Protocol Number: ADCT-301-201

Official Title: A Phase 2, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of Camidanlumab Tesirine (ADCT-301) in Patients with Relapsed or Refractory Hodgkin Lymphoma

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A Phase 2, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of Camidanlumab Tesirine (ADCT-301) in Patients with Relapsed or Refractory Hodgkin Lymphoma

PROTOCOL NO.: ADCT-301-201

Sponsor: **ADC Therapeutics SA**
Route de la Corniche, 3B
1066 Epalinges
Switzerland

Sponsor Contact: [redacted] - Oncology
ADC Therapeutics SA – Switzerland
Phone: [redacted]
email: [redacted]

Date of Protocol Amendment 5: **16 February 2022**

Confidentiality Statement

Protocol Approval – Sponsor Signatory

Study Title:	A Phase 2, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of Camidanlumab Tesirine (ADCT-301) in Patients with Relapsed or Refractory Hodgkin Lymphoma
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Protocol accepted and approved by:

[redacted] - Oncology
ADC Therapeutics SA – Switzerland
Phone: [redacted]
email: [redacted]

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled: "A Phase 2, Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of Camidanlumab Tesirine (ADCT-301) in Patients with Relapsed or Refractory Hodgkin Lymphoma" and the accompanying Investigator's Brochure (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 5, dated 16 February 2022, the current version of International Council for Harmonisation (ICH) harmonised tripartite guideline E6: Good Clinical Practice, and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer the study drug only to patients under my personal supervision or the supervision of a sub-Investigator.

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

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

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
AI	accumulation index
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration-time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration-time curve from time zero to the end of the dosing interval
BID	twice daily
β-HCG	human chorionic gonadotropin
BOR	best overall response
BP	blood pressure
C1D1	Cycle 1, Day 1
CD	cluster of differentiation
CFR	Code of Federal Regulations
cHL	classical Hodgkin lymphoma
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CMV	cytomegalovirus
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram(s)
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion
EOS	end of study
EOT	end of treatment

Abbreviation	Definition
EQ-5D-5L	EuroQoL–5 Dimensions–5 Levels
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
G-CSF	granulocyte colony-stimulating factor
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HR	heart rate
HRQoL	health-related quality of life
HSCT	hematopoietic stem cell transplant
HSV1	herpes simplex virus 1
HSV2	herpes simplex virus 2
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iDSMB	independent Data and Safety Monitoring Board
IEC	independent ethics committee
IL	interleukin
IFNγ	interferon gamma
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IVIg	intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
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
PK	pharmacokinetic(s)
PLEX	plasma exchange

Abbreviation	Definition
PR	partial response
Q3W	every 3 weeks
QoL	quality of life
QT	measure between Q wave and T wave in the electrocardiogram
QTcB	Bazett correction of the QT measure
QTcF	Fridericia correction of the QT measure
RBC	red blood cell
RFS	relapse-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	respiratory syndrome coronavirus 2
sCD25	soluble CD25
SD	stable disease
SoC	standard of care
SoE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
TANT	tumor-associated non-tumor cells
TEAE	treatment-emergent adverse event(s)
TIL	tumor infiltrating lymphocytes
TLS	tumor lysis syndrome
T_{half}	apparent terminal elimination half-life
T_{max}	time to maximum concentration
TNFα	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VAS	visual analog scale
V_{ss}	volume of distribution
VZV	varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

Summary of Changes

The primary reason for Protocol Amendment 5 is to extend the contraception period after last dose of camidanlumab tesirine, following an urgent safety measure. The contraception period is determined based on the compound properties and half-life, and has been updated due to a recently revised half-life value of camidanlumab tesirine.

- In Section 5.1, Inclusion criterion 10: For women of childbearing potential, the period of contraception after last dose of camidanlumab tesirine has been extended to at least 9.5 months. For men with female partners of childbearing potential the period of abstinence or use of condom has been extended to at least 6.5 months after last dose of camidanlumab tesirine. Section 7.4.6 Pregnancy Test, Section 8.6 Pregnancy Reporting, and Schedule of Assessments (Table 1) have been revised accordingly.

In addition, revisions to the protocol text have also been applied to the synopsis section.

List of Prior Protocol Versions

Document	Version Date	Rationale for Changes
Amendment 4	06 Nov 2020	The primary reasons for this global Protocol Amendment 4 were to implement the recommendations from the independent Data and Safety Monitoring Board (iDSMB), including the addition of varicella zoster virus prophylaxis, an update of the management guidance in respect to specific autoimmune toxicities, and to address the requests from the French and Belgian regulatory authorities.
Amendment 3	01 Jul 2020	The primary reason for this global Protocol Amendment 3 was to update the stopping rule and to exclude patients that are tested positive for influenza and respiratory syndrome coronavirus 2 (SARS-CoV-2) before initiating study treatment, based on the recommendations by the Food and Drug Administration (FDA).
Amendment 2	24 Apr 2020	The primary reason for this global Protocol Amendment 2 was to combine the updates required by the Regulatory Authorities and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) received to date in one global protocol version. In addition, updates in line with study needs had been introduced, such as the inclusion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) added to the list of pathogens associated to Guillain-Barré syndrome (GBS), additional recommendation to capture early signs of polyradiculopathy/GBS, and the update of the study stopping rule.
Amendment 1	24 Jun 2019	The primary reason for Protocol Amendment 1 was to include changes based on recommendations by the US Food and Drug Administration. In addition, substantial updates in line with study needs had been introduced, e.g., revision of study drug instructions or clarifications of male participant contraception methods.
Version 2	15 Mar 2019	The primary reasons for Protocol Version 2 (15 March 2019) were to include changes based on internal discussion and emerging data. This version is the first version that was used for submission purposes, thus to be considered as the actual Original Protocol.
Original Protocol	12 Jul 2018	This version has been distributed to sites but not for submission purposes.

Protocol Synopsis

Protocol Number:	ADCT-301-201
Title:	A Phase 2, Open-label, Single-Arm Study to Evaluate the Efficacy and Safety of Camidanlumab Tesirine (ADCT-301) in Patients with Relapsed or Refractory Hodgkin Lymphoma
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 2
Indication:	Classical Hodgkin Lymphoma (cHL, also known as classical Hodgkin Disease)
Rationale:	Camidanlumab tesirine is an antibody-drug conjugate (ADC) that has been designed to target and kill CD25-expressing cells. Given the encouraging overall response rate (ORR) and complete response (CR) rate reported with camidanlumab tesirine in the Phase 1 study in relapsed and refractory Hodgkin lymphoma (HL) patients at dose levels below the maximum tolerated dose (MTD) and the acceptable safety profile, camidanlumab tesirine presents a positive risk-benefit for further evaluation in this population.
Objectives:	**Primary Objective** • Evaluate the efficacy of single agent camidanlumab tesirine in patients with relapsed or refractory HL **Secondary Objectives** • Characterize additional efficacy endpoints of camidanlumab tesirine • Characterize the safety profile of camidanlumab tesirine • Characterize the pharmacokinetic (PK) profile of camidanlumab tesirine • Evaluate the immunogenicity of camidanlumab tesirine • Evaluate the impact of camidanlumab tesirine treatment on health-related quality of life (HRQoL) **Exploratory Objectives** • Assess the pharmacodynamic effects of camidanlumab tesirine • Characterize tumor and tumor-associated non-tumor cells (TANT), as well as immunological relevant parameters, in baseline tumor tissue • Evaluate genetic alterations characterizing HL and their evolution upon camidanlumab tesirine treatment • Explore exposure-response relationships affecting safety and efficacy of camidanlumab tesirine • Explore correlations between clinical activity or safety of camidanlumab tesirine and tumor and/or blood biomarkers

Endpoints:

Primary Endpoints

- ORR according to the 2014 Lugano classification as determined by central review

Secondary Endpoints

- Duration of response (DOR)
- CR rate
- Relapse-free survival (RFS)
- Progression-free survival (PFS)
- Overall survival (OS)
- Fraction of patients receiving hematopoietic stem cell transplant (HSCT)
- 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 camidanlumab tesirine total antibody, pyrrolobenzodiazepine (PBD)-conjugated antibody, and unconjugated warhead SG3199
- Frequency of confirmed positive anti-drug antibody (ADA) responses, their associated (ADA) titers and, if applicable, neutralizing activity to camidanlumab tesirine after treatment with camidanlumab 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)

Exploratory Endpoints

- Changes in levels of immunologically relevant biomarkers in blood such as, but not limited to, interleukin-2 (IL-2), IL-10, and soluble CD25 (sCD25)
- Measurement of CD25(+) tumor cells and TANT in baseline tumor tissue
- Measurement of tumor infiltrating lymphocytes (TILs) and other immunologically relevant parameters in baseline tumor tissue
- Detect HL alterations in plasma circulating free DNA (cfDNA) prior, during, and after camidanlumab tesirine treatment, including at disease progression
- Monitor residual disease prior to camidanlumab treatment and upon disease progression
- Relation between exposure (camidanlumab tesirine dose, PK metrics) and selected efficacy and safety endpoints
- Relation between tumor and/or blood biomarkers and selected efficacy and safety endpoints

Study Design:	This is a Phase 2, multi-center, open-label, single-arm study.
Patient Selection:	**Inclusion Criteria:** 1. Written informed consent must be obtained prior to any procedures. 2. Male or female patients aged 18 years or older. **For US sites only**: Male or female patients aged 16 years or older. 3. Pathologic diagnosis of cHL. 4. Patients with relapsed or refractory cHL, who have received at least 3 prior lines of systemic therapy (or at least 2 prior lines in HSCT ineligible patients) including brentuximab vedotin and a checkpoint inhibitor approved for cHL (e.g., nivolumab or pembrolizumab). Note 1: Receipt of HSCT to be included in the number of prior therapies needed to meet eligibility. Note 2: The reason(s) for HSCT ineligibility must be documented in patient medical records/source documents and eCRF. 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 1: Any biopsy since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred. Note 2: If a sufficient amount of tissue is not available, a fresh biopsy may be taken, provided the procedure is not deemed high-risk and is clinically feasible, and provided it is approved locally. 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 h). b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 2 weeks. c. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma glutamyl transferase (GGT) $\leq 2.5 \times$ the upper limit of normal (ULN) if there is no liver involvement; ALT or AST $\leq 5 \times$ ULN if there is liver involvement. 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 with direct bilirubin $\leq 1.5 \times$ ULN). e. Blood creatinine $\leq 3.0 \times$ ULN or calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-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 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 9.5 months after the last dose of camidanlumab tesirine. Men with female partners who are of childbearing potential must agree to use condom when sexually active or practice total abstinence from the time of giving informed consent until at least 6.5 months after the patient receives his last dose of camidanlumab tesirine.

Exclusion Criteria:

1. Previous treatment with camidanlumab tesirine.
2. Participation in another investigational interventional study. Being in follow-up of another investigational study is allowed.
3. Known history of hypersensitivity to or positive serum human ADA to a CD25 antibody.
4. Allogenic or autologous HSCT within 60 days prior to start of study drug.
5. Active graft-versus-host disease (GVHD), except for non-neurologic symptoms as a manifestation of mild (≤ Grade 1) chronic GVHD.
6. Post-HSCT lymphoproliferative disorders.
7. 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.
8. History of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]) (subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism, hypophysitis due to autoimmune condition only requiring hormone replacement may be enrolled).
9. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome and myasthenia gravis) or other central nervous system autoimmune disease (e.g., poliomyelitis, multiple sclerosis).
10. History of recent infection (within 4 weeks of Cycle 1, Day 1 [C1D1]) considered to be caused by one of the following pathogens: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Note: An influenza test and a pathogen-directed SARS-CoV-2 test (such as polymerase chain reaction) are mandatory and must be negative before initiating study treatment (tests to be performed 3 days or less prior to dosing on C1D1; an additional 2 days are allowed in the event of logistical issues for receiving the results on time).

