-recognized standard for evaluating new treatments. The study is an open label trial as the primary endpoint is tumor response as determined by central review, which is unlikely to be affected by investigator or subject knowledge of treatment assignment. The sample size is driven by a regulatory agency request to have safety data on ~100 FL patients treated with loncastuximab tesirine. With 100 patients treated in the loncastuximab tesirine arm and complete response rate as the primary endpoint, the study would be substantially overpowered with a standard 1:1 randomization scheme, so a 2:1 randomization is used to limit the number of patients required to complete the study, which still results in a power of >99%.

Idelalisib was chosen as the comparator for this study as it is the only PI3K inhibitor currently approved for treatment of R/R FL in both the US and Europe.

2.2 Rationale for Dose Selection

Loncastuximab tesirine will be administered intravenously (IV) at a dose of 150 µg/kg every 3 weeks for 2 doses, then at a dose of 75 µg/kg every 3 weeks at the subsequent doses.

The initial dose of 150 µg/kg every 3 weeks (Q3W) was based on the observation that response rate in patients treated in the Phase 1 trial appeared to increase with increasing exposure, but toxicity was substantially increased at 200 µg/kg compared to lower dose levels. Thus, 150 µg/kg was chosen as the highest initial dose with acceptable toxicity. The dose reduction after 2 cycles was based on the fact that a substantial portion of patients treated on the Phase 1 trial required dose reduction after 2 or more cycles, usually as a result of prolonged dose delays

because of adverse events (AEs). Decreasing the dose after 2 cycles was intended to reduce the incidence of dose delay and reduce the need for further dose reduction. This dosing regimen has been used in 145 patients in a Phase 2 study of loncastuximab tesirine in patients with R/R diffuse large B-cell lymphoma (R/R DLBCL) and appears to be well-tolerated with a manageable toxicity profile and comparable efficacy to that achieved in a similar patient population in Phase 1.

3 Study Objectives and Endpoints

Table 3. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of single agent loncastuximab tesirine compared to idelalisib in patients with relapsed or refractory follicular lymphoma.	Complete response rate (CRR) according to the 2014 Lugano classification as determined by central review in patients with FL. Complete response rate is the proportion of patients with a best overall response (BOR) of complete response (CR) assessed prior to any subsequent anticancer treatment.
Secondary	
To further evaluate the additional efficacy of single agent loncastuximab tesirine compared to idelalisib in patients with relapsed or refractory follicular lymphoma.	Key Secondary Endpoint • Overall response rate (ORR) defined as the percentage of patients with a BOR of CR or partial response (PR) by central review assessed prior to any subsequent anticancer treatment. Other Secondary Endpoints • Progression free survival (PFS) defined as the time between the randomization date and the first documentation of recurrence, progression, or death. • Overall survival (OS) defined as the time between the randomization date and death from any cause. • Duration of response (DOR) defined as the time from the documentation of tumor response to disease progression or death.
To assess the safety profile of loncastuximab tesirine in patients with relapsed or refractory follicular lymphoma.	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs). • Changes from baseline of safety laboratory values, vital signs, 12-lead electrocardiogram (ECG), and Eastern Cooperative Oncology Group (ECOG) performance status.

Objectives	Endpoints
To characterize the pharmacokinetics (PK) profile of loncastuximab tesirine.	Concentrations and PK parameters of loncastuximab tesirine total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated warhead SG3199.
To evaluate the immunogenicity of loncastuximab tesirine.	Anti-drug antibody (ADA) titers
To evaluate the impact of loncastuximab tesirine treatment compared to idelalisib on patients-reported outcomes (PROs) (eg, symptoms, functions, and overall health status).	• Change from baseline in PROs as measured by EuroQol–5 Dimensions–5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) • The occurrence, severity, and interference of specific symptomatic adverse events selected from Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

4 Study Design

4.1 Overview

This is a prospective, randomized, 2-arm, multi-center, and open-label Phase 2 study in patients with R/R FL. The study will enroll approximately 150 patients. Eligible patients will be randomly assigned to treatment with loncastuximab tesirine or idelalisib in a 2:1 ratio. A block randomization with stratification based on time since last systemic therapy (≤2 years vs >2 years) will be used. A non-binding futility analysis on the primary endpoint of CRR will be performed for the first 60 patients around 12 weeks after the 60th patient is randomized (enough time for 2 disease assessments). 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 (up to 28 days), a treatment period (cycles of 3 weeks for loncastuximab tesirine treatment and cycles of 4 weeks for idelalisib treatment), and a follow-up period (approximately every 12 weeks visits) for up to 3 years from treatment discontinuation (Section 4.2, study periods).

4.2 Study Periods

4.2.1 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 SOC may be used to satisfy screening requirements if they are performed in the appropriate window.

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

See Section 5.3 for the information to be collected on screening failures.

4.2.2 Randomization

Patients who are eligible will be randomized via Interactive Response Technology (see Interactive Response Technology manual for details). The randomization will be stratified based on time since last systemic therapy (≤2 years vs >2 years). Block randomization with size of 3 will be used to generate the randomization list. Approximately 150 patients will be randomized (2:1 ratio) to receive either loncastuximab tesirine or idelalisib. For details on randomization steps and for treatment assignment, see Section 6.3.

4.2.3 Treatment Period

The treatment period will start on the date when a patient is administered the first dose of study treatment and continues until the end of treatment (EOT) visit (see below).

A treatment cycle is defined as 3 weeks (i.e., 21 days) for patients assigned to loncastuximab tesirine treatment. A treatment cycle is defined as 4 weeks (i.e., 28 days) for patients assigned to idelalisib treatment. Patients will receive either IV loncastuximab tesirine on Day 1 of each cycle, or idelalisib 150 mg BID orally Days 1-28 every cycle. Patients may continue treatment until disease progression, unacceptable toxicity, death, or other discontinuation criteria, whichever occurs first.

4.2.4 End of Treatment

An EOT visit should be performed as soon as possible after the decision to discontinue the study treatment, but preferably at least 30 days after last dose of study treatment 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.

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

4.2.5 Follow-up Period

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

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

4.2.6 End of Study

The end of study (EOS) occurs at the last scheduled visit/procedure for the last patient, unless the study is terminated earlier by Sponsor. The death date will be considered as the EOS date for an individual patient whose survival status was informed at any later contact date.

4.3 Study Stopping Rules

Once at least 15 patients have been treated with idelalisib, study enrollment will be paused for safety evaluation if any of the following occur:

1. The number of patients with reported Grade 5 toxicity in the loncastuximab tesirine arm is more than twice the number of patients with reported Grade 5 toxicity in the idelalisib arm.
2. Grade 4 skin toxicity is reported in >2 patients treated with loncastuximab tesirine and the incidence of Grade 4 skin toxicity in patients treated with loncastuximab tesirine is >5% and the incidence is at least 50% higher than the incidence in patients treated with idelalisib.
3. Grade 4 toxicity of edema or effusion is reported in >2 patients treated with loncastuximab tesirine and the incidence of Grade 4 toxicity of edema or effusion in patients treated with loncastuximab tesirine is >5% and at least 50% higher than the incidence in patients treated with idelalisib.

Safety evaluation will be performed by ADCT.

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 during Screening, unless otherwise specified.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

1. Written informed consent must be obtained prior to any study procedures.
2. Male or female patients aged 18 years or older, with pathologic diagnosis of FL (Grade 1, 2, 3A) in the most recent tumor biopsy.
3. Relapsed or refractory disease following two or more treatment regimens, at least one of which must have contained an anti-CD20 therapy.
4. Patients who have received previous CD19-directed therapy must have a biopsy which shows CD19 expression after completion of the CD19-directed therapy.
5. Measurable disease as defined by the 2014 Lugano Classification as assessed by PET-CT or, if not FDG avid, CT or magnetic resonance imaging (MRI).
6. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block (or minimum 10 freshly cut unstained slides if block is not available).

