Protocol Number: ADCT-301-001

Official Title: A Phase 1 Adaptive Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-301 in Patients with Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma

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A Phase 1 Adaptive Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-301 in Patients with Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma

PROTOCOL NO.: ADCT-301-001

Sponsor: **ADC Therapeutics SA**

Sponsor Contact: [redacted]

Medical Monitor: [redacted]

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Protocol Approval – Sponsor Signatory

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Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 1 Adaptive Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-301 in Patients with Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma" and the accompanying Investigator Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Protocol Amendment 9, dated 04 January 2019, the current version of International Council for Harmonisation (ICH) harmonised tripartite guideline E6: Good Clinical Practice and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics SA or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the investigational 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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Protocol Synopsis

Protocol Number:	ADCT-301-001
Title:	A Phase 1 Adaptive Dose-Escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-301 in Patients with Relapsed or Refractory Hodgkin Lymphoma and Non-Hodgkin Lymphoma
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 1
Study Sites:	Approximately 10 sites during dose-escalation (Part 1) and 13 sites during dose expansion (Part 2)
Indication:	Refractory or relapsed lymphoma (per WHO Classification) defined as: • Non-Hodgkin lymphoma (NHL): Patients with histologically confirmed NHL (including stage ≥Ib cutaneous T-cell lymphoma [CTCL]) who have failed or are intolerant to any established therapy known to provide clinical benefit at current state of disease. • Hodgkin lymphoma: Patients with histologically confirmed classical Hodgkin lymphoma who have failed or are intolerant to any established therapy known to provide clinical benefit at current state of disease.
Rationale:	Lymphoma cells have been reported to express cluster of differentiation (CD) 25 on their cell surface. Expression of CD25 is positive (≥20% tumor cells) in approximately 58% to 78% of Hodgkin lymphoma, 42% to 50% of peripheral T-cell lymphoma, 54% of cutaneous T-cell lymphoma, and 40% of diffuse large B-cell lymphoma cases. ADCT-301 is an antibody drug conjugate (ADC), composed of the human monoclonal antibody, HuMax®-TAC, directed against CD25, and conjugated through a cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. PBD dimers are highly efficient anticancer drugs that bind in the minor groove of DNA and form highly cytotoxic DNA interstrand cross-links. After binding and internalization, ADCT-301 is transported to the lysosomes, where the protease sensitive linker is cleaved and free PBD dimers are released inside the target cell. The potential for ADCT-301 in treating hematological malignancies that demonstrate CD25 over-expression has been shown by complete responses in mouse xenograft models following single, low-dose administration. The efficacy of ADCT-301 in these models is due to

	targeted delivery of the PBD cytotoxin SG3199. The safety of ADCT-301 has been assessed in nonclinical testing. In mice, ADCT-301 is well tolerated at doses up to 9 mg/kg. A repeat-dose Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys investigated doses ranging from 0.15 to 0.9 mg/kg. Toxicities included body weight loss, nephrotoxicity, and cutaneous adverse events (AEs). The highest non-severe toxic dose was determined to be 0.15 mg/kg.
Objectives:	**Primary objectives**: The primary objectives for Part 1 (dose escalation) and Part 2 (expansion) of the study are: • Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCT-301 in patients with relapsed/refractory lymphoma (Part 1). • Determine the recommended dose of ADCT-301 for Part 2. • Evaluate the safety and tolerability of ADCT-301 in Part 2 at the dose level recommended in Part 1. **Secondary objectives**: The secondary objectives for Part 1 and Part 2 of the study are: • Evaluate the activity of ADCT-301 measured by overall response rate, duration of response, progression-free survival, and overall survival. • Characterize the pharmacokinetic (PK) profile of HuMax-TAC (total antibody; drug-to-antibody ratio [DAR] ≥0), PBD-conjugated HuMax-TAC (DAR ≥1), and free warhead SG3199. • Evaluate anti-drug antibodies (ADAs) in blood before, during, and after treatment with ADCT-301. [redacted]