11. Patients known to be or having been infected with human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV), and require anti-viral therapy or prophylaxis.

    Note: Serology testing is mandatory for patients with unknown status.
12. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.
13. Failure to recover ≤ Grade 1 (Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]) from acute non-hematologic toxicity (except ≤ Grade 2 neuropathy or alopecia), due to previous therapy, prior to screening.
14. HL with central nervous system involvement, including leptomeningeal disease.
15. 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).
16. Breastfeeding or pregnant.
17. Significant medical comorbidities, including uncontrolled hypertension (blood pressure [BP] ≥ 160/100 mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 3 months prior to screening, severe uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease.
18. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy, within 14 days prior to start of study drug, except shorter if approved by the Sponsor.
19. Use of any other experimental medication within 30 days prior to start of study drug.
20. Any live vaccine within 4 weeks prior to start of study drug and planned live vaccine administration after starting study drug.
21. Congenital long QT syndrome, or a corrected QTc interval of ≥ 480 ms, at screening (unless secondary to pacemaker or bundle branch block).
22. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.

Estimated Duration of Patient Participation and Study Duration:	The duration of the study participation for each patient is defined as the time from the date of signed written informed consent to the completion of the follow-up period, withdrawal of consent, loss to follow-up, or death, whichever occurs first. The study will include a Screening Period (of up to 28 days), a Treatment Period (cycles of 3 weeks), and a Follow-up Period (approximately every 12-week visits) for up to 3 years from End of Treatment (EOT). 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: Positron emission tomography-computed tomography (PET-CT) Note: If disease is not PET-avid at baseline, CT or MRI may be used for follow-up disease assessments. The assessment method determined to identify sites of disease at Baseline should be used for all subsequent assessments.
Safety Assessments:	• Physical examination, including neurological examination • ECOG performance status • Height and weight • Vital signs • Safety laboratories (hematology, chemistry, coagulation, urinalysis, and as applicable, viral detection and/or additional microbiological studies) • Pregnancy test, if applicable • 12 Lead-ECG (triplicate) • AEs/SAEs, graded according to CTCAE version 4.0.
Other Assessments:	• Blood sampling for PK, ADA, and biomarkers • Tumor tissue for biomarkers • HRQoL: EQ-5D-5L and FACT-Lym
Study Drug, Dosage, and Mode of Administration:	Camidanlumab tesirine will be administered in 3-week cycles as an intravenous (IV) infusion over 30 minutes on Day 1 of each cycle. Patients will receive 45 µg/kg for 2 cycles, then 30 µg/kg for subsequent cycles.
Sample Size:	The sample size of 100 patients will provide a robust population for safety evaluation and adequate precision for observed ORR in the expected range. For the test of efficacy, this study has >98% power to distinguish between an active therapy with a 55% true response rate from a therapy with a response rate of 35% or less with a 1-sided alpha of 0.025.

Statistical Considerations:	**Statistical Analysis:** ORR, CR rate with 95% confidence interval (CI) from all-treated patients will be presented. DOR, RFS, PFS, and OS will be analyzed in Kaplan-Meier approach. Safety analyses will be presented descriptively.

Schedule of Events

Table 1 Schedule of Events

	Protocol Section	Screening	Treatment Period					Follow-up Period (up to 3 years from EOT)
(1 Cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**			**C3 and beyond**	**EOT**	**Every 12 weeks (wks)**
Day (D)		**-28 to –1**	**1**	**8**	**15**	**1**		
Informed consent	7.1	X						
Eligibility criteria	5.1 5.2	X						
Demography	7.2	X						
Medical/Cancer history	7.2	X						
Tumor tissue shipment	7.5.3.2	X upon confirmed eligibility						
Disease assessment	7.3	X[1]	6 weeks and 12 weeks after C1D1, then every 9 wks[1]				X[1]	Every 12 weeks until 1 year from EOT, then every 6 months until disease progression[2]
Physical examination, incl. neurological examination	7.4.1	X	X	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	X	X	
Vital signs (BP, HR, RR, Temp)	7.4.4	X	X[3]	X	X	X[3]	X	
Hematology and Chemistry	7.4.5	X	X	X	X	X	X	
Coagulation and Urinalysis	7.4.5	X	X				X	
Thyroid function tests	7.4.5	X	On C1D1, thereafter on D1 of every other cycle				X	
Influenza and SARS-CoV-2	7.4.5	3 days[4] or less prior to dosing on C1D1						
Viral detection, if applicable[5]	7.4.5	X	On C1D1, thereafter on D1 of every other cycle				X	
Pregnancy test, if applicable	7.4.6	X	On C1D1, thereafter on D1 of every other cycle (max. 6 wks apart)				X[6]	

	Protocol Section	Screening	Treatment Period					Follow-up Period (up to 3 years from EOT)
(1 Cycle = 21 days)			**Cycle 1 and Cycle 2 (C1 and C2)**			**C3 and beyond**	**EOT**	**Every 12 weeks (wks)**
Day (D)		**-28 to –1**	**1**	**8**	**15**	**1**		
12-lead ECG	7.4.7 Table 3	X	X (Pre, EOI, Post)	X	X	C3 and C4 (Pre, EOI), C5 then every other cycle (Pre)	X	
Premedication	6.7.1		D-1 to D2			D-1 to D2		
Camidanlumab tesirine administration	6.3		X			X		
PK sample	7.5.1 Table 4		X (Pre, EOI, Post)	X	X	C3 through C6 (Pre, EOI), then every cycle (Pre)	X	
ADA sample	7.5.2 Table 4		X (Pre)		X C1 only	C3 (Pre), then every other cycle (Pre)	X[7]	
Soluble biomarkers	7.5.3.1 Table 5		X (Pre, Post)	X	X	C3 (Pre, EOI), then every other cycle (Pre)	X	
cfDNA samples (gDNA only at C1D1 and EOT)	7.5.3.1		X (Pre)			6 and 12 weeks postdose (with disease assessment)	X	X at disease progression
HRQoL[8]	7.6		X			X	X	
Concomitant medications[9]	6.8	From ICF signature date or D-14, whichever is earlier, until 30 days after last dose of study drug						
Adverse events	8	AE/SAEs from ICF signature date until 30 days after last dose of study drug; thereafter, related SAEs only						
1st New anticancer treatment	4.2.3						X	X
Survival	4.2.5						X	X

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BP, blood pressure; cfDNA: circulating cell-free DNA; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOI, end of infusion; EOT, end of treatment; HR, heart rate; gDNA, genomic DNA; HRQoL, health-related quality of life; ICF, informed consent form; PK, pharmacokinetics; post, postdose; pre, predose; RR, respiratory rate; SARS-CoV-2: respiratory syndrome coronavirus 2; SAE, serious adverse event; Temp, temperature; VZV, varicella zoster virus.

1. Screening imaging 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 1 week prior to C3D1 and Week 12 imaging should be performed within 1 week 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 6 weeks of EOT, it does not need to be repeated at EOT.
2. Disease assessments to be performed in patients having discontinued study drug for reasons other than disease progression or initiation of other anti-cancer therapy (except for hematopoietic stem cell transplant or CAR-T therapy).
3. Vital signs to be measured predose and at EOI.
4. Additional 2 days are allowed in the event of logistical issues for receiving the results on time.
5. Serology testing for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus is mandatory at screening for patients with unknown status. Seropositive patients for or with prior history of these infections at screening will be tested during the study (not needed if seropositivity is only due to vaccination).
6. The EOT visit pregnancy test should be performed ≥9.5 months after the last dose of study drug.
7. Patients who test positive for ADAs will be requested to supply additional ADA samples.
8. FACT-Lym not to be administered for patients <18 years old.
9. VZV prophylaxis is recommended for all enrolled patients as indicated in Section 6.7.6.

Visit Scheduling Windows:

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

1 Introduction and Background

1.1 Targeting CD25-positive Tumor Cells in Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a lymphoid malignancy of B-cell origin, which is classified into either nodular lymphocyte predominant Hodgkin lymphoma or classical Hodgkin lymphoma (cHL). The latter accounts for 95% of all HLs and is addressed by this protocol (Fields, 2017). Thus, for convenience, cHL/HL will be used interchangeably.

The epidemiology of HL is characterized by bimodal incidence (15-34 years and 55+ years). Therapeutic advances have resulted in durable remission rates of 60-80%. However, there is an unmet medical need for patients' refractory or relapsing from current treatments. Since many of these patients are of young age, the potential loss of life years is significant (Mehta-Shah, 2018; Fields, 2017; Glimelius, 2017).

Brentuximab vedotin as a single agent and checkpoint inhibitors have been approved for use in the relapsed setting, and thus patients coming onto this trial should have received both of these therapies. However, once these therapies fail or are not tolerated, treatment options are limited (Mehta-Shah, 2018; Mottok, 2018; Fields, 2017; Glimelius, 2017). It is in this setting where camidanlumab tesirine, an antibody-drug conjugate that is directed against human cluster of differentiation (CD25), will be clinically tested.

The CD25 is the alpha-chain of the interleukin (IL)-2 receptor and as such expressed on the cell surface of a number of normal cells of the immune system as well as malignant cells (Flynn, 2017).

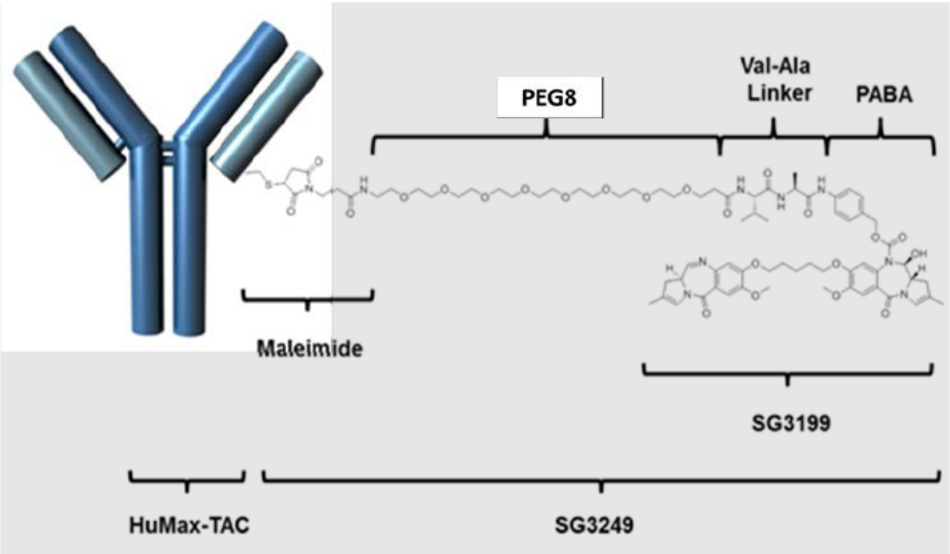
The presence of CD25-positive cells in hematologic malignancies and the relationship between increased CD25 expression and poor prognosis raises the possibility of using an anti-CD25 antibody to deliver a cytotoxin to these cells in patients. Hematologic malignancies expressing CD25 include adult T-cell leukemia (Waldmann, 1995), hairy cell leukemia (Shao, 2013), anaplastic large cell lymphoma (Strauchen, 1987), cutaneous T-cell lymphoma (Olsen, 2001; Prince, 2010), chronic lymphocytic leukemia (Shvidel, 2012), HL (Schnell, 1998), follicular lymphoma (Fujiwara, 2013a), diffuse large B-cell lymphoma (Fujiwara, 2013b), acute myeloid leukemia (Cerny, 2013), acute lymphocytic leukemia (Geng, 2012), and systemic mastocytosis (Lim, 2009). Expression of CD25 is positive (≥ 20% tumor cells) in approximately 58% to 78% of HL (Strauchen, 1987; LeMaistre, 1998).