   Note: Any biopsy since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
8. Adequate organ function as defined by screening laboratory values within the following parameters:
   a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^3/\mu L$ (off growth factors at least 72 hours),
   b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 2 weeks,
   c. Alanine aminotransferase, AST, and GGT $\leq 2.5 \times$ the upper limit of normal (ULN),
   d. Total bilirubin $\leq 1.5 \times$ ULN (patients with known Gilbert's syndrome may have a total bilirubin up to $\leq 3 \times$ ULN).
   e. Calculated creatinine clearance ≥ 30 mL/min by the Cockcroft and Gault equation.

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

9. Women of childbearing potential (WOCBP)* 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 study treatment. Men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of giving informed consent until at least 6 months after the patient receives his last dose of study treatment.

   * 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. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

   ** 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 associated with inhibition of ovulation (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.

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

5.2 Exclusion Criteria

1. Previous treatment with loncastuximab tesirine.
2. Previous treatment with idelalisib.
3. History of hypersensitivity to any of the excipients of loncastuximab tesirine or idelalisib.
4. Follicular lymphoma which has transformed to DLBCL or other aggressive lymphomas.
5. Requires treatment or prophylaxis with a strong cytochrome P450 (CYP) 3A inhibitor, inducer, or sensitive substrate.
6. History of or ongoing drug-induced pneumonitis.
7. History of or ongoing inflammatory bowel disease.
8. Any condition that could interfere with the absorption or metabolism of idelalisib including malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel.

9. 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.
10. Autologous transplant within 30 days prior to start of study treatment (C1D1).
11. Allogenic transplant within 60 days prior to start of study treatment (C1D1).
12. Active graft-versus-host disease.
13. Post-transplantation lymphoproliferative disorders.
14. Human immunodeficiency virus (HIV) seropositive with any of the following:
    a. CD4+ T-cell counts <350 cells/μL.
    b. Acquired immuno-deficiency syndrome (AIDS)-defining opportunistic infection within 12 months prior to screening.
    c. Not on anti-retroviral therapy, or on anti-retroviral therapy for < 4 weeks at the time of screening.
    d. HIV viral load ≥400 copies/mL.
15. Serologic evidence of chronic hepatitis B infection and unable or unwilling to receive standard prophylactic anti-viral therapy or with detectable hepatitis B virus (HBV) viral load.
16. Serologic evidence of hepatitis C infection without completion of curative treatment or with detectable hepatitis C virus (HCV) viral load.
17. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.
18. Lymphoma with active central nervous system involvement, including leptomeningeal disease.
19. 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).
20. Breastfeeding or pregnant.
21. Significant medical comorbidities, including but not limited to, uncontrolled hypertension (BP ≥160/100 mm Hg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 6 months prior to screening, uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease.
22. Any Grade ≥3 active infection which requires IV antibiotics, IV antiviral, or IV antifungal treatment.
23. Major surgery, radiotherapy, chemotherapy or other anti-neoplastic therapy within 14 days prior to start of study treatment (C1D1), except shorter if approved by the Sponsor.

24. Use of any other experimental medication within 30 days prior to start of study treatment (C1D1).
25. Live vaccine administration within 4 weeks prior to Cycle(C) 1 Day (D) 1.
26. Failure to recover to ≤ Grade 1 (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) from acute non-hematologic toxicity (except ≤Grade 2 neuropathy or alopecia) due to previous therapy prior to screening.
27. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.

5.3 Screening Failures

Patients who signed the ICF but were found not eligible for the study prior to receiving study treatment 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
- Serious adverse event (SAE) and/or death occurring during the Screening Period
- Screen fail (documenting primary reason for screen failure)

5.4 Re-screening Procedures

A patient who did not meet the eligibility criteria (screen failure) may be considered for re-screening. Decision for re-screening must be confirmed by the Sponsor/Medical monitor. A re-screened patient should be assigned a new patient number.

Participants who are rescreened are required to sign a new ICF.

5.5 Discontinuation

The reason for discontinuation, whether it is from study treatment or from study, 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.

5.5.1 Discontinuation from Study Treatment

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

- Disease Progression
- Adverse events
- Patient decision

- Physician decision
- Major protocol deviation
- Lost to follow-up
- Study termination by the Sponsor

A patient must discontinue from the study drug for any of the following reasons:

- Pregnancy
- Death

The reason(s) patients initiate subsequent anti-lymphoma therapy should be captured.

IMPORTANT: Study treatment discontinuation is not equivalent to discontinuation from the study. Patients discontinuing the study treatment will be asked to perform an EOT visit (Section 4.2.4) and continue with the Follow-up period (Section 4.2.5) 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.

5.5.2 Discontinuation from the Study

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

- Study completion
- Withdrawal of consent
- Physician decision
- Lost to follow-up
- Study termination by the Sponsor
- Death

If a patient withdraws informed consent for study participation, no additional study data will be collected.

The Sponsor may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The study may be terminated at any time, for any reason, by the Sponsor. Patients still receiving study treatment should have an EOT visit as described in Section 4.2.4 and Schedule of Events (SoE) (Table 1 or Table 2).

5.5.3 Lost 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.

5.5.4 Patient Replacements

Any patient who is randomized will not be replaced.

6 Study Treatment

6.1 Study Drugs

Loncastuximab tesirine is an investigational medicinal product for this trial. It will be supplied by the study sponsor. Idelalisib is the comparator regimen in the study. Idelalisib will be supplied by the Sponsor when required by applicable local laws and regulations.

6.1.1 Loncastuximab tesirine

Loncastuximab tesirine will be provided as a lyophilized white to off-white powder in 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, this 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. Sterile Water for Injection is to be provided by study sites. See the Pharmacy Manual for additional details on dose handling and administration.

6.1.2 Idelalisib

Idelalisib tablets are for oral administration. Each tablet contains either 100 mg or 150 mg of idelalisib with the following inactive ingredients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, and a tablet coating. The tablet coating consists of polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide and of FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake (for the 100 mg tablet) and red iron oxide (for the 150 mg tablet). See the Pharmacy Manual/ idelalisib Prescribing Information/SmPC for additional details on dose handling and administration.

6.2 Management of Clinical Supplies

The investigator or designee must confirm appropriate temperature conditions have been maintained for study drug(s) received and any discrepancies are reported as instructed in the pharmacy manual.

Study drug(s) must be stored in a secure, monitored (manual or automated) area in accordance with the storage conditions specified in the pharmacy manual with access limited to authorized site staff.

The investigator or designee is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Detailed instructions regarding study treatment shipment, handling, storage, preparation, administration, and final disposition of unused study treatment are included in the study pharmacy manual and in the prescribing information or SmPC for idelalisib.

6.2.1 Packaging and Storage

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

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

Study drugs must be stored according to the pharmacy manual/prescribing information or SmPC, in a secure area.

Loncastuximab tesirine will be provided as a refrigerated lyophilized formulation, and stored at 2-8°C. Loncastuximab tesirine should be stored in the original box to protect from long-term exposure to light. Light protection is not required for dose preparation and during administration of the diluted drug in the IV bag.

Refer to the IB (loncastuximab tesirine), prescribing information or SmPC (idelalisib), and pharmacy manual for storage instructions.

6.2.2 Preparation and Administration

Loncastuximab tesirine

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 diluted will depend on the dose level and the body mass of the patient. The weight of the patient at C1 D1 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 C1 D1, then the dose should be recalculated. Additional details are included in the pharmacy manual.