Patient Selection:	**Inclusion Criteria:** **1.** Male or female age 18 years or older. **2.** Refractory or relapsed lymphoma (per WHO Classification system) defined as: • Non-Hodgkin lymphoma (NHL): Patients with histologically confirmed NHL (including stage ≥ Ib cutaneous T-cell lymphoma [CTCL]) who have failed or are intolerant to any established therapy known to provide clinical benefit at current state of disease. There is no upper limit to the number of prior therapies. • Hodgkin lymphoma: Patients with histologically confirmed classical Hodgkin lymphoma who have failed or are intolerant to brentuximab vedotin. Patients must have received a checkpoint inhibitor. There is no upper limit to the number of prior therapies. **3.** Pathologically confirmed relapsed or refractory lymphoma; a biopsy at any relapse is acceptable. **4.** Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block. An FFPE block from a current biopsy is preferred; however, archival tissue taken at any prior relapse is acceptable. If tissue block is not available, slides from a FFPE block may be acceptable for eligibility upon consultation with the Sponsor. **5.** Measurable disease, defined by the 2014 Lugano Classification Criteria (including CTCL patients without evidence of skin disease). CTCL patients with skin disease and modified Severity-Weighted Assessment Tool (mSWAT) criteria > 0, or absolute Sézary count ≥1000 cells/μL are eligible. **6.** Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. **7.** Absolute neutrophil count (ANC) ≥1500/μL. Criterion not applicable to adult T cell leukemia/lymphoma (ATLL) patients. **8.** Platelet count of ≥75000/μL. Criterion not applicable to ATLL patients. **9.** Hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Day 1. Criterion not applicable to ATLL patients. **10.** Serum/plasma creatinine ≤1.5 mg/dL, or if the patient has a creatinine >1.5 mg/dL, a measured creatinine clearance must be >80 mL/min as calculated by the Cockcroft and Gault equation. **11.** Serum/plasma alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase ≤2 times the upper limit of normal (ULN); ≤5 times ULN if there is liver or bone involvement.

	12. Total serum/plasma bilirubin ≤1.5 times ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 times ULN). **13.** Women of childbearing potential must have a negative blood beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to Day 1. **14.** Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-301. Men with female partners who are of childbearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-301. *Defined as: Sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year. **Defined as: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient. Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception. **Exclusion Criteria:** **1.** Patients who have an option for any treatment with proven clinical benefit for their lymphoid malignancy at current state of disease. **2.** Active graft-versus-host disease. **3.** Autologous or allogenic transplant within the 60 days prior to Cycle 1 Day 1 **4.** Evidence of myelodysplasia or myeloid leukemia by morphology, immunostains, flow cytometry, or cytogenetics on a bone marrow aspirate or biopsy. **5.** Known history of positive serum human ADA or known allergy to any component of ADCT-301. **6.** 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]).

	7. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome (GBS) and myasthenia gravis); other central nervous system autoimmune disease (e.g., poliomyelitis, multiple sclerosis). **8.** History of recent infection (within 4 weeks of C1D1) considered to be caused by one of the pathogens listed in Section 7.3.4.5: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, Campylobacter jejuni, or enterovirus D68. **9.** Known seropositive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring anti-viral therapy. **Note:** testing is not mandatory to be eligible. If patient is at risk for having undiagnosed HCV (e.g., history of injection drug use), HCV testing should be considered. **10.** History of Steven's Johnson's syndrome or toxic epidermal necrolysis syndrome. **11.** Pregnant or breastfeeding women. **12.** Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure > 115 mm Hg), unstable angina, congestive heart failure (greater than New York Heart Association class II), severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia, poorly controlled diabetes, severe chronic pulmonary disease, coronary angioplasty, or myocardial infarction within 6 months prior to screening, or uncontrolled atrial or ventricular cardiac arrhythmias. **13.** Use of any other experimental medication(s) within 14 days or 5 half-lives, but in no case < 14 days prior to the start of study treatment on Cycle 1, Day 1, except if approved by the Sponsor. **14.** Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy (including prednisone ≥ 40 mg/day or equivalent) within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1, Day 1 treatment, or shorter if approved by the Sponsor. **15.** Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE Version 4.0] Grade 0 or Grade 1) from acute non-hematologic toxicity (except all grades of alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to Screening. **16.** Congenital long QT syndrome or a corrected QTc interval ≥ 450 ms at screening (unless secondary to pacemaker or bundle branch block). **17.** Active second primary malignancy other than non-melanoma skin cancers, nonmetastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that