1.2 Description of Investigational Study Drug

Camidanlumab tesirine (ADCT-301) is an antibody-drug conjugate (ADC), composed of the human monoclonal antibody, HuMax®-TAC, which is directed against human CD25. The antibody is conjugated through a protease cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin.

The schematic representation of camidanlumab tesirine is presented in Figure 1.

Figure 1 Schematic Representation and Chemical Structure of Camidanlumab Tesirine



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

Camidanlumab tesirine binds with picomolar affinity to human CD25. After binding and internalization, camidanlumab tesirine is transported 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 in a sequence-selective manner, and form highly cytotoxic DNA interstrand cross-links. The cross-links result in a stalled DNA replication fork, blocking cell division and causing cell death (Hartley, 2011). The cross-links formed by PBD dimers are relatively nondistorting to the DNA structure, making them hidden to repair mechanisms (Adair, 2012; Beck, 2017).

1.3 Safety and Efficacy of Camidanlumab Tesirine in Phase 1 Study, ADCT-301-001

ADCT-301-001 is a first-in-human (FIH) Phase 1 dose-escalation and dose-expansion study of camidanlumab tesirine in patients with relapsed or refractory HL and non-HL, who have failed or are intolerant to established therapies, or have no other treatment options available.

As of the data cut-off date of 14 April 2019, a total of 128 patients received at least one infusion of camidanlumab tesirine. Up to 150 µg/kg every 3 weeks (Q3W) was tested and the maximum tolerated dose (MTD) had not been reached (1 HL patient was dosed by error with a single dose of 300 µg/kg, then continued with the planned dose of 30 µg/kg). Out of these patients, 77 were cHL patients.

Treatment-emergent adverse events (TEAEs) were reported in 73 (97%) out of 77 cHL patients treated with camidanlumab tesirine. Overall, the most common TEAEs (observed in at least in 15% of patients), regardless of causality, included: fatigue (42%); rash maculopapular (35%); pyrexia (29%); gamma glutamyl transferase (GGT) increased (26%); nausea (25%); alanine aminotransferase (ALT) increased (24%); aspartate aminotransferase (AST) increased and cough (21% each); rash (20%); dyspnea (18%); blood alkaline phosphatase (ALP) increased and anemia (17% each); and abdominal pain and constipation (16% each).

The TEAEs ≥ Grade 3 were reported in 51 (66%) cHL patients, with the most common (observed in at least 5% of patients), regardless of causality, including: GGT increased and rash maculopapular (17% each); ALT increased (9%); anemia (8%); AST increased and Guillain-Barré syndrome (GBS)/radiculopathy (7% each); and lipase increased (5%).

The TEAEs in 20 (26%) patients led to treatment discontinuation. At the dose level of 45 µg/kg, approximately 89% of HL patients tolerated at least 2 cycles of camidanlumab tesirine before an AE leading to dose delay/modification occurred.

Treatment-emergent serious adverse events (SAEs), irrespective of causality, were reported in 36 (47%) out of 77 HL patients. Of these, 24 patients (31%) experienced a treatment-emergent SAE(s) considered at least possibly related to study drug. The following drug-related treatment-emergent SAEs were observed in multiple patients: pyrexia (6), GBS/radiculopathy (5), dyspnea (4), pleural effusion (4), acute kidney injury (2), blood creatine phosphokinase increased (2), cough (2), febrile neutropenia (2), nausea (2), edema peripheral (2), stomatitis (2), and vomiting (2).

Out of 37 evaluable patients with cHL at the dose of 45 µg/kg Q3W, 18 (49%) achieved complete response (CR) and 14 (38%) achieved partial response (PR), for an overall response rate (ORR) of 87%, as per Investigator evaluation. Albeit with lower observed response rates, 30 µg/kg Q3W is an active dose (ORR 50%, 9/18 patients), with both CR (28%) and PR (22%) observations. The lowest dose in which antitumor activity has been observed was 13 µg/kg Q3W.

Taking into account all patients treated with camidanlumab tesirine (as of the date of this protocol amendment), GBS, dyspnea, pleural effusion, rash, and maculopapular rash have been classified as expected serious adverse drug reactions. All events of GBS, even though expected, will continue to be subject to expedited reporting.

As of the date of this protocol amendment, a total of 8 patients with treatment-emergent GBS/polyradiculopathy events were reported across the entire camidanlumab tesirine development program including 4 studies, 2 of which reported such cases: 5 cHL patients in the Phase 1 study (described above) and 3 cHL patients in this ongoing Phase 2 study.

Neurologic and immune-related adverse events (AEs) including polyradiculopathy and GBS have been classified as important identified risks. Increased liver enzymes, skin toxicity (epidermal degeneration), and nephropathy have been classified as important potential risks.

Additional details may be found in the current camidanlumab tesirine (ADCT-301) Investigator's Brochure (IB).

2 Study Rationale

Camidanlumab tesirine is an ADC that has been designed to target and kill CD25-expressing cells. Given the encouraging ORR and complete response (CR) rate reported with camidanlumab tesirine in the Phase 1 study in relapsed and refractory HL at dose levels below the MTD and the acceptable safety profile (Section 1.3), camidanlumab tesirine presents a positive risk-benefit for further evaluation in this population.

2.1 Rationale for Study Design

This is a Phase 2, open-label, single-arm study and will enroll approximately 100 patients.

A single-arm design is commonly used to evaluate efficacy as a primary objective and the benefit-risk ratio of an oncology product with considerable anti-tumor activity within a well-defined patient population with high unmet medical need. Overall response rate is considered an appropriate endpoint in this setting.

Additionally, because of the considerable ORR observed in the ADCT-301-001 Phase 1 trial in HL patients and the anticipated recruitment projections, an interim analysis for futility is not warranted.

2.2 Rationale for Dose Selection

Doses ranging from 3 µg/kg Q3W up to 300 µg/kg Q3W were planned to be investigated in the FIH camidanlumab tesirine clinical study ADCT-301-001, which target CD25-positive tumors (Section 1.3); the highest dose level tested as of 14 April 2019 was 150 µg/kg Q3W and the MTD had not been reached. The recommended dose for Phase 2 for HL has been determined as 45 µg/kg Q3W dosed for 2 cycles, followed by 30 µg/kg Q3W.

The decision for initial dosing at the 45 µg/kg Q3W dose level is based on a number of considerations including:

1) the favorable ORR (87%) and CR rate (49%) together with an acceptable safety profile
2) the high fraction of patients with cHL who could tolerate at least 2 cycles of camidanlumab tesirine before an AE leading to a dose delay/modification occurred
3) the ability to manage some of the severe TEAEs at this dose level

Given that the attribution of toxicity to disease itself can be variable, it is recognized that a relatively high incidence of severe TEAEs in the relapsed/refractory lymphoma population is not uncommon.

Dose reduction from 45 to 30 µg/kg following 2 cycles of camidanlumab tesirine Q3W treatment would provide lower dose intensity, while still being an active dose (ORR 56%), which can mitigate the frequency and severity of AEs foreseen in patients treated with 45 µg/kg beyond 2 cycles.

Continued dosing at a reduced dose of 30 µg/kg with demonstrated antitumor activity is expected to decrease the necessity for dose delay/modification due to toxicity and thus increase the duration of response (DOR).

Therefore, the safety profile of camidanlumab tesirine administered as 45 µg/kg Q3W for 2 cycles, then 30 µg/kg Q3W thereafter is considered a reasonable regimen to investigate in patients with cHL, which can optimize potential response to treatment while maintaining an acceptable degree of manageable toxicity.

3 Study Objectives and Endpoints

Study objectives and associated endpoints are presented below in Table 2.

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the efficacy of single agent camidanlumab tesirine in patients with relapsed or refractory HL	• ORR according to the 2014 Lugano classification as determined by central review in all-treated patients
Secondary	
Characterize additional efficacy endpoints of camidanlumab 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 best overall response (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 from first dose of study drug until the first date of either disease progression or death due to any cause • Overall survival (OS) defined as the time from first dose of study drug until death due to any cause • Fraction of patients receiving hematopoietic stem cell transplant (HSCT).
Characterize the safety profile of camidanlumab tesirine	• Frequency and severity of AEs and SAEs • Changes from Baseline of safety laboratory values, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiograms (ECGs)
Characterize the PK profile of camidanlumab tesirine	• Concentrations and PK parameters of camidanlumab tesirine total antibody, PBD-conjugated antibody, and unconjugated warhead SG3199
Evaluate the immunogenicity of camidanlumab tesirine	• Frequency of confirmed positive anti-drug antibody (ADA) responses, their associated ADA titers and, if applicable, neutralizing activity to camidanlumab tesirine after treatment with camidanlumab tesirine

Objectives	**Endpoints**
Evaluate the impact of camidanlumab 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)
Exploratory	
Assess the pharmacodynamic effects of camidanlumab tesirine	• Changes in levels of immunologically relevant biomarkers in blood such as but not limited to IL-2, IL-10, and soluble CD25 (sCD25)
Characterize tumor and tumor-associated non-tumor cells (TANT), as well as immunological relevant parameters in tumor tissue	• Measurement of CD25(+) tumor cells and TANT in baseline tumor tissue • Measurement of tumor infiltrating lymphocytes (TILs) and other immunologically relevant parameters in baseline tumor tissue
Evaluate genetic alterations characterizing HL and their evolution upon camidanlumab tesirine treatment	• Detect HL alterations in plasma circulating free DNA (cfDNA) prior, during, and after camidanlumab tesirine treatment, including at disease progression • Monitor residual disease prior to camidanlumab tesirine treatment and upon disease progression
Explore exposure-response relationships affecting safety and efficacy of camidanlumab tesirine	• Relation between exposure (camidanlumab tesirine dose, PK metrics) and selected efficacy and safety endpoints
Explore correlations between clinical activity or safety of camidanlumab tesirine and tumor and/or blood biomarkers	• Relation between tumor and/or blood biomarkers and selected efficacy and safety endpoints

4 Study Design

4.1 Overview

This is a Phase 2, multi-center, open-label, single-arm study.

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 from End of Treatment (EOT) (Section 4.2).

An independent Data and Safety Monitoring Board (iDSMB) will be established to ensure the safety of patients enrolled in this study (Section 8.7).

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 standard of care 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 Treatment Period

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

A treatment cycle is defined as 3 weeks (i.e., 21 days).

Patients may continue treatment for up to 1 year or until disease progression, unacceptable toxicity, or other discontinuation criteria (Section 5.4), whichever occurs first. Additionally, patients benefiting clinically at 1 year may continue treatment after a case by case review with the Sponsor.

4.2.3 End of Treatment

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

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

4.2.4 Follow-up Period

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

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

4.2.5 End of Study

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

4.3 Study Stopping Rules

This study has no formal study stopping rule.

However, upon a confirmed case of GBS/polyradiculopathy of any grade, other ≥Grade 3 relevant severe neurologic toxicity, or other ≥Grade 3 potentially immune-mediated toxicity, the sponsor will calculate the overall incidence rate of such events in the study. The denominator used to calculate this rate will be the number of patients who have received at least 2 doses of study drug for GBS/polyradiculopathy of any grade and at least 1 dose of study drug for other ≥Grade 3 relevant severe neurologic and potentially immune-mediated toxicities.