Administration of loncastuximab tesirine will be performed by the Investigator or a qualified designee according to the pharmacy manual.

Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

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.

Idelalisib

Idelalisib is available as 100 mg and 150 mg oval-shaped tablets in a high-density polyethylene bottle with a polyester fiber coil, capped with a child-resistant closure. Each bottle contains 60 film-coated tablets and is to be dispensed only in original container.

If supplied through the study sufficient idelalisib will be dispensed until the next visit.

6.3 Study Treatment Assignment and Dosing

- Patients who are eligible will be randomized via Interactive Response Technology to either of the study treatment arms, loncastuximab tesirine or idelalisib in a 2:1 ratio. Loncastuximab Tesirine Arm: Administration of loncastuximab tesirine will be performed by the Investigator or a qualified designee. Patients will receive a 30 minutes IV infusion of loncastuximab tesirine on Day 1 of each cycle (150 µg/kg Q3W for 2 cycles, then 75 µg/kg Q3W for subsequent cycles).

  Refer to Section 6.4 for premedication and Section 6.8 for supportive care.

- Idelalisib Arm: Patients will receive 150 mg idelalisib tablet orally BID. Please refer to idelalisib prescribing information or idelalisib SmPC for detailed instructions.

6.4 Premedication

Unless contraindicated, administer dexamethasone 4 mg orally BID, the day before loncastuximab tesirine administration (if possible), the day of loncastuximab tesirine administration (give at least 2 hours prior to administration when not given the day before; otherwise any time prior to administration), and the day after loncastuximab tesirine administration. Dexamethasone may be given IV if clinically indicated.

Patients who experience an infusion-related hypersensitivity reaction will receive the alternative premedication regimen specified in Section 6.8.2 for more details.

6.5 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense the study treatments only to patients enrolled in the study in accordance with the protocol. Compliance will be verified by the study treatment administration information recorded in the electronic data capture (EDC).

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

6.6 Definition and Management of Overdose

An overdose is any dose of study drug administered to the patient that exceeds the maximum dose described in the protocol by 15% or more. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor (see Section 8.5.3). There are no data available to determine what the effects of overdose of loncastuximab tesirine and idelalisib are and whether they can be reversed. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

If feasible, a sample for pharmacokinetic (PK) analysis should be taken as close as possible to the overdose event.

6.7 Dose Delays and Modifications

6.7.1 Dose Delays and Modifications for Loncastuximab Tesirine and Idelalisib

The criteria and guidance for dose delay and dose modifications of loncastuximab tesirine and idelalisib are summarized in Table 4 and Table 5, respectively.

Table 4. Criteria for Dose Delay or Dose Modification of Loncastuximab Tesirine

Toxicity	Loncastuximab Tesirine
Grade ≥3 non-hematologic adverse events	• Hold until the toxicity resolves to Grade ≤1, (Grade 1 or baseline for peripheral neuropathy) • If dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses must be reduced by 50%. If the toxicity recurs, subsequent doses must be reduced by an additional 50% • A maximum of 2 dose reductions are allowed • Note: Patients who have a toxicity meeting the criteria for dose reduction following Cycle 2 will receive the protocol-specified dose of 75 µg/kg for Cycle 3, i.e., they will not have an additional dose reduction for Cycle 3
Grade ≥2 edema, effusion	• Hold until the toxicity resolves to Grade ≤1 • If dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses must be reduced by 50%. If the toxicity recurs, subsequent doses must be reduced by an additional 50% • A maximum of 2 dose reductions are allowed • Note: Patients who have a toxicity meeting the criteria for dose reduction following Cycle 2 will receive the protocol-specified dose of 75 µg/kg for Cycle 3, i.e., they will not have an additional dose reduction for Cycle 3

Toxicity	**Loncastuximab Tesirine**
Grade ≥3 neutropenia or thrombocytopenia	• Hold until toxicity resolves to Grade ≤2 • If dosing is delayed by more than 3 weeks and the toxicity is considered at least possibly related to loncastuximab tesirine, then subsequent doses must be reduced by 50%. If the toxicity recurs, subsequent doses must be reduced by an additional 50% • A maximum of 2 dose reductions are allowed • Note: Patients who have a toxicity meeting the criteria for dose reduction following Cycle 2 will receive the protocol-specified dose of 75 µg/kg for Cycle 3, i.e., they will not have an additional dose reduction for Cycle 3
Grade 4 infusion related reaction	• 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

Table 5. Criteria for Dose Delay or Dose Modification of Idelalisib

Toxicity	Idelalisib
Grade ≥2 symptomatic pneumonitis of any severity	Permanently discontinue idelalisib
Grade 2 increased ALT/AST/bilirubin or diarrhea	Maintain idelalisib dose. Monitor at least weekly until normal
Grade 3 increased ALT/AST/bilirubin or diarrhea	Withhold idelalisib. Monitor at least weekly until normal, then may resume idelalisib at 100 mg BID.
Grade 4 increased ALT/AST/bilirubin or diarrhea	Discontinue idelalisib permanently
Grade 3 neutropenia and/or thrombocytopenia	Maintain Idelalisib dose. Monitor ANC and/or platelet count at least weekly
Grade 4 neutropenia and/or thrombocytopenia	Withhold idelalisib. Monitor ANC and/or platelet count at least weekly. When neutropenia and thrombocytopenia are Grade 3 or less, may resume idelalisib at 100 mg BID
Grade ≥3 sepsis or pneumonia	Withhold idelalisib until infection has resolved.
Active CMV infection of any grade or viremia (positive PCR or antigen test)	Withhold idelalisib until the infection and viremia have resolved. If idelalisib is resumed, monitor by PCR or antigen for CMV reactivation at least monthly.
Suspected PJP infection of any grade.	Withhold idelalisib. Permanently discontinue idelalisib if PJP infection is confirmed.
Other Grade ≥3 non-hematologic toxicities	Withhold idelalisib until resolved, then may resume idelalisib at 100 mg BID. If the same grade ≥3 toxicity recurs after resuming idelalisib, permanently discontinue idelalisib
Anaphylaxis, Intestinal Perforation, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Permanently discontinue idelalisib

Abbreviations: ALT=alanine aminotransferase; ANC= Absolute neutrophil count; AST=aspartate aminotransferase; BID=twice daily; CMV=cytomegalovirus; PCR=polymerase chain reaction; PJP=Pneumocystis jirovecii pneumonia.

Reference: Idelalisib® Prescribing Information For additional information on management of toxicities, please refer to the Investigator Brochure for loncastuximab tesirine and to the prescribing information or SmPC for idelalisib.

6.8 Supportive Care

Supportive care specific to loncastuximab tesirine are detailed in below subsections. Additional information is available in the loncastuximab tesirine IB. Supportive care for idelalisib should be provided based on the idelalisib prescribing information or SmPC, and/or according to institutional SOC.

6.8.1 Management of Edema and Serosal Effusion

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

6.8.2 Prevention and Management of Infusion-related Hypersensitivity Reactions

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

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

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

6.8.3 Prevention and Management of 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 hours. Also, fragrance-free detergents and soaps are recommended.

Treatment recommendations for skin toxicities include topical treatment to affected areas:

- Maculopapular rash or 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; and triamcinolone 0.1% and triamcinolone 0.1% cream BID.
- Blistering rash: silvadene 1% cream BID and consider laboratory testing for blistering disorder (Varicella Zoster Virus (VZV)/Herpes Simplex Virus (HSV) and bacterial infection; bullous pemphigoid; pemphigus)

Consideration should be given to corticosteroid therapy in patients who develop clinically significant skin toxicity. Also, for grade ≥2 skin toxicities consider a dermatology consult.

