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

Endpoints:

Primary Endpoint

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

Secondary Endpoints

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

[redacted]

Study Design:

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

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

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

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

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

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

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

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

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

[6] Cycle 1 only

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

Visit Scheduling Windows:

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

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

4 Study Design

4.1 Overview

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

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

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

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

4.2 Screening Period

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

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

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

4.3 Treatment Period

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

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

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

4.4 End of Treatment

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

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

4.5 Follow-up Period

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

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

4.6 End of Study

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

8.2 Adverse Events

8.2.1 Definition of Adverse Events and Serious Adverse Events

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

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

A SAE is defined as any AE that:

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

8.2.2 Eliciting and Reporting Adverse Events/Serious Adverse Events

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

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

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

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

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

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

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

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

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

8.2.3 Assessment of Severity

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

Table 3. Definition of Severity Grades for CTCAE

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

[a] ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

8.3.1 Physical Examination

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

8.3.2 ECOG Performance Status

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

8.3.3 Height and Weight

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

Additional measurements will be performed if clinically indicated.

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

8.3.4 Vital Signs

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

8.3.5 Laboratory Tests

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

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

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

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

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

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

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

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

8.4 Pharmacokinetics, Pharmacodynamics, and Immunogenicity

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

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

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

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

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

8.4.1 Pharmacokinetics

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

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

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

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

[redacted]

8.5 Health-Related Quality of Life (HRQoL) Questionnaires

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

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

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

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

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

9 Statistical Considerations

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

9.1 Sample Size Calculation

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

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

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

9.2 Analysis Populations

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

9.3 Interim Analysis for Futility

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

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

9.7.3 Additional Safety Assessments

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

9.8 Pharmacokinetic Analyses

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

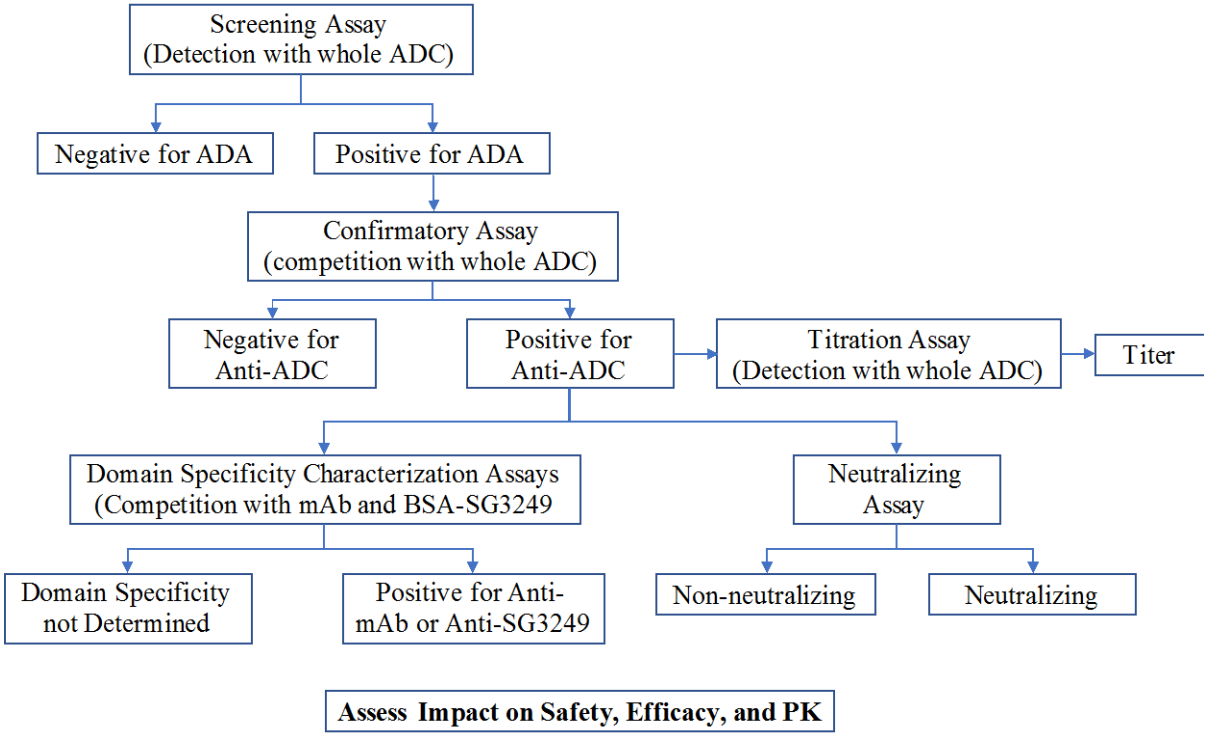
PK parameters will be determined for all PK-evaluable patients using a non-compartmental method with Phoenix WinNonlin (Certara USA, Inc., Princeton, NJ, US) or other appropriate software. Supplemental population PK analyses will be undertaken and reported separately to characterize the PK parameters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