- Should the incidence of GBS/polyradiculopathy of any grade reach an incidence threshold of >8.1% (8.1% being the incidence of GBS/polyradiculopathy cases of any grade observed in the HL population of the ADCT-301-001 Phase 1 study at 45 µg/kg), enrollment will be paused while a comprehensive safety review is completed and the iDSMB convenes to advise on study continuation based on their assessment of benefit-risk.
- Should the incidence of other ≥Grade 3 relevant severe neurologic toxicity and potentially immune-mediated toxicity reach an incidence threshold of >10.0% (10.0% being consistent with observations made for checkpoint inhibitors; Brahmer, 2018 and Davies, 2017), enrollment will be paused while a comprehensive safety review is completed and the iDSMB convenes to advise on study continuation based on their assessment of benefit-risk.

All ongoing patients who could receive clinical benefit will be allowed to continue on the study after being informed of the new safety information and consenting to continuation.

The Sponsor will notify Regulatory Agencies if the threshold has been exceeded and enrollment has been paused.

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. Written informed consent must be obtained prior to any procedures.
2. Male or female patients aged 18 years or older.

   For US sites only: Male or female patients aged 16 years or older.
3. Pathologic diagnosis of cHL.
4. Patients with relapsed or refractory cHL, who have received at least 3 prior lines of systemic therapy (or at least 2 prior lines in HSCT ineligible patients) including brentuximab vedotin and a checkpoint inhibitor approved for cHL (e.g., nivolumab or pembrolizumab).

   Note 1: Receipt of HSCT to be included in the number of prior therapies needed to meet eligibility.

   Note 2: The reason(s) for HSCT ineligibility must be documented in patient medical records/source documents and eCRF.
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 1: Any biopsy since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred.

   Note 2: If a sufficient amount of tissue is not available, a fresh biopsy may be taken, provided the procedure is not deemed high-risk and is clinically feasible, and provided it is approved locally.
7. Eastern Cooperative Oncology Group (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 h).
   b. Platelet count $\geq 75 \times 10^3/\mu L$ without transfusion in the past 2 weeks.
   c. ALT, AST, or GGT $\leq 2.5 \times$ the upper limit of normal (ULN) if there is no liver involvement; ALT or AST $\leq 5 \times$ ULN if there is liver involvement.
   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 with direct bilirubin $\leq 1.5 \times$ ULN).
   e. Blood creatinine $\leq 3.0 \times$ ULN or calculated creatinine clearance ≥ 30 mL/min by the Cockcroft-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 for women of childbearing potential.
10. 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 9.5 months after the last dose of camidanlumab tesirine. 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 6.5 months after the patient receives his last dose of camidanlumab tesirine.

    * Women of childbearing potential are defined as sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal. 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, and 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, postovulation), 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 camidanlumab tesirine.
2. Participation in another investigational interventional study. Being in follow-up of another investigational study is allowed.
3. Known history of hypersensitivity to or positive serum human anti-drug antibody (ADA) to a CD25 antibody.
4. Allogenic or autologous HSCT within 60 days prior to start of study drug.
5. Active graft-versus-host disease (GVHD), except for non-neurologic symptoms as a manifestation of mild (≤ Grade 1) chronic GVHD.
6. Post-HSCT lymphoproliferative disorders.

7. 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.
8. History of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]) (subjects with vitiligo, type 1 diabetes mellitus, residual hypothyroidism, hypophysitis due to autoimmune condition only requiring hormone replacement may be enrolled).
9. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome and myasthenia gravis) or other central nervous system autoimmune disease (e.g., poliomyelitis, multiple sclerosis).
10. History of recent infection (within 4 weeks of C1D1) considered to be caused by one of the following pathogens: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

    Note: An influenza test and a pathogen-directed SARS-CoV-2 test (such as polymerase chain reaction [PCR]) are mandatory and must be negative before initiating study treatment (tests to be performed 3 days or less prior to dosing on C1D1; an additional 2 days are allowed in the event of logistical issues for receiving the results on time).
11. Patients who are carriers of human immunodeficiency (HIV) virus, hepatitis B virus (HBV), or hepatitis C virus (HCV), and require anti-viral therapy or prophylaxis.

    Note: Serology testing is mandatory for patients with unknown status.
12. History of Stevens-Johnson syndrome or toxic epidermal necrolysis.
13. Failure to recover ≤ Grade 1 (Common Terminology Criteria for Adverse Events version 4.0 [CTCAE v4.0]) from acute non-hematologic toxicity (except ≤ Grade 2 neuropathy or alopecia), due to previous therapy, prior to screening.
14. HL with central nervous system involvement, including leptomeningeal disease.
15. 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).
16. Breastfeeding or pregnant.
17. Significant medical comorbidities, including uncontrolled hypertension (blood pressure [BP] ≥ 160/100 mmHg repeatedly), unstable angina, congestive heart failure (greater than New York Heart Association class II), electrocardiographic evidence of acute ischemia, coronary angioplasty or myocardial infarction within 3 months prior to screening, severe uncontrolled atrial or ventricular cardiac arrhythmia, poorly controlled diabetes, or severe chronic pulmonary disease.
18. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy, within 14 days prior to start of study drug, except shorter if approved by the Sponsor.
19. Use of any other experimental medication within 30 days prior to start of study drug.

20. Any live vaccine within 4 weeks prior to start of study drug and planned live vaccine administration after starting study drug.
21. Congenital long QT syndrome, or a corrected QTc interval of ≥ 480 ms, at screening (unless secondary to pacemaker or bundle branch block).
22. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.

5.3 Screening Failures

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

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

- Informed consent
- Demographics
- Inclusion/exclusion criteria
- SAE and/or death occurring during the Screening Period
- Screening failure details

5.4 Re-screening Procedures

A patient who did not meet the eligibility criteria (screening 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.

5.5 Discontinuation

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

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

5.5.1 Discontinuation from Study Drug

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

- Planned for HSCT
- Major protocol deviation
- Discontinuation of the study by the Sponsor

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

- Investigator's decision
- Patient decision
- Disease progression (radiographic and/or clinical) based on Investigator's assessment
- Unacceptable toxicity
- Pregnancy
- Death

IMPORTANT: Study drug discontinuation is not to be automatically considered as withdrawal from the study. Patients discontinuing the study drug will be asked to perform an EOT visit (Section 4.2.3) and continue with the Follow-up period (Section 4.2.4) 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:

- Withdrawal of consent
- Investigator/Sponsor decision
- Death
- Loss to follow-up (Section 5.5.3)
- Study completion

If a patient withdraws informed consent for the study, 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.

The study may be terminated at any time, for any reason, by the Sponsor. Patients still receiving study drug should have an EOT visit as described in Section 4.2.3 and Schedule of Events (SoE) (Table 1).

5.5.3 Loss to Follow-up

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

5.6 Patient Replacements

No patients will be replaced.

6 Treatment

6.1 Study Drug

Camidanlumab tesirine will be provided as a lyophilized white to off-white powder in 2 mL glass vials (5 mg camidanlumab tesirine per vial) and stored at 2°C to 8°C. The lyophilized camidanlumab tesirine is formulated in 20 mM histidine, 175 mM sucrose, and 0.04% polysorbate 20, at pH 6.0. Prior to use, the study drug is reconstituted with 1.2 mL of sterile water for injection to deliver 1.0 mL at a concentration of 5 mg/mL. After reconstitution, the vial should be gently swirled (do not shake the vial) to ensure complete dissolution and homogeneity, and visually inspected prior to use. Sterile water for injection is to be provided by study sites.

Additional study drug description is included in the pharmacy manual.

6.2 Management of Clinical Supplies

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

6.2.1 Packaging and Storage

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

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

The lyophilized formulation of camidanlumab tesirine should be protected from long-term exposure to light and stored refrigerated (2°C to 8°C). Light protection is not required for dose preparation and during administration of the diluted drug in the IV bag.

6.2.2 Preparation and Administration

The study drug solution at a 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. Of note, a cap on the administered dose is to be applied for patients with a body mass index ≥35 kg/m^2. Additional details are included in the pharmacy manual.

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

Camidanlumab tesirine is administered as a 30-minute intravenous (IV) infusion on Day 1 of each cycle.

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

Extravasation of camidanlumab 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 camidanlumab tesirine should be managed according to institutional protocol for management of extravasation of cytotoxic chemotherapy.

For patients who have a central line, administration of camidanlumab tesirine via this central line should be considered.

6.2.3 Accountability

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

6.3 Camidanlumab Tesirine Dosing

Camidanlumab tesirine will be administered at a dose of 45 µg/kg Q3W for 2 cycles, then 30 µg/kg for subsequent cycles.

Refer to Section 6.7 for premedication and supportive care.

6.4 Dose Delays and Modifications

The Investigator may suspend camidanlumab tesirine dosing for up to 21 days, for any patient who experiences any toxicity of any grade.

Resumption of dosing with camidanlumab tesirine after any suspension, even when longer than 21 days, is at the discretion of the Investigator, on assessment of the patient's clinical condition and whether or not the patient is deriving potential clinical benefit from treatment with camidanlumab tesirine.

The Investigator may also suspend camidanlumab tesirine dosing for any patient scheduled for HSCT in the near future, and resumption of dosing is only allowed if the patient has not received in the meantime any chemotherapy-based mobilization/conditioning therapy or HSCT.

Management of toxicities, when considered to be at least possibly related to camidanlumab tesirine, must be performed according to:

- Section 6.4.1 for general events (i.e., not specified in the below sections),
- Section 6.4.2 for specific non-hematologic events,
- Section 6.4.3 for specific hematologic events,
- Section 6.4.4 for specific neurologic events,

- Section 6.4.5 for specific skin events.

6.4.1 Guidelines for Dose Modification: General

AE Grade	Camidanlumab Tesirine Management Guideline
1/2	No dose adjustment is required.
3/4	**First Occurrence:** • Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline. • If improvement to ≤ Grade 1 or Baseline occurs prior to the next scheduled dose, proceed with the originally planned camidanlumab tesirine dose level. • If improvement to ≤ Grade 1 or Baseline occurs > 21 days from the last scheduled (but missed) camidanlumab tesirine dose, continue camidanlumab tesirine and reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Second Occurrence:** • Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline, reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Third Occurrence:** Permanently discontinue camidanlumab tesirine.

6.4.2 Guidelines for Dose Modification: Specific Non-hematologic Toxicities

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
Infusion-related reactions	**1**	The infusion rate may be decreased or temporarily interrupted to permit resolution of the event. If the total time for dilution into the IV bag and infusion takes longer than 4 hours, the remaining solution of camidanlumab tesirine will be discarded and the dosing will continue with the assigned dose at the next scheduled dosing visit. Please refer to Section 6.7.3 for treatment recommendation.
	2	Interrupt camidanlumab tesirine infusion to permit resolution of the event. If the event resolves within the total time of 4 hours after dilution into the IV bag and infusion time, resume camidanlumab tesirine infusion at 50% of the prior infusion rate, still not exceeding the total of 4 hours after infusion has restarted. If the resolution takes longer than the total 4 hours, the remaining solution of camidanlumab tesirine will be discarded, and the dosing will continue with the assigned dose at the next scheduled dosing visit at 50% of the prior infusion rate. Please refer to Section 6.7.3 for treatment recommendation.
	3	Permanently discontinue camidanlumab tesirine. However, if the AE resolves within 24 hours after onset (with or without clinical management), dosing may continue with the assigned dose at the next scheduled dosing visit at 50% of the prior infusion rate. Please refer to Section 6.7.3 for treatment recommendation.
	4	Permanently discontinue camidanlumab tesirine.
AST, ALT, or GGT abnormalities **or** **Edema** **or** **Effusion**	**2/3**	**First Occurrence:** • Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline. • If improvement to ≤ Grade 1 or Baseline occurs prior to the next scheduled dose, proceed with the originally planned camidanlumab tesirine dose level. • If improvement to ≤ Grade 1 or Baseline occurs > 21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Second Occurrence:** • Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline. • If improvement to ≤ Grade 1 or Baseline occurs, reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
		Third Occurrence: Permanently discontinue camidanlumab tesirine.
	4	**First Occurrence:** • Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline. • If improvement to ≤ Grade 1 or Baseline occurs, continue camidanlumab tesirine and reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Second Occurrence:** Permanently discontinue camidanlumab tesirine.
Hy's law (AST and/or ALT > 3 × ULN and bilirubin > 2 × ULN)	**-**	Permanently discontinue camidanlumab 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.
Autoimmune toxicities (e.g., hyperthyroidism, hypothyroidism, hepatitis, other endocrinopathies)	**≥ 1**	Need to be followed at least weekly to quickly detect deterioration and modify dosing as per general recommendations in Section 6.4.1 (can be done by telephone unless symptoms worsen). Consider using ASCO guidelines for management of immune-mediated toxicities (Brahmer, 2018), or local guidelines. Specific guidelines for management of hyperthyroidism, hypothyroidism, and hepatitis are provided in the Appendix 13.5.
Selected Types of Infection: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, or SARS-CoV-2.	**Any Grade**	No dose adjustment is required; however, hold camidanlumab tesirine. Re-dosing must be delayed so that there is at least a 4-week window between symptom resolution and the next dose of camidanlumab tesirine. If there is suspicion that a patient may have contracted the coronavirus disease COVID-19 (e.g., recent contacts with persons who tested positive and/or recent symptoms of respiratory tract infection and/or recent loss of smell and/or taste), a pathogen-directed SARS-CoV-2 test, such as polymerase chain reaction (PCR), should be performed. If the patient tests positive, a repeat test should be conducted 7 to 14 days later. If the patient repeatedly tests positive without having developed symptoms, dosing may proceed at the discretion of the Investigator.