6.8.4 Contraceptive Guidance

Women of childbearing potential* must agree to use a highly effective method of contraception, and men with female partners who are of childbearing potential must agree to use a condom when sexually active or practice total abstinence from the time of giving informed consent until the study drug is safely cleared from the body. Please refer to Section 5.1 Inclusion Criterion #9 for information on the definition of WOCBP and recommended highly effective methods of contraception.

- For patients with loncastuximab tesirine treatment, if applicable, the highly effective birth control must be followed from the date of signing the ICF until at least 9 months after last dose of loncastuximab tesirine administration for WOCBP, and at least 6 months after the last dose of loncastuximab tesirine for male patients with female partners of reproductive potential.
- For patients with idelalisib treatment, if applicable, the highly effective birth control mut be followed from the date of signing the ICF until 1 month after the last dose of idelalisib for WOCBP, and 3 months after the last dose of idelalisib for male patients with female partners of reproductive potential.
- If WOCBP use hormonal contraceptives such as birth control pills, a second barrier method of contraception (e.g., condoms) must be used during idelalisib treatment until 1 month after last dose of idelalisib.

Please refer to Section 7.4.6 for pregnancy test, and Section 8.5.2 for reporting pregnancy.

6.8.5 Other Supportive Care

- Patients receiving idelalisib treatment should receive Pneumocystis jirovecii pneumonia (PJP) prophylaxis based on institutional standard of care.
- Patients receiving idelalisib and who have positive CMV serology or a history of CMV infection should be monitored for CMV viremia using CMV antigen or PCR. Patients who develop CMV viremia should have idelalisib held and CMV treatment based on institutional standard of 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.

6.9 Concomitant Medications and Procedures

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

6.9.1 Permitted During Study

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 6.9.2.

6.9.2 Prohibited During Study

The following treatments are prohibited during study treatment but are allowed in the follow-up period.

- Other anticancer therapy with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Other investigational agents
- Live vaccines until 3 months after last dose of study drug.
- In patient receiving idelalisib, strong CYP3A inducers/inhibitors and sensitive substrates should be avoided. Information on strong CYP3A inducers, inhibitors and sensitive substrates may be found in Section 12.3 (Appendix 3) or at http://medicine.iupui.edu/clinpharm/ddis/main-table/

7 Study Assessments and Procedures

Study assessments and procedures are to be completed as described below; however, there may be situations (e.g., safety issues) preventing their completion. In such case, the Investigator should take all actions necessary to ensure the safety and well-being of the patient and document the reason for not performing the assessment.

The Schedule of Events (SoE) tables are listed per treatment arm for the study. Table 1 is for loncastuximab tesirine arm and Table 2 is for idelalisib arm.

7.1 Informed Consent

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 may be used for determination of patient eligibility only if obtained as part of standard care. For additional details, please refer to Section 10.3.

7.2 Demographics and Baseline Characteristics

These assessments include:

- Demographic information such as age, gender, ethnicity, and race; to the extent allowed by local regulations.
- Cancer medical history, which includes a complete history of all surgeries and significant diagnoses, and all cancer treatments, including surgery, radiation therapy, chemotherapy, etc.
- Any significant medical history.
- Collection of information on prior medications used from ICF signature date or at least within 14 days prior to study drug administration, whichever is earlier.

7.3 Efficacy Assessments

Disease assessment will occur as per SoE (Table 1 or Table 2).

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

During the treatment period, imaging will be performed 6 weeks and 12 weeks after C1D1, then every 12 weeks until 2 years from C1D1, then every 6 months. Imaging for disease assessment will continue until disease progression or initiation of other anti-cancer therapy (except for hematopoietic stem cell transplant). Week 6 and Week 12 imaging should be performed within ±5 days of the scheduled time point; all other imaging should be performed within ±2 weeks of the scheduled time point. Disease assessments should take place at the timepoints specified even if study drug dosing is delayed. Additional disease assessments may be obtained, if clinically indicated.

Response data from investigators may be collected for patients who receive chimeric antigen receptor T cells (CAR-T) therapy until 90 days after receiving CAR-T therapy.

Positron emission tomography-computed tomography (PET-CT) of the neck/chest/abdomen/pelvis and other areas of known disease or newly suspected disease, as well as a clinical examination for lymphoma, will be performed. If it is known that the tumor is FDG-avid, the baseline CT as part of the PET-CT does not have to be performed with contrast medium; however, if the baseline PET-CT shows that the tumor is not FDG-avid, diagnostic CT with IV contrast will need to be obtained as a baseline examination. For this reason, if it is known that the tumor is not FDG-avid on previous imaging, consideration should be given to obtaining a diagnostic quality CT with IV contrast as part of the initial PET-CT examination. Patients who have a contraindication to CT IV contrast medium should have MRI examinations performed instead. The assessment method determined to identify sites of disease at Baseline (i.e., PET-CT, CT, MRI) should be used for all subsequent assessments.

Patients whose tumor is not FDG-avid should have a bone marrow biopsy as part of their baseline staging and disease assessment if clinically appropriate.

The patient's response to treatment will be determined according to the 2014 Lugano Classification Criteria (Appendix 2) as CR, PR, stable disease (SD), or progressive disease (PD). Patients with clinical progression should have a radiographic disease assessment to confirm progression unless contraindicated. Radiographic disease assessment modality should be the same as that used to identify sites of disease at Baseline.

Images will be obtained according to imaging requirements as outlined in the imaging manual and will be submitted for a central/independent review. Central imaging review will be performed using two blinded independent reviewers with adjudication by a third blinded independent reviewer in cases of discordance. Submission instructions for the central/independent review will be provided in a separate manual.

7.4 Safety Assessments

Safety will be assessed based on the procedures in the subsection below. Adverse events/SAEs collection and reporting is described in Section 8.

Unless otherwise specified, all safety assessments on dosing days will be done prior to study treatment administration. Additional safety assessments may be performed by the Investigator when clinically indicated.

7.4.1 Physical Examination

Planned time points for physical examination are provided in the SoE (Table 1 or Table 2).

A complete physical examination will be performed at screening.

Limited, symptom-directed physical examinations should be performed at specified post baseline visits and as clinically indicated.

7.4.2 ECOG Performance Status

Eastern Cooperative Oncology Group performance status grades are presented in Section 12.1, Appendix 1 and will be captured at the planned timepoints provided in the SoE (Table 1 or Table 2).

7.4.3 Height and Weight

Planned time points for height and weight are provided in the SoE (Table 1 or Table 2).

7.4.4 Vital Signs

Planned time points for vital signs are provided in the SoE (Table 1 or Table 2).

Vital signs include the measurements of arterial blood pressure (systolic and diastolic), heart rate, respiratory rate, and body temperature and will be performed according to the institutional standards.

For Day 1 of each cycle, vital signs are to be measured before the start of the infusion and at the end of infusion for patients on the loncastuximab tesirine arm; vital signs will be measured once during visit for patients on the idelalisib arm.

7.4.5 Laboratory Tests

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

Additional sample(s) may be collected and analyzed if clinically indicated. The C1D1 laboratory tests do not need to be repeated if the laboratory tests for eligibility were done within 3 days of C1D1.

Hematology: red blood cell (RBC), 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 bilirubin is abnormal), sodium, potassium, chloride, phosphorus/phosphate, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, creatinine, creatinine clearance, creatine phosphokinase, total protein, albumin, glucose, and lactate dehydrogenase, uric acid.

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

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

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

Other tests:

HBV and/or HCV serology tests, and viral load test if clinically indicated.

HIV serology tests, and HIV viral load and /or CD4+ T cell count if clinically indicated.

CMV screening tests: CMV IgG test, and CMV antigen or PCR test for all patients during screening period.

CMV monitoring tests: CMV antigen or PCR test for patients with positive CMV serology or history of CMV infection who are receiving treatment with idelalisib.