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

9.9 Immunogenicity Analyses

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

Figure 2. Anti-drug Antibody Tiered Immunogenicity Testing Strategy



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

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

[redacted]

11.9 Monitoring of the Study

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

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

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

11.10 Records Retention

Essential documents should be retained for at least 15 years from the completion of the study (last patient last visit) and until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational study drug. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

11.11 Publications

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

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

Patient Selection:

Inclusion Criteria:

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

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

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

1 Introduction and Background

1.1 Diffuse Large B-Cell Lymphoma

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

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

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

3 Study Objectives and Endpoints

Table 2. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the efficacy of single agent loncastuximab tesirine in patients with relapsed or refractory DLBCL	ORR according to the 2014 Lugano classification (Cheson et al. 2014) as determined by central review in all treated patients; ORR is defined as the proportion of patients with a best overall response (BOR) of CR or PR
Secondary	
Further evaluate the efficacy of loncastuximab tesirine	• DOR defined as the time from the first documentation of tumor response to disease progression or death • CR rate defined as the percentage of treated patients with a BOR of CR • Relapse-free survival (RFS) defined as the time from the documentation of CR to disease progression or death • PFS defined as the time between start of treatment and the first documentation of recurrence, progression, or death • OS defined as the time between the start of treatment and death from any cause
Characterize the safety profile of loncastuximab tesirine	• Frequency and severity of adverse events (AEs), and SAEs • Changes from baseline of safety laboratory variables, vital signs, ECOG performance status, and 12-lead electrocardiograms (ECGs)
Characterize the pharmacokinetic (PK) profile of loncastuximab tesirine	Concentrations and PK parameters of loncastuximab tesirine total antibody, PBD-conjugated antibody, and unconjugated warhead SG3199
Evaluate the immunogenicity of loncastuximab tesirine	Anti-drug antibody (ADA) titers and, if applicable, neutralizing activity to loncastuximab tesirine after treatment with loncastuximab tesirine
Evaluate the impact of loncastuximab tesirine treatment on health-related quality of life (HRQoL)	Change from baseline in HRQoL as measured by EuroQol–5 Dimensions–5 Levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]

5 Patient Population

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

5.1 Inclusion Criteria

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

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

   Note: A laboratory assessment may be repeated a maximum of two times during the Screening period to confirm eligibility.
9. Negative beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to start of study drug (C1D1) for women of childbearing potential.

8.2.4 Assessment of Causality

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

8.2.5 Regulatory Reporting

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

8.2.6 Pregnancy

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

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

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

8.2.7 Overdose

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

8.3 Safety Assessments

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

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

8.3.6 Pregnancy Test

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

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

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

8.3.7 ECG

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

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

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

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

Table 4. Schedule for Triplicate ECG Collection

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

Abbreviations: ECG, electrocardiogram; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.
*Post-dose timepoint is counted from start of infusion.

Table 5. Sampling Schedule for PK and ADA

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

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.
*Post-dose timepoint is counted from start of infusion.

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

8.4.2 Immunogenicity

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

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

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

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

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

9.4 Final Analysis

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

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

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

9.5 Demographics and Baseline Characteristics

The analyses include:

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

9.6 Efficacy Analyses

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

9.6.1 Overall Response Rate

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

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

10 Data Management and Quality Assurance

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

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

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

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

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

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