6.4.3 Guidelines for Dose Modification: Specific Hematologic Toxicities

Consider use of granulocyte colony-stimulating factor (G-CSF) as per institutional guidelines or as per American Society of Clinical Oncology (ASCO) guidelines for neutropenia/febrile neutropenia.

For anemia, consider use of erythropoietin as per institutional guidelines.

If a patient experiences hematologic toxicity of ≥ Grade 3 neutropenia or thrombocytopenia, camidanlumab tesirine must be held until the toxicity resolves to ≤ Grade 2.

6.4.4 Guidelines for Dose Modification: Specific Neurologic Toxicities

Patients experiencing any new neurological toxicities and/or new onset of pain refractory to common pain medications ≥ Grade 1, not explained by previous medical history, that could be linked to or may be an early indicator of polyradiculopathy/GBS, such as ascending (bilateral) sensory loss or motor weakness, need to be immediately evaluated by a neurologist and dosing of camidanlumab tesirine must be held until polyradiculopathy/GBS is ruled out. Please refer to Section 6.7.5 for management of polyradiculopathy/GBS, especially for the recommendation of prompt initiation of therapy upon reasonable suspicion of polyradiculopathy/GBS. Should further clinical, radiologic, or laboratory evidence support the diagnosis of polyradiculopathy/GBS with Level 1 diagnostic certainty (Section 6.7.5 and Appendix 13.2), treatment with camidanlumab tesirine must be permanently discontinued.

Patients with ≥ Grade 3 neurologic toxicities defined as peripheral sensory and peripheral motor neuropathies and not explained by previous medical history must have treatment with camidanlumab tesirine permanently discontinued.

Other new neurological findings not explained by previous medical history with an increase of ≥ 1 Grade over Baseline will result in dose delay; dosing may be resumed after resolution to Baseline, at the Investigator's discretion. The patient must be carefully monitored at least weekly until such resolution (can be done by telephone unless symptoms worsen).

6.4.5 Guidelines for Dose Modification: Specific Skin Toxicities

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
Maculopapular rash **or** **Photosensitivity rash** **or** **Pruritus** **or** **Xerosis** **or** **Hyperpigmentation**	**1**	No dose adjustment is required and monitor for change in severity. Topical treatment to affected areas is indicated: - maculopapular rash, photosensitivity rash, or pruritus: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report).
	2	No dose adjustment is required and monitor for change in severity. Topical treatment to affected areas is indicated: - maculopapular rash or photosensitivity rash: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%). - pruritus: high potency topical steroid cream and consider oral antipruritic (e.g., hydroxyzine, gabapentin, or pregabalin). - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report). In case these Grade 2 rashes become intolerable, Grade 3 recommendations may be applied.
	3	Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline and consider dermatology consult. Topical treatment to affected areas is indicated and consider systemic corticosteroid treatment e.g., prednisone 0.5 mg/kg for 10 days: - maculopapular rash or photosensitivity rash: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider prednisone 0.5 mg/kg for 10 days. - pruritus: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider oral antipruritic (e.g., hydroxyzine, gabapentin, or pregabalin). - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID; and triamcinolone 0.1% cream BID.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
		Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then: **First Occurrence:** • If improvement to ≤ Grade 1 or Baseline occurs prior to the next scheduled dose, proceed with the originally planned camidanlumab tesirine dose level. • If improvement to ≤ Grade 1 or Baseline occurs > 21 days from the last scheduled (but missed) camidanlumab tesirine dose, reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Second Occurrence:** • If improvement to ≤ Grade 1 or Baseline occurs, reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Third Occurrence:** Permanently discontinue camidanlumab tesirine.
	4	Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline and consider dermatology consult. Topical treatment to affected areas is indicated and consider systemic corticosteroid treatment, e.g., prednisone 0.5 mg/kg for 10 days: - maculopapular rash or photosensitivity rash: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider prednisone 0.5 mg/kg for 10 days. - pruritus: high potency topical steroid cream (e.g., clobetasol propionate 0.05%, halobetasol propionate 0.05%) and consider oral antipruritic (e.g., hydroxyzine, gabapentin, or pregabalin). - xerosis or hyperpigmentation: consider ammonium lactate 12% or urea 20% BID; and triamcinolone 0.1% cream BID. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then: **First Occurrence:** • If improvement to ≤ Grade 1 or Baseline occurs, continue camidanlumab tesirine and reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Second Occurrence:** Permanently discontinue camidanlumab tesirine.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
Blistering rash	**1**	No dose adjustment is required and monitor for change in severity. Consider dermatology consult Topical treatment to affected areas is indicated, e.g., silvadene 1% cream BID and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus). Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report).
	2/3	Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline and consider dermatology and wound care consult. Topical treatment to affected areas is indicated, e.g., silvadene 1% cream BID, and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus) and consider systemic corticosteroid treatment, e.g., prednisone 0.5 mg/kg for 10 days. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then: **First Occurrence:** • If improvement to ≤ Grade 1 or Baseline occurs prior to the next scheduled dose, proceed with the originally planned camidanlumab tesirine dose level. • If improvement to ≤ Grade 1 or Baseline occurs > 21 days from the last scheduled (but missed) camidanlumab tesirine dose, continue camidanlumab tesirine and reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Second Occurrence:** • If improvement to ≤ Grade 1 or Baseline occurs, reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg. **Third Occurrence:** Permanently discontinue camidanlumab tesirine.
	4	Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline and consider dermatology consult. Topical treatment to affected areas is indicated, e.g., silvadene 1% cream BID, and consider laboratory testing for blistering disorder (VZV/HSV and bacterial infection; bullous pemphigoid; pemphigus) and consider systemic corticosteroid treatment, e.g., prednisone 0.5 mg/kg for 10 days. Reassessment every 2 weeks is indicated (either by healthcare professional or patient self-report); if reactions do not improve, then: **First Occurrence:** • If improvement to ≤ Grade 1 or Baseline occurs, continue camidanlumab tesirine and reduce from 45 to 30 µg/kg or from 30 to 20 µg/kg.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
		Second Occurrence: Permanently discontinue camidanlumab tesirine.

6.5 Overdose Management

An overdose is any dose of study drug given to a patient that exceeds the maximum dose described in the protocol by 15% or more. Any overdose, with or without associated AEs, must be promptly (i.e., within 24 hours after the time site personnel first learn about the event) reported to the Sponsor.

There are no data available to determine what the effects of overdose are and whether they can be reversed. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

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

6.6 Treatment Compliance

Administration of the study drug will be performed by the Investigator or a qualified designee; therefore, compliance will be verified by the study drug administration information.

6.7 Premedication and Supportive Care

6.7.1 Premedication

Unless contraindicated, administer dexamethasone 4 mg orally twice daily (BID), or equivalent, the day before camidanlumab tesirine administration (if possible), the day of camidanlumab 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 camidanlumab tesirine administration.

[**For Italy Sites Only:** Prednisone 25 mg BID is the only equivalent to the dexamethasone 4 mg BID dose permitted as alternative premedication. The dosing schedule of dexamethasone and prednisone is the same.]

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

6.7.2 Treatment of Edema and Pleural Effusion

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

6.7.3 Treatment and Prophylaxis of Infusion-Related Hypersensitivity Reactions

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

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

- On Day 1 of each cycle, patients will be instructed to take dexamethasone 20 mg orally 12 and 6 hours before the start of the camidanlumab 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 camidanlumab 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 camidanlumab tesirine infusion.
- For 2 days following administration of camidanlumab tesirine on Day 1, patients are to take dexamethasone 4 mg orally BID.

6.7.4 Consideration for Skin Toxicity

Skin toxicity has been reported in patients receiving camidanlumab 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, avoidance of being outside with no protection). Also, fragrance-free detergents and soaps are recommended.

Consideration should be given to corticosteroid therapy in patients who develop clinically significant skin toxicity (guidelines for dose modification in Section 6.4.5).

Photographs of skin toxicity may be taken for documentation purposes at the discretion of the Investigator provided the patient has given consent.

6.7.5 Diagnostic, Work-up, and Management of Polyradiculopathy/ Guillain-Barré Syndrome

It is strongly recommended starting prompt management of polyradiculopathy/GBS with either intravenous immunoglobulin (IVIg) 0.4 g/kg/day for 5 days or plasma exchange (PLEX) once diagnosis of polyradiculopathy/GBS has been considered by a neurologist; this could be at CTCAE Grade 2 symptoms for neuropathy or Score 1 as per GBS disability scale (Appendix 13.3). It has to be considered that manifestation of polyneuropathy can be variable.

Diagnostic workup should include:

- Neurology consultation
- Magnetic resonance imaging (MRI) spine with and without contrast to rule out compressive lesion and evaluate for nerve root enhancement or thickening
- Electrodiagnostic studies (nerve conduction studies)
- Serologic test for SARS-CoV-2 (Alberti, 2020; Toscano, 2020; Zhao, 2020)
- Pulmonary function tests
- Lumbar puncture: cerebrospinal fluid (CSF) typically has albuminocytologic dissociation, i.e., protein elevation disproportionate to white blood cells (WBCs—although note that CSF WBCs are often elevated in GBS associated with immune checkpoint inhibitors)
- Serum antibody testing for GBS (ganglioside antibodies) when possible

Management includes:

- IVIg or PLEX as above
- If IVIg and/or PLEX do not result in improvement, consider using steroids (Gu, 2017)
- Admission to inpatient unit with capability for rapid transfer to intensive care unit-level monitoring
- Frequent focused neurological examination (at least twice daily)
- Frequent pulmonary function monitoring
- Monitoring for autonomic dysfunction
- Non-opioid management of neuropathic pain
- Treatment of constipation/ileus
- Anticoagulation
- Physical therapy

6.7.6 Other Supportive Care

Although the study patient population has a low risk for development of tumor lysis syndrome (TLS) compared to patients with acute disease (Cairo, 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 camidanlumab tesirine, where applicable.

The iDSMB recommended VZV prophylaxis according to institutional guidelines for all patients enrolled in this study (whether already receiving camidanlumab tesirine or newly enrolled).

6.8 Concomitant Medications and Procedures

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

6.8.1 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 6.8.2.

Hematopoietic growth factors are permitted as per ASCO guidelines (Smith, 2006).