7.4.6 Pregnancy Test

A highly sensitive β subunit of Human chorionic gonadotropin (β-HCG) test in blood or urine will be performed in WOCBP for eligibility (see Section 5.1) and throughout the study as per SoE (Table 1 or Table 2) and as needed.

When possible, for WOCBP patients treated with loncastuximab tesirine, a final pregnancy test should be performed ≥9 months post last drug dose, however, remote pregnancy test is acceptable.

Pregnancy test must be negative prior to study drug infusion.

If a urine pregnancy test is positive, the study treatment must be held pending pregnancy confirmation. If the pregnancy is confirmed by serum β-HCG test, study treatment will be discontinued permanently for the patient. Refer to Section 8.5.2 for the handling of the patient and reporting the event.

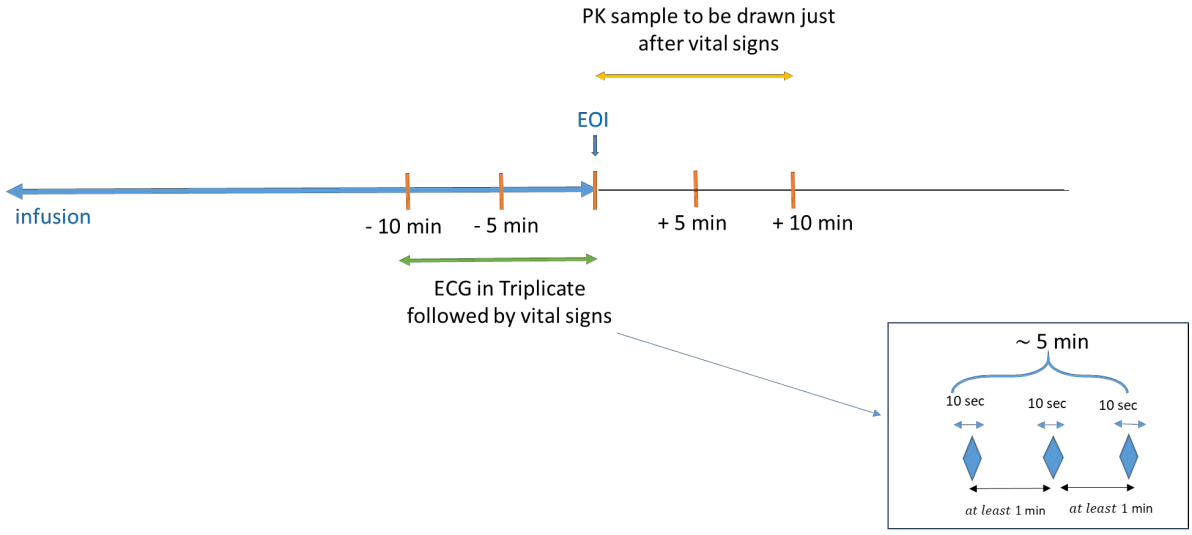
7.4.7 Electrocardiograms

Three consecutive (also called triplicate) 12-lead electrocardiograms (ECGs) will be conducted at defined timepoints as per SoE (Table 1 or Table 2) and Table 6. The 12-lead ECGs will be performed after the patient is resting for at least 5 minutes.

At timepoints coinciding with blood sample collection, including PK, ECGs should be taken prior to blood collection, and, when applicable, before vital signs measurements. For loncastuximab tesirine arm a preferred sequence for triplicate ECG, vital signs, and PK sample assessments at End of Infusion (EOI) is demonstrated in Figure 2.

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. Eligibility and clinical decisions may be made based on the local ECG assessment.

Figure 2. Preferred Sequence for Triplicate Electrocardiogram (ECG), Vital Signs, and Pharmacokinetic (PK) Sample Assessments at End of Infusion (EOI)



7.5 Pharmacokinetics, Pharmacodynamics, and Immunogenicity

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

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

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

Biological samples may be retained for up to 10 years to further address scientific questions as new information in 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).

7.5.1 Pharmacokinetics

The concentration in serum of loncastuximab tesirine (total antibody), PBD-conjugated antibody, and unconjugated warhead SG3199 for samples taken prior to and immediately after dosing on Cycles 1 through 6, and end of treatment in patients on loncastuximab tesirine will be assessed by a central laboratory designated by the Sponsor using validated bioanalytical methods. In addition, matching PK samples will be drawn at ADA collection time points from Cycle 7 and beyond during study treatment.

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

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

At timepoints coinciding with ECG collection, PK blood collection should occur immediately after the end of the ECG recording and, when applicable, after vital signs.

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.

Table 6. Sampling Schedule for ECG, PK, ADA and [redacted]

Cycle	**Day**	**ECG timepoint**	**PK timepoint** loncastuximab tesirine arm only	**ADA timepoint** loncastuximab tesirine arm only
Screening	-28 to -1	X		
C1-C6	D1	C1: Pre-dose only C2: Pre-dose for all subjects & EOI (Within 10 min prior to EOI) for loncastuximab tesirine arm only	X Pre-dose & EOI: Within 10 min post EOI	**C1, C3, and C5 only**: Pre-dose
C7 & Beyond	D1		**C7, then every other cycle** Pre-dose	**C7, then every other cycle** Pre-dose
EOT		Anytime during EOT visit	X	X
Follow-Up				If ADA positive is detected, additional ADA samples may be requested for testing every 12 weeks until the ADA titer falls to the baseline level

**Pre-dose: preferably within 2 h prior to start of infusion

Abbreviations: ADA=anti-drug antibody; C=cycle; D=day; ECG=electrocardiogram; EOI=end of infusion; EOT=end-of-treatment; h=hour; min=minute; PK=pharmacokinetics; [redacted]; [redacted] IP=Investigational Product

7.5.2 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. If an ADA is confirmed, a functional assay for the assessment of the neutralizing capacity of the ADA will be performed.

Blood samples for ADA testing will be collected pre-dose on C1D1, then Day 1 of every other cycles from patients assigned to loncastuximab tesirine arm only. Up to 6 mL of whole blood will be collected each time as per Table 1 and Table 6.

Blood should be drawn from a vein away from the one used for study drug infusion.

For patients who test positive for ADA, additional ADA samples may be requested for testing every 12 weeks following the EOT visit until the ADA titer falls to the baseline level

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

[redacted]

7.6 Patient Reported Outcomes

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

- EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) (Appendix 4).
- Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) (Appendix 5).

- GP5 item of FACT-Lym (Appendix 6)
- Selected symptomatic adverse events from the PRO-CTCAE library, including fatigue, swelling, rash, nausea, diarrhea, abdominal pain, and cough (Appendix 7).

Questionnaires will be completed in the respondent's native language, at the scheduled time points as per Table 1 or Table 2. Responses to PRO questionnaires will be collected electronically.

1. Both EQ-5D-5L and FACT-Lym will be completed at study site with the exception of EQ-5D-5L follow -up assessments, which may be completed by phone (see Table 1 or Table 2).
2. Both GP5 item of FACT-Lym and selected PRO-CTCAE items will be completed by patients at home, with the exception of the PRO-CTCAE items at baseline (Cycle 1 Day1), which will be answered at study site (see Table 1 or Table 2).

Questionnaires should always be administered prior to clinical assessment if applicable. 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.