	Sponsor medical monitor and Investigator agree and document should not be exclusionary. **18.** 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.
Study Design:	This is a Phase 1, first-in-human (FIH), open-label study of ADCT-301 in patients with relapsed and refractory lymphoma that will be conducted in 2 parts. In Part 1 (dose-escalation), patients will receive a 1-hour intravenous (IV) infusion of ADCT-301 on Day 1 every 3 weeks (21-day cycle) and the MTD will be determined. If ADCT-301 is well tolerated after the first cycle, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient, at the Investigator's discretion. The starting dose of ADCT-301 will be 3 µg/kg (Dose Level 1) and dose escalation will be conducted according to a continual reassessment method (CRM). The first patient to be treated at each new dose will be monitored for any AEs for 7 days before proceeding with dosing for a second patient. In Part 2 (expansion), patients will be assigned to receive the recommended dose(s) of ADCT-301 as determined by the Dose Escalation Steering Committee (DESC) during Part 1 of the study. The following dosing regimen(s) may be investigated based on safety and PK emerging information: • 45 µg/kg every 3 weeks for 3 cycles followed by 30 µg/kg every 3 weeks for patients who have not progressed. • 45 µg/kg every 3 weeks for 3 cycles followed by 20 µg/kg every 3 weeks for patients who have not progressed. • 45 µg/kg every 3 weeks for 4 cycles followed by 30 µg/kg every 3 weeks for patients who have not progressed. • 45 µg/kg every 3 weeks for 4 cycles followed by 20 µg/kg every 3 weeks for patients who have not progressed. The initial dose level for Part 1 will be 3 µg/kg (Dose Level 1). The highest allowed dose will be 300 µg/kg. The MTD will be the highest safe dose that has at least a 60% probability that the dose-limiting-toxicity (DLT) rate is < 30%. The dose escalation design is described below. After discontinuation of treatment, patients without documented objective disease progression will be followed until progression of disease or initiation of new anticancer therapy for up to 12 months. All patients will be followed for survival (by telephone contact or retrospective chart review) until a new anticancer therapy is initiated or for up to 12 months after treatment discontinuation.

	A DESC will be responsible for safety monitoring and overall supervision of the study.
Estimated Duration of Patient Participation and Study Duration:	For each patient, the study will include a screening period (up to 28 days), a treatment period (until withdrawal, see below), and a follow-up period to assess disease progression and survival for up to 12 months after the last dose of study drug. The total study duration will be dependent on overall patient tolerability to the study drug and response to treatment. It is anticipated that the entire study (Parts 1 and 2) could last approximately 3 years from first patient treated to last patient completed. A patient may be withdrawn from the treatment for any of the following reasons: • Objective disease progression • Clinical progression • AE • Withdrawal of consent • Major protocol deviation • Required treatment delay > 21 days (except in case of potential patient benefit, which must be approved by the Sponsor) • Non-compliance, including lost to follow-up • Pregnancy • Other (e.g., development of contraindications with use of the study dug) • The Investigator determines if it is in the best interest of the patient to discontinue the patient's participation in the study. • Discontinuation of the study by the Sponsor. • Death

Efficacy Assessments:	Response to ADCT-301 will be assessed through the evaluation of complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) determined by the Investigator based on the Lugano Classification Criteria (2014) and Global Response Score Grading Scales for CTCL. Disease assessments will occur every other cycle for the first 2 evaluations (6 and 12 weeks), and every third cycle (every 9 weeks) thereafter until progression or more frequently, if clinically indicated. Patients who discontinue treatment for any reason other than objective disease progression will continue to be followed with scans approximately every 12 weeks from the last tumor assessment until disease progression, or initiation of a new anticancer treatment. If a patient discontinues treatment for a hematopoietic stem cell transplant, the frequency of imaging will be as per the transplant center standard of care. After documentation of disease progression or start of a new anticancer treatment, patients will be contacted by telephone approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.
Pharmacokinetic and Anti-drug Antibody Assessments:	The concentration versus time profile of total antibody HuMax-TAC, PBD-conjugated HuMax-TAC and free warhead SG3199 in serum will be determined centrally in Cycles 1 and 2. In Cycles 1 and 2, sample collection for analysis of PK parameters will be performed before the start of the ADCT-301 infusion, end of the infusion, and at 1, 3, 6, 24, 48, 96, 168 (Day 8), and 336 hours (Day 15) after the end of the ADCT-301 infusion. In all subsequent cycles, PK blood samples will be collected before the start of the ADCT-301 infusion, at end of the infusion, at End of Treatment (EOT), and at 12 weeks following the last ADCT-301 infusion. Antidrug (ADCT-301) antibodies in serum will be measured centrally before the start of each ADCT-301 infusion, at EOT, at 12 weeks following the last ADCT 301 infusion, and optionally in PK samples if needed. [redacted]