6.8.2 Prohibited During Study

- Other anticancer therapy during the Treatment Period (including palliative radiotherapy), with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Other investigational agents during the Treatment Period.
- Live vaccines during the Treatment Period and for 3 months after last dose of study drug.

7 Study Assessments and Procedures

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 for screening may be used for determination of patient eligibility only if obtained as part of standard care. For additional details, please refer to Section 11.3.

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 treatment, including surgery, radiation therapy, chemotherapy, etc.
- Immune-related adverse events of prior checkpoint inhibitors.
- Any other relevant medical history. Importantly, according to the iDSMB recommendation patients with signs or symptoms of Grade 2 neuropathy should be examined by a neurologist at Screening.
- Collection of information on prior medications used from ICF signature date or at least within 14 days prior to camidanlumab administration, whichever is earlier.

7.3 Efficacy Assessments

Disease assessments will occur as per SoE (Table 1) until progression.

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

During the treatment period, imaging will be performed 6 weeks and 12 weeks after C1D1, then every 9 weeks until EOT. Week 6 imaging should be performed within 1 week prior to C3D1 and Week 12 imaging should be performed within 1 week prior to C5D1. 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.

During the follow-up period, patients who discontinued study drug for reasons other than disease progression or initiation of other anti-cancer therapy will have imaging performed every 12 (± 2) weeks until 1 year from EOT, then every 6 months until disease progression, up to 3 years from EOT; when patients discontinue the study drug because they are planned to undergo a HSCT or to receive CAR-T therapy, imaging will continue the same way. Moreover, HSCT information such as but not limited to type of HSCT, conditioning therapy

should be recorded in the eCRF. Likewise for CAR-T therapy, the type of CAR-T used including conditioning therapy should be recorded in the eCRF.

If a scan has been performed within 6 weeks of EOT, it does not need to be repeated at EOT.

Additional disease assessments may be obtained, if clinically indicated.

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 tracer-avid, the baseline CT as part of the PET-CT does not have to be performed with contrast medium; however, if the tumor is not tracer-avid, diagnostic CT should be used and contrast medium considered, however 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 PET-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 13.4) as CR, PR, stable disease (SD), or progressive disease (PD). Upon indication of clinical progression (non-radiographic), a radiographic disease assessment to confirm the PD is expected, if clinically indicated, in order to ensure appropriate data collection toward the primary endpoint of this protocol.

Images will be obtained according to local site imaging requirements 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. AEs/SAEs collection and reporting is described in Section 8.

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

7.4.1 Physical Examination

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

Physical examinations will also include a neurological examination of strength, sensation, and deep tendon reflexes. In addition, patients will be asked whether they are or have been experiencing subjective neurologic symptoms (at screening or since the last visit), such as blurred vision, muscle weakness, or paresthesia, and the response must be documented in the

CRF; refer to Section 6.4.4 for dose modification due to specific neurologic toxicities and Section 6.7.5 for details on polyradiculopathy/GBS management. This examination does not need to be conducted by a neurologist. Neurologic consultation needs to be obtained for any abnormal findings not explained by previous medical history (e.g., a patient with left sided weakness known to be a result of a previous cerebrovascular accident would not need to see a neurologist as part of this study) that could be linked to or may be an early indicator of polyradiculopathy/GBS, such as ascending (bilateral) sensory loss, motor weakness, or new onset of pain, which is refractory to common pain medications and with or without any additional neurological deficiencies.

The examination must include a determination if the patient has had any recent infection. At the discretion of the Investigator, evaluation of any reported infection must be conducted to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s) as specified in the exclusion criteria (Section 5.2) and Section 7.4.5.

7.4.2 ECOG Performance Status

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

7.4.3 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 detect potential edema/effusions. Refer to Section 6.7.2 for further details.

7.4.4 Vital Signs

Vital signs will be measured as per SoE (Table 1).

Vital signs include the measurements of arterial BP (systolic and diastolic), heart rate (HR), 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 camidanlumab tesirine infusion and at the end of infusion (example in Figure 2).

7.4.5 Laboratory Tests

Samples will be collected at the time points specified as per SoE (Table 1) and will be analyzed locally. Additional sample(s) may be collected and analyzed if clinically indicated. The C1D1 laboratory test(s) can be waived if the laboratory test(s) for eligibility was done within 3 days of C1D1.

Hematology: WBCs 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, creatine phosphokinase, total protein, albumin, glucose, and lactate dehydrogenase.

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

Urinalysis: pH, specific gravity, protein, WBCs, red blood cell (RBCs), 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.

Thyroid function tests: Thyroid-stimulating hormone (TSH); reflex free T4 (FT4) and/or free triiodothyronine (FT3), as applicable, only when TSH is abnormal.

Influenza and SARS-CoV-2: An influenza test and a pathogen-directed SARS-CoV-2 test (such as PCR) must be performed and be negative for eligibility purposes.

Viral detection: Seropositive patients for, or with prior history of, HIV, HBV, or HCV not receiving antiviral therapy at screening will be monitored during the study (not needed if seropositivity is only due to vaccination).

Additional microbiological studies: Pathogens of interest are: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, *Campylobacter jejuni*, enterovirus D68, and SARS-CoV-2.

Patients will be regularly examined and asked whether they have been suffering from or exhibit symptoms of an infection during their participation in the trial. If there is a reasonable suspicion that such infection could have been caused by one of the pathogens listed above, appropriate microbiological workup must be conducted. See Section 6.4.2 for dose delay recommendation upon confirmation of infection by one of these microorganisms.

If there is suspicion that a patient may have contracted the coronavirus disease COVID-19 (e.g., recent contacts with persons who tested positive and/or recent symptoms of respiratory tract infection and/or recent loss of smell and/or taste), a pathogen-directed SARS-CoV-2 test, such as PCR, should be performed. If the patient tests positive, a repeat test should be conducted 7 to 14 days later. If the patient repeatedly tests positive without having developed symptoms, dosing may proceed at the discretion of the Investigator.

7.4.6 Pregnancy Test

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

The C1D1 pre-dose pregnancy test can be waived if the test for eligibility was done within 7 days of C1D1. After starting the study drug, the interval between 2 consecutive pregnancy tests should be no more than 6 weeks.

The EOT pregnancy test should be performed ≥9.5 months after the last dose of study drug (i.e., end of relevant systemic exposure considering 5 half-lives plus 6 months for other than aneugenic genotoxic compound). If the EOT visit is planned less than 9.5 months after the last dose of study drug, the patient will be asked either to come back to the site for a pregnancy test or she will be given a pregnancy kit to perform the test at home and the result collected over the phone. Both the phone contact and the result of the pregnancy test must be documented on source documents at the site.

If a pregnancy test is positive, the study drug must be held pending confirmation. If the pregnancy is confirmed, camidanlumab tesirine treatment will be discontinued permanently for the patient. Refer to Section 8.6 for the handling of the patient and reporting the event.

7.4.7 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 3 for the detailed schedule of ECGs. The 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 (example in Figure 2). If a patient experiences Torsade de Pointes, additional concomitant PK samples (i.e., unscheduled) should be collected.

The ECGs will be submitted for a central review. Submission instructions for the central review will be provided in a separate manual. Assessments will include determination of heart rate and rhythm and the PR, QRS, QT, QTcF, and QTcB intervals. Eligibility and clinical decisions may be made based on the local ECG assessment.

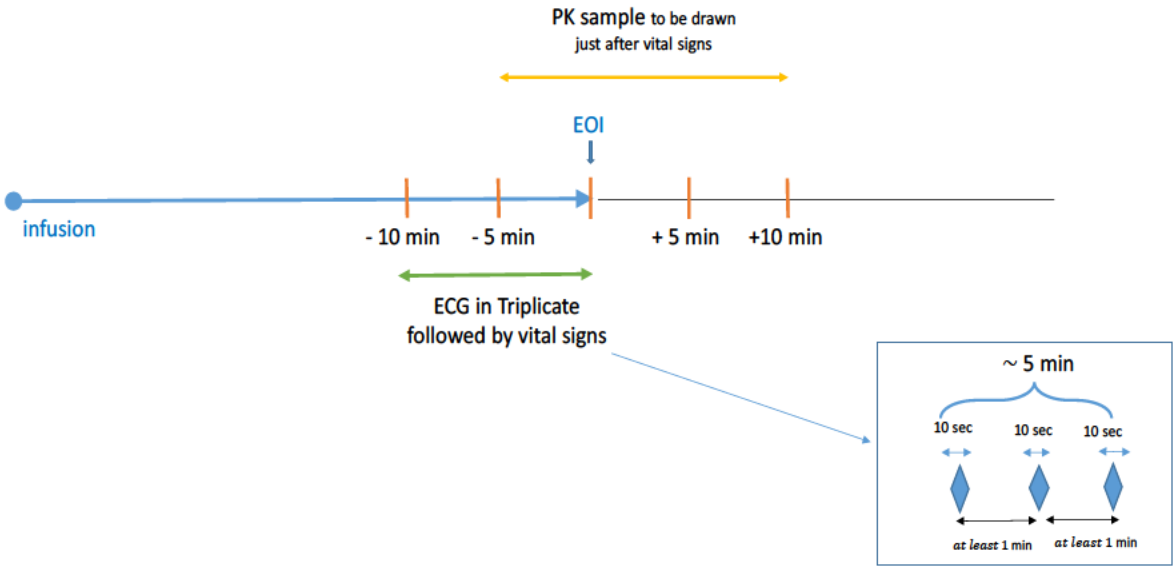
Table 3 Schedule for Triplicate ECG Collection

Cycle	Day	ECG timepoint (window)
Screening	-	Any time within 28 days prior to C1D1
C1	D1	Predose (preferably within 2 h prior to start of infusion) EOI (within 10 min prior to EOI) Postdose* 4 h (± 15 min)
	D8	Postdose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Postdose* 336 h (± 48 h; but within 30 min prior to PK sample)
C2	D1	Predose (within 30 min prior to PK sample) EOI (within 10 min prior to EOI) Postdose* 4 h (± 15 min)
	D8	Postdose* 168 h (± 48 h; but within 30 min prior to PK sample)
	D15	Postdose* 336 h (± 48 h; but within 30 min prior to PK sample)
C3 and C4	D1	Predose (within 30 min prior to PK sample) EOI (within 10 min prior to EOI)
C5, C7 … every other cycle	D1	Predose (within 30 min prior to PK sample)
EOT		Any time (but within 30 min prior to PK sample)
Unscheduled		Any time

Abbreviations: C1D1, Cycle 1, Day 1; ECG, electrocardiogram; EOI, end of infusion; EOT, end of treatment; PK, pharmacokinetics.

* Postdose timepoint is counted from start of infusion.

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, ADA, and biomarker samples 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, and/or biomarker testing.

When multiple samples are required at the same timepoint, collection of safety samples should be first, followed by PK, then ADA, and finally biomarkers.

In order to better understand the disease, metabolic disposition, and pharmacologic behavior of camidanlumab 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 PK profile of camidanlumab tesirine PBD-conjugated antibody, total antibody, and unconjugated warhead SG3199 will be assessed in serum by a central laboratory designated by the Sponsor using validated bioanalytical methods.

Up to 6 mL of whole blood will be collected as per Table 1 and Table 4. Blood should be drawn from a vein away from the one used for study drug infusion.

The serum 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 (example in Figure 2). If a patient experiences Torsade de Pointes, concomitant PK samples (e.g., unscheduled) should be collected.