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

EQ-5D-5L is a standardized, generic instrument for describing health status as the patient experiences them "today." It is used for clinical and economic evaluation (EuroQol Research Foundation, 2019). The EQ-5D-5L consists of two parts:

- The descriptive system: consists of five single-item dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises five levels of perceived problems (e.g., none, slight, moderate, severe, extreme/unable to).
- The visual analog scale (VAS): patients are asked to rate their current health on a 100-point scale, ranging from 'the best health you can imagine' (score 100) and 'the worst health you can imagine' (score 0). Patients are asked to mark an "X" on the VAS to indicate their own health and then to report the score in a text box. If there is a discrepancy between where the patient has placed the X and the number, he/she has written in the box, the number in the box is to be entered in the CRF together with a comment indicating the discrepancy. Patients will complete this questionnaire as per the SoE (Table 1 or Table 2).

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

FACT-Lym (Version 4) is a HRQoL questionnaire validated in patients with B-cell and other types of NHL (Cella et al., 2005; Hlubocky et al., 2013). It has been widely used in NHL trials, for example, the phase III GADOLIN study in patients with rituximab-refractory indolent NHL including FL (Cheson et al., 2017), the phase III GALLIUM study in previously untreated, advanced indolent NHL including FL (Thielen et al., 2019), and the RESORT E4402 study in patients with low–tumor burden NHL including FL (Wagner et al., 2015). FACT-Lym consists

of a general HRQoL assessment (FACT-G) and a disease-specific subscale (Lymphoma subscale, LymS). FACT-G (27 items) measures four functional dimensions: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). The LymS (15 items) addresses symptoms and functional limitations that are important to patients with NHL, such as pain, lump or swelling, fatigue, fever, night sweats, itching, and weight loss. All items use a 0-4 ordinal measurement where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. The summary scores for PWB, SWB, EWB, FWB and LymS are computed as the sum of corresponding items (after reversed coding for the negatively stated items) with higher values indicating better quality of life. Three composite scores are also derived: Trial Outcome Index (TOI: sum of PWB, FWB, LymS), FACT-G total (sum of PWB, SWB, EWB, FWB), and FACT-Lym total (sum of FACT-G total and LymS). Patients will complete this questionnaire as per the SoE (Table 1 or Table 2).

7.6.3 FACT-Lym GP5

A single item from the FACT-Lym, GP5, will be administered to assess the extent of perceived bother due to symptomatic AEs. Evidence exists for the validity of this item and its usefulness as an overall summary measure of burden due to symptomatic treatment toxicities (Pearman, 2018). Patients will complete this question as per the SoE (Table 1 and Table 2).

7.6.4 Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) – Selected Items

PRO-CTCAE is a patient-reported outcome measurement system developed to evaluate symptomatic toxicity in patients on cancer clinical trials. The PRO-CTCAE Item Library contains 124 items representing 78 symptomatic toxicities drawn from the Common Terminology Criteria for Adverse Events (CTCAE). PRO-CTCAE items assess the symptom attributes of frequency, severity, interference, amount, presence/absence. Each symptomatic AE is evaluated by 1-3 attributes. The PRO-CTCAE has been developed as a standardized measurement that can provide a flexible fit-for-purpose approach to assess relevant symptomatic AEs for the trial (Kluetz 2016). The PRO-CTCAE Measurement System are validated in accordance with well-established PRO instruments (Dueck 2015). The PRO-CTCAE items included in this study are fatigue, swelling, rash, nausea, diarrhea, abdominal pain, and cough. These AEs are selected in an unbiased manner based on the symptomatic adverse events reported in Loncastuximab tesirine 402-201 trial of patients with R/R DLBCL (Carmelo Carlo-Stella, EHA 2020) and Idelalisib package insert for FL indication. Specifically, symptomatic AEs with occurrence in at least 20% of patients treated with either therapy are selected. Patients will complete these questions as per the SoE (Table 1 or Table 2).

8 Adverse Events

Reporting of AEs to competent authorities and Independent Review Boards (IRBs)/Independent Ethics Committees (IECs) will be consistent with current laws, regulations, and guidelines.

8.1 Definition of Adverse Events and Serious Adverse Events

8.1.1 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.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)

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

8.1.2 Serious Adverse Events

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.
- an important medical event that does not meet the preceding criteria but based on appropriate medical judgment may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed above.

8.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities/other abnormal assessments that require medical or surgical intervention or lead to pharmaceutical product interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. If the laboratory abnormality/other abnormal assessment is consistent with a clinical diagnosis, report the adverse event using the diagnosis (i.e., anemia), not the laboratory result (i.e., decreased hemoglobin).

8.2 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 nonleading question to elicit any medically related changes in their well-being. Patients may also report AEs voluntarily and they will be instructed to contact the Investigator between visits if any symptoms develop or worsen.

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

All AEs, regardless of relationship to study treatment, will be reported from the time the patient signs the ICF until 30 days after the last dose of study treatment.

All SAEs, regardless of relationship to study treatment, will be reported from the date patient signs the ICF until at least 76 days after last dose of study drug, or start of new anticancer therapy, whichever is earlier; thereafter, only related SAEs will be reported.

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 8.3), seriousness (Section 8.1), relationship to study treatment (Section 8.4), action taken with study treatment, 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 EDC system.

8.3 Assessment of Severity

The AEs will be graded according to CTCAE v5.0. For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5 as shown in Table 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.

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

8.4 Assessment of Causality

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

The investigator or qualified subinvestigator is responsible for providing an assessment of the relationship to the study drug(s) using clinical judgment and the following considerations:

Causality	Definition
Not related	An adverse event is not related to the study drug
Unlikely related	An adverse event where evidence exits for an alternative explanation other than the study drug e.g concomitant medication(s), concomitant disease(s), or time to onset suggests unlikely relationship.
Possibly related	An adverse event that might be due to study drug. An alternative explanation (e.g concomitant medication(s), concomitant disease(s), or time to onset) is inconclusive, where a causal relationship with study drug cannot be ruled out.
Probably related	An adverse event that might be due to study drug. An alternative explanation (e.g concomitant medication(s), concomitant disease(s)) is less likely, and where a causal relationship with study drug is more suggestive (ie time to onset, positive dechallenge/rechallenge).
Related	An adverse event where an alternative explanation cannot be explained and, therefore, considered related to study drug.

8.5 Special Situations Reports

8.5.1 Definitions of Special Situations

Any special situation occurring in a participant that may require expedited reporting or safety review may include the following with the study drug:

- Pregnancy reports (see Section 8.5.2)
- Overdose reports (see Section 8.5.3)
- Other special situations (see Section 8.5.4), such as:
    - Suspected misuse or abuse
    - Accidental exposure
    - Medication error
    - Exposure to the study drug from breast-feeding
    - Adverse events associated with product complaints

8.5.2 Reporting Pregnancy

Any pregnancy in a participant 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 idelalisib treatment during the study must be reported using the Pregnancy Report Form. Any pregnancy in a partner of a male participant that occurs from signing the ICF up to 6 months

post last loncastuximab tesirine or up to 3 months post last idelalisib 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 the 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 treatment must be promptly reported in the same manner.

Once pregnancy is confirmed in a study participant, study treatment will be discontinued, see Section 7.4.6 for additional information.

8.5.3 Reporting Overdose

An overdose of the study drug(s) is defined under Section 6.6.

An overdose itself is not considered an AE. However, if such an overdose occurs during the study, with or without any signs or symptoms, it must be reported to ADC Therapeutics within 24 hours after the time site personnel first learn about the event.

8.5.4 Reporting Other Special Situations

All other special situation reports must be reported within 24 hours after the time site personnel first become aware of the situation.

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).

9.1 Sample Size Determination

Approximately 150 patients will be enrolled and randomly assigned to treatment with loncastuximab tesirine or idelalisib in a 2:1 ratio. The study is over-powered for the primary efficacy endpoint when a 55% of CRR in loncastuximab tesirine (compared to observed 64.3% CRR in Phase 1 trial) and 15% from idelalisib (Salles G, 2017) are assumed. The purpose of a larger sample size and 2:1 randomization ratio is to provide a more robust safety data set (~100 FL patients treated with loncastuximab tesirine). Table 8 and Table 9 summarizes the study power when different CRR and ORR are expected.