	• [redacted]
Safety Assessments:	Safety will be assessed based on the evaluation of AEs, serious AEs (SAEs), treatment discontinuations due to AEs, DLTs, periodic 12-lead electrocardiogram (ECG) recordings, physical examinations, vital signs measurements, ECOG performance status, hematology, coagulation panel, biochemistry, pregnancy testing (for women of child-bearing potential) and urinalysis test results obtained at various time points during the study. Adverse events will be graded according to CTCAE Version 4.0.
Definition of DLT	A DLT is defined as any of the following events, except those that are clearly due to underlying disease or extraneous causes: • A hematologic DLT is defined as (not applicable for ATLL patients): o Grade 3 or 4 febrile neutropenia or neutropenic infection. o Grade 4 neutropenia lasting > 7 days. o Grade 4 thrombocytopenia. o Grade 3 thrombocytopenia with clinically significant bleeding, or Grade 3 thrombocytopenia requiring a platelet transfusion. o Grade 4 anemia. • For ATLL patients, a hematologic DLT is defined as: o Any Grade 4 neutropenia lasting ≥ 42 days from the start of the cycle in the absence of evidence of residual leukemia. o Grade 3 or higher event of thrombocytopenia or a Grade 4 anemia, with a hypocellular bone marrow lasting for ≥ 42 days from the start of the cycle, in the absence of evidence of residual leukemia (i.e., with <5% malignant cells). • A non-hematologic DLT is defined as: o Grade 4 tumor lysis syndrome (Grade 3 TLS will not constitute DLT unless it leads to irreversible end-organ damage). o Grade 3 or higher (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting ≥ 48 hours despite optimal therapy [excluding all grades of alopecia]). o Grade 3 or higher hypersensitivity reaction (regardless of premedication).

	○ Skin ulceration ≥ Grade 2. ○ Peripheral sensory or motor neuropathy ≥ Grade 2. **Note:** The DLT observation period for dose escalation will be 1 cycle; however, the adaptive dose-escalation algorithm will incorporate cumulative DLTs occurring through Cycle 3.
Investigational Product, Dosage, and Mode of Administration:	ADCT-301 is a sterile formulation containing PBD-conjugated HuMax-TAC (DAR ≥1), HuMax-TAC (DAR = 0), and SG3249. It is provided pre-formulated in 10 mL glass vials containing approximately 30 mg ADCT-301 per vial (deliverable volume 5.4 mL at 6 mg/mL). Patients will receive ADCT-301 administered initially as a 1-hour IV infusion on Day 1 of each 3-week cycle. If ADCT-301 is well tolerated after the first cycle, the infusion duration may be shortened to 30 minutes for subsequent cycles at the Investigator's discretion.
Dose-Escalation Design:	Dose levels from 3 to 300 µg/kg are possible. Dose escalation will be conducted according to a CRM. Non-DLT toxicity events (i.e., Grade 2 or higher toxicities) will inform the probability of DLT at each dose level. Dose escalation is also conducted according to a set of rules that govern entry into the study and assignment of dose level. These rules allow that untried dose levels may be skipped. The trial is continuously monitored for safety and early stopping for successfully identifying the MTD. The final number of doses will be dependent on the emergent toxicity profile and will be decided by a DESC; PK and pharmacodynamic evaluations may also inform decision making. The DLT observation period for dose escalation will be 1 cycle; however, the adaptive dose-escalation algorithm will incorporate cumulative DLTs occurring through Cycle 3. No intra-patient dose escalation will be allowed during the study. However, once the recommended Part 2 dose(s) is determined, patients receiving lower or higher dose levels of ADCT-301 may be offered continued treatment at the recommended dose. During Part 1, the DESC may expand enrollment at doses below the current dose level being evaluated as part of the dose escalation process. Additional patients may only be added at a lower dose level provided there is at least 1 patient with documented stable disease. Not more than 10 patients in total can be treated at any dose level unless at least 3 of the 10 patients have documented partial response or better using the 2014 Lugano Classification criteria[2] or other appropriate measures of response.
Sample Size:	This is a Phase 1 study with a total sample size of approximately 140 patients. Part 1 may enroll approximately 80 patients and Part 2 will enroll approximately 60 patients.

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody drug conjugate
AE	adverse event
AI	accumulation index
ANC	absolute neutrophil count
ATLL	adult T cell leukemia/lymphoma
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
AUC_{0-last}	area under the concentration-time curve from time zero to the last quantifiable concentration
$AUC_{0-\tau}$	area under the concentration-time curve from time zero to the end of the dosing interval
β-HCG	beta human chorionic gonadotropin
BSA	body surface area
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
C_L	clearance
C_{max}	maximum concentration
CMV	cytomegalovirus
CR	complete response
CRM	continual reassessment method
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
D5W	5% dextrose in water
DAR	drug-to-antibody ratio
DESC	Dose Escalation Steering Committee
DLT	dose-limiting toxicity
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment
FDA	Food and Drug Administration
FDG	^{18}F-fluorodeoxyglucose
FIH	first-in-human
FFPE	formalin-fixed paraffin-embedded
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCV	hepatitis C virus