Table 4 Sampling Schedule for PK and ADA

Cycle	Day	PK timepoint (window)	ADA timepoint (window)
C1	D1	Predose (preferably within 2 h prior to start of infusion) EOI (-5 to +10 min) Postdose* 4 h (± 10 min)	Predose (preferably within 2 h prior to start of infusion)
	D8	Postdose* 168 h (± 48 h)	-
	D15	Postdose* 336 h (± 48 h)	Postdose* 336 h (± 48 h)
C2	D1	Predose (within 2 h prior to start of infusion) EOI (-5 to +10 min) Postdose* 4 h (± 10 min)	Predose (within 2 h prior to start of infusion)
	D8	Postdose* 168 h (± 48 h)	-
	D15	Postdose* 336 h (± 48 h)	-
C3, C4, C5, and C6	D1	Predose (within 2 h prior to start of infusion) EOI (-5 to +10 min)	-
C3, C5, … every other cycle	D1	-	Predose (within 2 h prior to start of infusion)
C7, C8, … every cycle	D1	Predose (within 2 h prior to start of infusion)	-

Cycle	Day	PK timepoint (window)	ADA timepoint (window)
EOT		At any time during visit day	At any time during visit day
Unscheduled		Any time	Any time (if applicable, together with PK sample)

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

* Postdose timepoint is counted from start of infusion.

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

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.

Up to 6 mL of whole blood will be collected as per Table 1 and Table 4.

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 will be requested for testing every 12 weeks following the EOT visit until the ADA titer falls to a background level, as long as the patient is still on-study.

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

7.5.3 Biomarkers

7.5.3.1 Blood Samples for Biomarkers

Blood samples for biomarkers analyses will be collected as per SoE (Table 1) and a more detailed presentation of soluble markers timepoints is provided in Table 5.

Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

Soluble Biomarkers: Up to 6 mL of blood for the quantification of immunologically relevant biomarkers (e.g., IL-2, IL-6, IL-8, IL-10, IFNγ, TNFα, sCD25, CCL17) will be taken at multiple timepoints. This will include analyses of biomarkers that may be predictive of or associated with GBS (at a minimum on C1D1 and C3D1 predose).

cfDNA/gDNA: Up to 30 mL of whole blood will be taken at multiple timepoints for investigating genetic alterations characterizing Hodgkin lymphoma in cfDNA. gDNA will be analyzed to confirm the somatic origin of the genetic alterations and will be measured at predose C1D1 and EOT only.

Table 5 Sampling Schedule for Soluble Biomarkers

Cycle	Day	Timepoint (window)
C1	D1	Predose (preferably within 2 h prior to start of infusion) Postdose* 4 h (± 10 min)
	D8	Postdose* 168 h (± 48 h)
	D15	Postdose* 336 h (± 48 h)
C2	D1	Predose (within 2 h prior to start of infusion) Postdose* 4 h (± 10 min)
	D8	Postdose* 168 h (± 48 h)
	D15	Postdose* 336 h (± 48 h)
C3	D1	Predose (within 2 h prior to start of infusion) EOI (within 10 min prior to EOI)
C5, C7, … every other cycle	D1	Predose (within 2 h prior to start of infusion)
EOT		At any time during visit day
Follow-up		-
Unscheduled		Any time (if applicable, together with PK sample)

Abbreviations: EOT, end of treatment; PK, pharmacokinetics.

* Postdose timepoint is counted from start of infusion.

7.5.3.2 Tumor Tissue for Biomarkers

Available tumor tissue will be collected to investigate potential predictive markers of clinical response. Any sample since initial diagnosis is acceptable, but if several samples are available, the most recent sample is preferred. Tumor tissue (FFPE block preferred) should be submitted once it has been determined that the patient meets all other eligibility criteria and is scheduled to proceed with study drug administration.

Please refer to the laboratory manual for detailed instructions regarding specimen handling and shipment.

7.6 Health-Related Quality of Life (HRQoL) Questionnaires

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

The EQ-5D-5L is designed as an international, standardized, generic instrument for describing and evaluating QoL (EuroQoL Group, 1990). This questionnaire can be completed by patients ≥12 years of age. The EQ-5D-5L consists of 2 parts:

- The descriptive system: QoL is classified according to 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 5 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.

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

The FACT-Lym is a lymphoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT) questionnaire (Hlubocky, 2013). As this questionnaire has been validated for patients ≥18 years old; therefore, it will not be adminitered to patients <18 years old (age at screening). 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.

8 Adverse Events

8.1 Definition of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

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.

An 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 judgment may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed above.

Adverse Events of Special Interest (AESIs) are significant AEs that are judged to be of special interest because of clinical importance, known class effects, or based on preclinical signals. Events considered to be AESIs are identified in Section 8.1.1.

8.1.1 Adverse Events of Special Interest

For this study the following adverse events, irrespective of seriousness and causality, are considered AESIs:

- GBS (including variants such as acute motor and sensory axonal neuropathy)
- Polyradiculopathy
- Autonomic nervous system imbalance
- Nerve palsy
- ≥Grade 3 neurologic toxicities

- ≥Grade 3 immune-mediated toxicities. Of note, rashes will not be considered as immune-mediated skin toxicities, since they are well described toxicities of PBD-dimers; with exception for Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, exfoliative dermatitis, and drug reaction with eosinophilia and systemic symptoms.
- Autoimmune-mediated events (such as, but not limited to, pneumonitis, hepatitis, colitis, endocrinopathies, type 1 diabetes mellitus, and nephritis/renal dysfunction)

For all AESIs it is important to provide as much information as possible: e.g., time of onset (including changes in severity), duration of events, time to resolution, and relationship to camidanlumab tesirine. It is also important to specify if any AEs are autoimmune mediated.

AESIs will be closely monitored and followed.

8.2 Eliciting and Reporting Adverse Events/Adverse Events of Special Interest/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.

All 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, AESIs, and 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; thereafter, only related SAEs will be reported [**For German Sites Only**: thereafter, only SAEs will be recorded (irrespective of the relationship to the study drug)]. The exception to this is patients who have responded to camidanlumab tesirine and undergo HSCT (either autologous or allogeneic) after permanent discontinuation of camidanlumab tesirine treatment without any intervening anti-cancer therapy to treat relapsing disease (mobilization/conditioning treatment for HSCT is allowed) or who have received CAR-T as the immediate subsequent anticancer therapy (mobilization/conditioning treatment for CAR-T is allowed). These patients will have the following safety information reported until 180 days post-HSCT/post-CAR-T regardless of relationship to camidanlumab tesirine:

- ≥ Grade 3 AEs suggestive of hepatic toxicity, veno-occlusive disease/sinusoidal obstruction syndrome, graft-versus-host disease, infectious complications, potentially immune-mediated adverse events, prolonged cytopenia(s), and pulmonary toxicity
- In addition, for CAR-T therapy, any ≥ Grade 3 AEs of cytokine-release-syndrome and neurological 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 8.3), seriousness (Section 8.1), relationship to study drug (Section 8.4), 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 serious AESIs/SAEs and any recurrent episodes, progression, or complications of the original AESI/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.

Any recurrence of GBS/polyradiculopathy, irrespective of the relationship to study drug, has to be reported to the Sponsor, including when the recurrence occurs when the patient has already completed the study. The reporting of such events after the patient has completed the study will be captured via the Sponsor's safety database and therefore will not impact database lock.

Non-serious AESIs must be entered in the EDC system and reported to the Sponsor or delegate (e.g., CRO) within 48 hours after the time site personnel first learn about the event.

8.3 Assessment of Severity

All 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 6.

Table 6 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 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.

8.5 Regulatory Reporting

Reporting of AEs to competent authorities and Independent Ethics Committees (IECs) will be consistent with local laws, regulations, guidelines, and requests.

8.6 Pregnancy Reporting

Any pregnancy in a patient that occurs from signing the ICF up to 9.5 months after the last dose of study drug, whichever occurs last, must be reported using the Pregnancy Report Form. Any pregnancy in a partner of a male patient that occurs from signing the ICF up to 6.5 months after last dose of study drug 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) 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 7.4.6 for additional information.

8.7 Independent Data and Safety Monitoring Board

An iDSMB will primarily ensure the safety of patients enrolled in this study by providing expertise and recommendations for further study conduct and progress, which concern the continuation, modification, or termination of the study.

The iDSMB will be composed of at least one clinician with immuno-oncology expertise and a biostatistician. The board will meet periodically to review data, and as soon as possible upon occurrence of polyradiculopathy/GBS and possibly other relevant ≥ Grade 3 autoimmune or neurologic toxicities (see Section 4.3) or other concerning safety issues.

Details regarding the iDSMB responsibilities, authorities, and procedures will be included in a separate iDSMB charter.

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). Results for the exploratory/correlative analyses may be reported separately.

9.1 Sample Size Calculation

This study uses a single-arm design to test for an improvement in response rate in the HL population. A sample size of 100 will provide a robust population for safety evaluation and adequate precision for observed ORR in the expected range. For the test of efficacy, this study has > 98% power to distinguish between an active therapy with a 55% true response rate from a therapy with a response rate of 35% or less with a 1-sided alpha of 0.025.

9.2 Analysis Populations

- All-Treated Population: All patients who receive at least 1 dose of camidanlumab 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 important protocol deviations, which will be further described in detail in the SAP.
- The PK Population: All patients who receive study drug and have at least 1 pre- (C1D1) and 1 postdose valid assessment.
- The Pharmacodynamic Population: All patients who receive study drug and have at least 1 valid pharmacodynamics/biomarker assessment.

9.3 Interim Analysis

No formal interim analysis is planned.

9.4 Final Analysis

For primary and key secondary endpoints analyses, a database snapshot will be taken when all patients who achieve PR or CR have a minimum of 12 months follow-up after initial documented response (may be less for patients undergoing HSCT). All efficacy, safety, and PK endpoints will be analyzed and reported in the clinical study report (CSR).

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 100 patients (≤ 110 patients expected, see Table 7).

Table 7 Number of Responses Needed to Have 95% CI Low Bound of ORR >35%

Total Patients Enrolled	100	102	105	108	110
Number of Responders	45	46	47	49	49
Lower Bound of 95% Exact CI	35.03%	35.22%	35.05%	35.76%	35.07%

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

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

9.6 Exposure to Treatments

Exposure to study drug, prior, and concomitant medications will be summarized for the All-Treated analysis set by dose level. Dose interruptions, reductions, and relative dose intensity will also be summarized.

9.7 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.

9.7.1 Overall Response Rate

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

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

9.7.2 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). A sensitivity analysis of DOR is planned to be conducted in which the DOR for patients undergoing SCT is not censored at the last evaluable disease assessment prior to SCT. The data will be analyzed by the Kaplan-Meier method. The median DOR and 95% CI will be presented. DOR will be analyzed by response subgroup (CR, PR). Further details will be outlined in the SAP.

9.7.3 Complete Response Rate

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

9.7.4 Relapse-free Survival

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

9.7.5 Progression-free Survival

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

9.7.6 Overall Survival

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

9.7.7 Patients Receiving Transplant

The fraction of patients receiving HSCT following camidanlumab tesirine, and without any other anticancer therapy in between other than the therapies preparing for HSCT, will be summarized.

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 drug to 30 days after the last dose of study drug in this study or start of a new anticancer therapy/procedure, whichever comes 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 or higher); study drug-related AEs; AEs leading to treatment interruption, modification, or discontinuation; AESIs; serious AEs; and death.