Table 8. Power for Primary Endpoint CRR with 2-Sided Significance Level 0.05

Expected CRR from loncastuximab tesirine arm*	55%	45%	40%
CRR from idelalisib arm**	15%	15%	15%
Power***	99%	96.1%	87.3

* Data from Phase 1 trial (ADCT-402-101) shows that CRR is approximately 64%, lower CRRs are assumed in this study
** CRR from idelalisib is assumed to be 15% (Salles G, 2017)
*** Based on nquery fisher's exact test

Table 9. Power for Key Secondary Endpoint ORR with 2-Sided Significance Level 0.05

Expected ORR from loncastuximab tesirine arm*	79%	75%	70%
ORR from idelalisib arm**	54%	54%	54%
Power***	84.1%	67.3%	41.7%

* Data from Phase 1 trial (ADCT-402-101) shows that ORR is approximately 79%.
**ORR from idelalisib is assumed to be 54% (Idelalisib® US- Prescribing Information).
*** Based on nquery fisher's exact test

9.2 Analysis Populations

- Intent-to-treat (ITT) Population: All patients who are randomized. This population will be used in the primary analyses of efficacy.
- All-Treated Population: All patients who receive at least 1 dose of loncastuximab tesirine or idelalisib. This population will be used in the primary analyses of safety.
- Per-Protocol Population: All patients in the all-treated population without important protocol deviations, which will be further described in detail in the SAP.
- The PK Population: All patients who receive loncastuximab tesirine and have at least 1 pre-(C1D1) and 1 post dose valid assessment.
- The Immunogenicity Population: All patients who receive loncastuximab tesirine and have at least 1 valid ADA assessment.
- The Pharmacodynamic Population: All patients who receive study drug and have at least 1 valid pharmacodynamics/[redacted]
- Patient-reported Outcomes Population: All patients who receive at least 1 dose of study treatment and complete at least one questionnaire at baseline and at one postbaseline visit.

9.3 Interim Analysis

A non-binding futility analysis on the primary endpoint of CRR will be performed for the first 60 patients (40% patients) around 12 weeks after the 60th patient is randomized (enough time for 2 disease assessments). O'Brien-Fleming spending function as the non-binding lower bound (futility) will be used. The details will be provided in SAP.

9.4 Final Analysis

For primary and key secondary endpoint analyses, a database snapshot will be taken 12 months after last patient is randomized in order to allow approximately 9 months of duration of response follow up. All efficacy and safety endpoints will be analyzed and reported in the clinical study report (CSR).

Results of the population PK analysis will be reported separately.

The CR rate will be tested in the intent-to-treat population between two treatment arms by using Cochran–Mantel–Haenszel (CMH) method adjusted by stratification factors from randomization list. The point estimates for odds ratio and difference in CRR with 95% confidence interval (CI) will be presented. If CRR is significantly different between two arms, the key secondary endpoint ORR will be sequentially tested using the same approach as CRR.

The PFS and OS analysis will be performed using PROC LIFETEST adjusted by stratification factor from randomization list. Kaplan-Meier plot for PFS, OS, and DOR will be presented by treatment.

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

9.5 Demographics and Baseline Characteristics

Demographics and Baseline characteristics, such as cancer history and medications history, will be summarized for the ITT Population.

The Follicular Lymphoma International Prognostic Index (FLIPI) (Solal-Celigny P, 2004) will be calculated based on 5 clinical and laboratory parameters (age, Ann Arbor stage, number of nodal areas, LDH, and hemoglobin level) derived from baseline visit. In case required data point is missing for the baseline visit, then data from the screening visit will be used.

9.6 Exposure to Treatments

Exposure to study treatment, prior, and concomitant medications will be summarized for the All-treated Population. Dose interruptions, reductions, and relative dose intensity will also be summarized.

9.7 Efficacy Analyses

Efficacy analyses will be based on disease assessment by central review. The primary efficacy analysis will be CRR analysis, and ORR will be a key secondary endpoint. Additional secondary efficacy analyses will include analyses of PFS, OS, and DOR.

Response reported by investigators (CRR, PFS, ORR, DOR) will be used for sensitivity analyses.

When best overall response (BOR) is determined, 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 treatment. 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.

9.7.1 Complete Response Rate

Complete Response Rate assessed according to the 2014 Lugano classification will be defined as the proportion of patients with a BOR of CR, based on response assessments obtained prior to any subsequent cancer treatment. The percentage of CRR with its 95% CI will be presented. For the primary CRR and secondary ORR analysis in the ITT population, patients with missing response or not evaluable information will be counted as failures.

The CR rate will be tested in the ITT population between two treatment arms by using CMH method adjusted for stratification factor in randomization list. The point estimates for odds ratio and difference in CRR with 95% CI will be presented.

A sensitivity analysis using exact method for CRR without adjusting for the covariate will also performed. In addition, CRR will be analyzed using CMH method adjusted for prognostic baseline covariates (e.g., age, disease characteristics, FLIPI, region etc.) in the sensitivity analysis. If there are continuous variables, logistics regression may be used.

9.7.2 Overall Response Rate

The ORR will be defined as the proportion of patients with a BOR of CR or PR. The overall response category will be derived based on response assessment performed on or before the start of subsequent anti-cancer therapy. For the primary ORR analysis in the all-treated population, patients with a CR or PR will be counted as successes and all other patients (including those with missing response information) will be counted as failures. The ORR will be tested in the ITT population by using the same approach as primary analysis and it will be tested only after primary analysis is significant. Similar sensitivity analyses will be performed for primary endpoint.

9.7.3 Progression-Free Survival

The PFS will be defined among ITT patients as the time from randomization date until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression based on central review. For patients whose disease has not progressed at the time of the analysis, censoring will be performed using the date of the last valid disease assessment prior to initiation of a new anticancer therapy including Hematopoietic Stem Cell Transplantation (HSCT). Stratified Log-rank testing will be used to compare PFS between the 2 treatment arms. The hazard ratio along with the 95% confidence interval (CI; 2-sided) will be estimated using the stratified Cox model with treatment as the explanatory variable. The stratification factor from the randomization list will be used. The Kaplan-Meier (K-M) survival curves, 25th, 50th (median), 75th percentiles (if estimable), and survival probability at 0.5, 1, and 2 years along with the 2-sided 95% CIs will also be provided for each treatment group. Further details will be outlined in the SAP.

A sensitivity analysis of PFS will be conducted in which the PFS for patients undergoing HSCT will not be censored at HSCT.

In addition, a stratified Cox regression model may be used to further evaluate the treatment effects on PFS after adjusting for some prognostic factors. Besides treatment and the stratification factor from the randomization list, the following prognostic factors may be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, FLIPI, baseline cancer stage. [redacted]

9.7.4 Overall Survival

Median OS will be defined as the time from the randomization date 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. Stratified Log-rank testing will be used to compare OS between the 2 treatment arms. The hazard ratio along with the 95% confidence interval (CI; 2-sided) will be analyzed by using stratified Cox model with treatment as the explanatory variable. The stratification factors from randomization list will be used. The median OS time, The Kaplan-Meier (K-M) survival curves, 25th, 50th (median), 75th percentiles (if estimable), and survival probability at 0.5, 1, and 2 years along with the 2-sided

95% CIs will also be provided for each treatment group. Further details will be outlined in the SAP.