9.8.2 Clinical Laboratory Results

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

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

9.8.3 Additional Safety Assessments

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

9.9 Pharmacokinetic Analyses

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

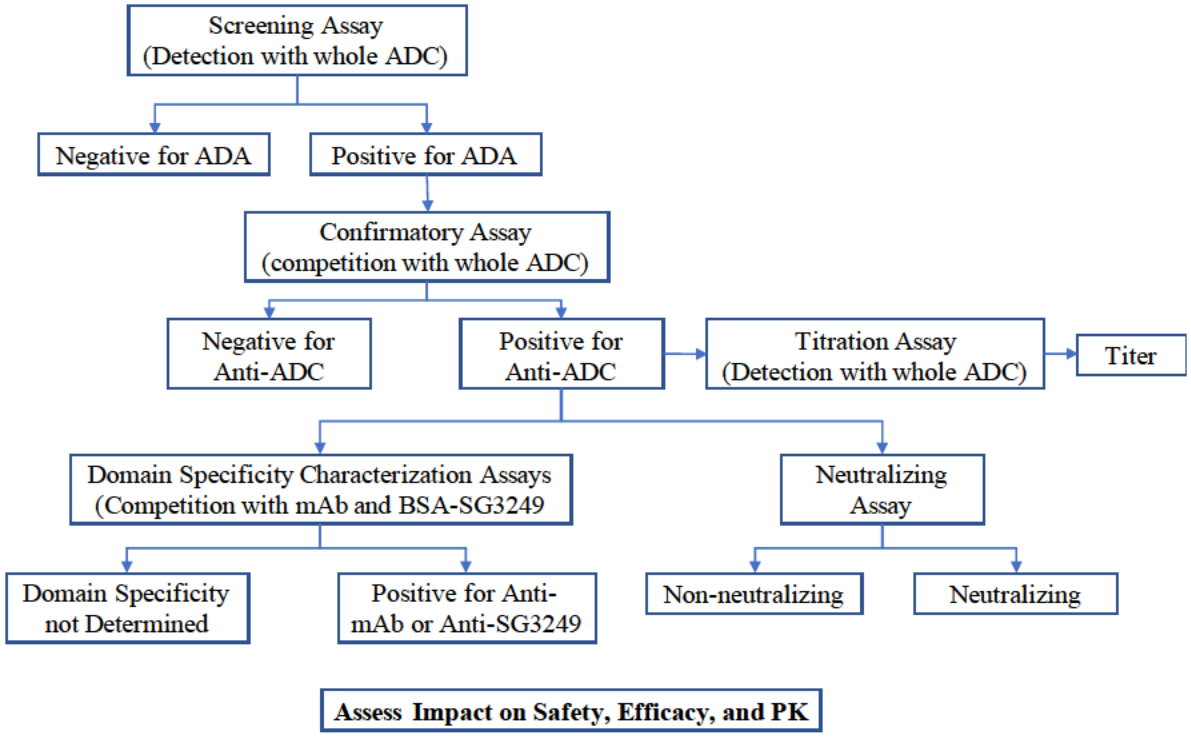
PK parameters will be determined for all PK-evaluable patients using a non-compartmental population PK analysis using Phoenix WinNonlin (Certara US, Inc., Princeton, NJ, US) or other appropriate software. Supplemental integrated population PK analyses will be undertaken and reported separately to evaluate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

Potential correlations of PK parameters to Baseline characteristics and safety observations will be assessed but may be reported separately. In addition, the influence of camidanlumab tesirine PBD-conjugated antibody and unconjugated warhead SG3199 concentrations on the QTc interval will be assessed but reported separately.

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 the new Food and Drug Administration (FDA) Draft Guidance for Industry (April 2016): 'Assay Development and Validation for Immunogenicity testing of Therapeutic Protein Products'.

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 predose ADA response, number of patients with postdose 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 Exploratory Analyses

Exploratory analyses may be reported separately as an amendment to the CSR.

10 Data Management and Quality Assurance

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

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

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

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

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

11 Ethical, Regulatory, and Study Management Considerations

11.1 Regulatory and Ethical Conduct of the Study

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

11.2 Independent Ethics Committee or Institutional Review Board

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

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

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

11.3 Patient Information and Consent

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

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

11.4 Confidentiality

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

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

11.5 Financial Disclosure and Obligations

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

11.6 Study Conduct

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

11.7 Protocol Amendments

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

11.8 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.

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.

11.9 Records Retention

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

11.10 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).

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13 Appendices

13.1 Appendix: Eastern Cooperative Oncology Group Performance Status

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

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

Reference: Oken, 1982

13.2 Appendix: Clinical Case Definitions: Level 1 of Diagnostic Certainty for Guillain-Barré Syndrome (GBS)

- Bilateral AND flaccid weakness of the limbs[1, 2, 3]

  AND

- Decreased or absent deep tendon reflexes in weak limbs[4]

  AND

- Monophasic illness pattern[5] AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau[6]

  AND

- Electrophysiologic findings consistent with GBS[7]

  AND

- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count < 50 cells/μL)[8]

  AND

- Absence of an identified alternative diagnosis for weakness[9]

Reference: Sejvar, 2011

1. Weakness is usually, but not always, symmetric in nature, and usually has a pattern of progression from legs to arms (ascending). However, other patterns of progression may occur (e.g., beginning in the arms). The degree of weakness can range from mild to moderate to severe, i.e., complete paralysis.
2. Respiratory or cranial nerve-innervated muscles may also be involved.
3. It is important that strength be assessed in a manner that takes into account subject age, sex, and level of functioning.
4. Decreased or absent tendon reflexes may also be seen in limbs without weakness. However, to meet case definition criteria, decreased or absent tendon reflexes must be observed in weak limbs.
5. Fluctuations in level of weakness, before reaching nadir, or during the plateau or improvement phases, occur in some cases, usually associated with the use of disease-modifying therapies. Such fluctuations usually occur within the first 9 weeks after onset and are followed by eventual improvement.
6. The eventual outcome is either stabilization at nadir OR subsequent improvement OR death.
7. Electrophysiologic patterns consistent with polyneuropathy of the types described for GBS. Electrophysiologic studies performed sooner than 7 days after weakness onset may be normal and should thus be repeated at a later time if possible, and "normal" studies may occur in otherwise typical cases of GBS. However, cases with persistently "normal" studies will not meet Level 1 criteria.
8. CSF (cerebrospinal fluid) protein concentrations should be elevated above what is considered normal reference values for the testing laboratory. CSF may be "normal" in otherwise typical cases of GBS; this is particularly true within the first week of illness. However, cases with persistently "normal" CSF, or CSF with ≥ 50 WBC, will not meet Level 1 criteria.
9. If an alternative diagnosis explaining flaccid weakness/paralysis is present a diagnosis of Guillain–Barré syndrome is excluded. However, in many, if not most cases, a comprehensive documentation of testing for various other etiologies will either be incomplete or unavailable. These case definitions are provided to give guidance in the absence of detailed information on investigations for alternative etiologies of flaccid paralysis.

13.3 Appendix: Guillain–Barré Syndrome Disability Scale

Score	Description
0	Healthy
1	Minor symptoms or signs of neuropathy but capable of manual work/capable of running
2	Able to walk without support of a stick (5 m across an open space) but incapable of manual work/running
3	Able to walk with a stick, appliance, or support (5 m across an open space)
4	Confined to bed or chair bound
5	Requiring assisted ventilation (for any part of the day or night)
6	Death

Reference: Sejvar, 2011

13.4 Appendix: Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (Lugano Classification)

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

Response/Site	PET-CT-Based Response	CT-Based Response
Bone marrow	• Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	• Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	• Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	• < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	• Not applicable	• No increase consistent with progression
Organ enlargement	• Not applicable	• No increase consistent with progression
New lesions	• None	• None
Bone marrow	• No change from baseline	• Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease** **(**requires at least 1 of the following)
Individual target nodes/nodal masses	• Score 4 or 5 with an increase in intensity of uptake from baseline and/or	• PPD progression
Extranodal lesions	• New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment	An individual node/lesion must be abnormal with: • LDi > 1.5 cm and • Increase by ≥ 50% from PPD nadir and • An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm • In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline • New or recurrent splenomegaly
Nonmeasured lesions	• None	• New or clear progression of preexisting nonmeasured lesions

Response/Site	PET-CT-Based Response	CT-Based Response
New lesions	• New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	• New or recurrent FDG-avid foci	• New or recurrent involvement

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

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

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

Reference: Cheson, 2014

13.5 Appendix: Management of Specific Autoimmune Toxicities: Hyperthyroidism, Hypothyroidism, and Hepatitis

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
Hyperthyroidism	**1**	No dose adjustment is required. Close follow-up (at least weekly; by phone if stable) and monitoring of TSH, reflex FT4 and/or FT3 (as applicable), every 2-3 weeks, until it is clear whether there will be persistent hyperthyroidism (>6 weeks) or hypothyroidism.
	2	Consider endocrine consultation. Dose delay is at the Investigator's discretion. Rechallenge without dose adjustment is permitted. β-blocker (e.g., atenolol) for symptomatic relief, hydration, and supportive care may be needed. For persistent hyperthyroidism or clinical suspicion (e.g., ophthalmopathy or thyroid bruit), work-up for Graves disease and consider thionamide.
	3/4	Endocrine consultation is indicated. Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline with appropriate therapy. Rechallenge is then permitted as per General Guidelines for Dose Modification (Section 6.4.1). Give β-blocker (e.g., atenolol) for symptomatic relief. For severe symptoms or concern for thyroid storm, hospitalize patient and initiate prednisone 1-2 mg/kg/day or equivalent tapered over 1-2 weeks; consider also use of saturated solutions of potassium iodide or thionamide.
Hypothyroidism	**1**	Asymptomatic; TSH generally <10 mIU/L. No dose adjustment is required. Close follow-up (at least weekly; by phone if stable) and monitoring of TSH, FT4/FT3 (as applicable) every 4-6 weeks.
	2	TSH generally persists >10 mIU/L. Consider endocrine consultation. Dose delay is at the Investigator's discretion. Rechallenge without dose adjustment is permitted. Give thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist >10 mIU/L. Monitor TSH, FT4/FT3 (as applicable) every 6-8 weeks while titrating hormone replacement to normal TSH. Thereafter, monitor TSH, FT4 and/or FT3 (as applicable) every 6 weeks during camidanlumab tesirine treatment or as needed for symptoms to ensure appropriate hormone replacement; repeat testing annually or as indicated by symptoms once stable.

Adverse Event	Grade	Camidanlumab Tesirine Management Guideline
	3/4	Endocrine consultation is indicated. Hold camidanlumab tesirine until improvement to ≤ Grade 1 or Baseline, or control with appropriate supplementation. Rechallenge is then permitted as per General Guidelines for Dose Modification (Section 6.4.1). May admit for IV therapy if signs of myxedema (bradycardia, hypothermia) Provide thyroid supplementation and reassessment as in Grade 2.
Hepatitis	**1/2**	Asymptomatic LFT elevations and Hy's law should be managed per guidances given in the Section 6.4.2. Consider work-up for other causes of elevated liver enzymes (CIOMS Working Group consensus, 2020): e.g., viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, cross-sectional imaging for potential liver metastasis. Antinuclear antibodies, antismooth muscle antibodies, and/or antineutrophil cytoplasmic antibodies testing can be considered if suspicion for primary autoimmune hepatitis.
	3	Consider hepatology consult and biopsy. Work-up for alternative causes as in Grade 2. Permanently discontinue camidanlumab tesirine. Closely monitor chemistries (every 1-2 days). Consider inpatient monitoring for patients with AST/ALT > 8 x ULN and/or elevated total bilirubin > 3 x ULN. Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent; seek hepatology consultation. If corticosteroid refractory or no improvement after 3 days, consider additional treatments such as mycophenolate mofetil or azathioprine. Corticosteroid tapering can be attempted around 4-6 weeks; re-escalate if needed.
	4	Consider hepatology consult and biopsy. Work-up for alternative causes as in Grade 2. Permanently discontinue camidanlumab tesirine. Monitor chemistries daily, consider inpatient monitoring. Administer 2 mg/kg/day methylprednisolone or equivalent, avoid use of infliximab. Corticosteroid tapering can be attempted around 4-6 weeks when symptoms improve to ≤ Grade 1 or Baseline; re-escalate if needed.