A stratified Cox regression model may be used to further evaluate the treatment effects on OS after adjusting for some prognostic factors. Besides treatment and the stratification factors from the randomization list, the following prognostic factors may be included in the model simultaneously: age, race (white, non-white), baseline ECOG score, FLIPI, baseline cancer stage. [redacted]

9.7.5 Duration of Response

The DOR will be defined among responders (CR or PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression based on central review. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment prior to initiation of a new anticancer therapy (including HSCT). The Kaplan-Meier plot, median DOR and 95% CI will be presented by treatment. Further details will be outlined in the SAP. A sensitivity analysis of DOR will be conducted in which the DOR for patients undergoing HSCT will not be censored at HSCT.

9.7.6 Subgroup analysis

Subgroup analyses such as age, gender, region and other important baseline characteristics may be conducted for CRR, ORR, PFS, OS and DOR.

9.8 Safety Analyses

Safety analyses will be presented descriptively.

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 treatment until 30 days after the last dose of study treatment or start of new anti-cancer therapy, whichever is earlier.

All 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); study treatment-related AEs; AEs leading to treatment interruption, modification, or discontinuation; SAEs; 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 v5.0 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 treatment. Further details will be provided in the SAP.

9.8.3 Additional Safety Assessments

The results of scheduled assessments of vital signs, physical examinations, 12-lead ECGs and ECOG performance status 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 treatment. All data will be listed. Further details will be provided in the SAP.

9.9 Pharmacokinetic and Pharmacodynamic Analyses

The PK profile will include, but is not limited to, determination of clearance and volume of distribution. As appropriate, other parameters of exposure may be derived at the patient level for cross-study comparisons [redacted]

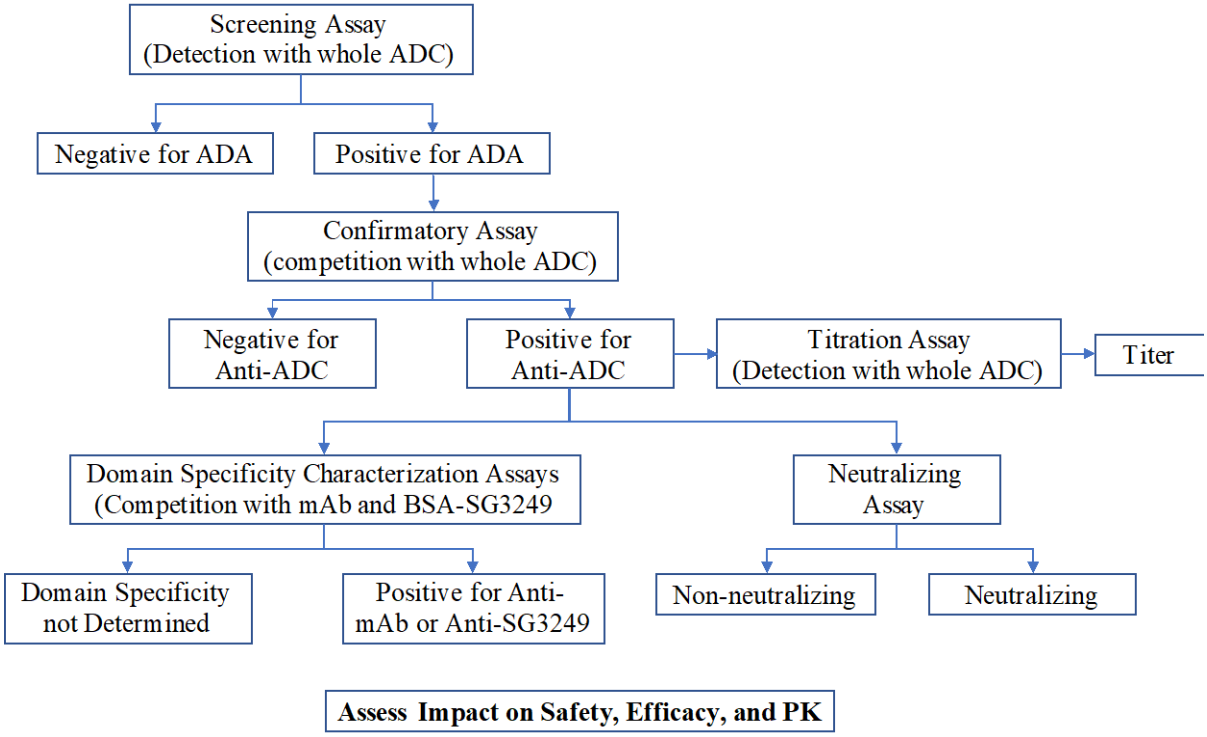
PK parameters for the typical patient will be determined using a population PK analysis approach. A subset of relevant intrinsic and extrinsic covariate factors will be identified prior to analysis and assessed for their influence on drug disposition. As appropriate, PK data from prior loncastuximab tesirine studies may be leveraged to support the population PK model.

[redacted]

9.10 Immunogenicity Analyses

A tiered immunogenicity strategy (Figure 3) 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 FDA Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection Guidance for Industry (Jan 2019).

Figure 3. 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. For patients exhibiting a positive ADA, PK, safety and efficacy correlates will be assessed and reported.

9.11 PROs Data Analyses

Patient-reported outcomes will be analyzed using PRO population. Completion rate of each PRO questionnaire (completed questionnaires as a proportion of the expected) will be calculated. Item level missing values will be imputed as per recommendation by the instrument developers.

Changes from baseline (Cycle 1 Day 1) in PRO scores for physical well-being, LymS subscale, FACT-G total, TOI, and FACT-Lym total of FACT-Lym, as well as EQ-5D VAS will be estimated at each cycle for each treatment arm. The changes from baseline in these scores will be compared between the two treatment arms. Patients will be classified as improvement/deterioration based on the established minimally important differences for each measure. Proportion of patients with improvement/deterioration as well as time to improvement/deterioration will be estimated for each treatment arm and compared between the two treatment arms.

The occurrence, severity, and interference (per relevance) of specific symptomatic adverse events selected from PRO-CTCAE, as well as the proportion of patients reporting ‘quite a bit’ or ‘very much’ in GP5 item of FACT-Lym will be presented at approximately 3 months and 6 months for each treatment arm, and compared between the two treatment arms.

Full details will be further described in the SAP.

[redacted]

10 Regulatory, Ethical, and Study Oversight/Management Considerations

10.1 Regulatory and Ethical Considerations

The study will be performed in accordance with the protocol and with the Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to applicable laws and regulations.

Study information from this protocol will be posted on publicly available clinical study registries before enrollment of patients begins.

10.2 Financial Disclosure and Obligations

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.3 Patient Information and Consent

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of any applicable regulations, guidelines, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study, 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.

A copy of the ICF(s) must be provided to the participant.

10.4 Data Protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

Sponsor maintains organizational and security measures (e.g. pseudonymisation, data protection policy, backups, network security, physical access control, monitoring network activity, etc.) to safeguard patient's personal data that are transferred to Sponsor from loss, misuse, unauthorized access, disclosure, alteration or destruction and, when required, will cause third parties accessing your Personal Data to maintain the same and to assist Sponsor in complying with its obligations under applicable laws regarding personal data protection.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.5 Data Quality Assurance

Study personnel involved in conducting this study will be qualified by education training and experience to perform their respective tasks.

All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., central laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, Sponsor/CRO audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source

documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Upon completion of the study, the Sponsor shall prepare a summary of the study outcome in accordance with the ICH E3 guidelines for submission to the appropriate regulatory authority(ies).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.6 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Investigator Site File.

10.7 Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

Discontinuation of further study intervention development

10.8 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.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Investigators and institutions involved in the study will permit study-related monitoring, Sponsor/CRO audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and 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.

10.9 Publications

Following completion of the study, the results from the study will be publicly disclosed through posting the results on appropriate registries such as ww.clinicaltrials.gov and 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).

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