Abbreviation	Definition
HIV	human immunodeficiency virus
HbsAg	hepatitis B surface antigen (HbsAg)
HSV1 / 2	Herpes Simplex Virus Type 1 / Type 2
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IL-2R	Interleukin 2 receptor
INR	International Normalized Ratio
IRB	institutional review board
IV	intravenous
IVF	intravenous fluid
IVIg	intravenous immunoglobulin
MRI	magnetic resonance imaging
mSWAT	modified Severity-Weighted Assessment Tool
MRT	mean residence time
MTD	maximum tolerated dose
NHL	non-Hodgkin lymphoma
PBD	pyrrolobenzodiazepine
PBMC	peripheral blood mononuclear cell
PD	Progressive Disease
PET	positron emission tomography
PK	pharmacokinetic
PLEX	plasma exchange
PR	partial response
PT	prothrombin time
PTT	Partial prothrombin time
QWBA	Quantitative Whole Body Autoradiography
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SPD	sum of the product of the perpendicular diameters
TAC	T-cell activation antigen
TBSA	total body surface area
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
λz	terminal elimination phase rate constant
T_{max}	time to maximum concentration
$T_{1/2}$	terminal half-life
ULN	upper limit of normal
V_{ss}	volume of distribution at steady-state
V_Z	volume of distribution
VZV	varicella zoster virus
WBC	white blood cell

1 Introduction

ADCT-301 is an antibody drug conjugate (ADC), composed of the human monoclonal antibody, HuMax®-TAC, directed against human cluster of differentiation 25 (CD25), and conjugated through a cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. PBD dimers are highly efficient anticancer drugs that bind in the minor groove of DNA and form highly cytotoxic DNA interstrand cross-links. The schematic representation of ADCT-301, and the different components that may be formed following the administration of this ADC to humans, are presented in Figure 1.

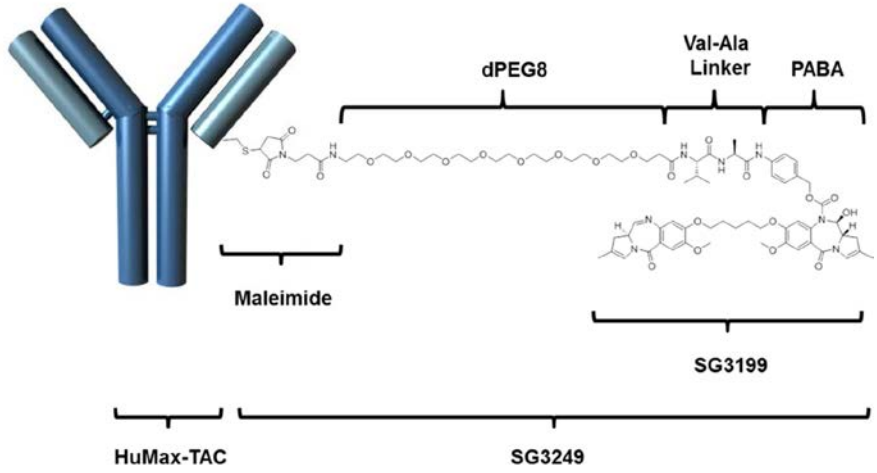

Figure 1. Schematic Representation and Chemical Structure of ADCT-301

Abbreviations: PABA, para-aminobenzoic acid; PEG, polyethylene glycol.

The make-up of ADCT-301 includes:

- HuMax®-TAC: A human monoclonal antibody of the IgG1, kappa isotype, specific for human CD25.
- SG3249: A PBD linker that comprises the PBD dimer SG3199 and all linker components, including the maleimide, 8-polyethylene glycol, a protease-sensitive valine-alanine linker and a para-aminobenzoic acid self-immolative group.
- SG3199: A PBD dimer cytotoxin, which is a highly efficient anticancer drug due to its interstrand cross-linking, a consequence of its specifically designed strong binding to the minor groove of DNA.

CD25 or T-cell activation antigen (TAC) is the 55 kDa alpha chain of the interleukin-2 receptor (IL-2R). The IL-2R is made up of three subunits: α (CD25), β (CD122) and γ (CD132). Lymphoma cells have been reported to express CD25 on their cell surface. Expression of CD25 as detected by flow cytometry is positive (≥20% tumor cells) in approximately 58% to 78% of Hodgkin lymphoma, 42% to 50% of peripheral T-cell lymphoma, 54% of cutaneous T-cell lymphoma, and 40% of diffuse large B-cell lymphoma cases.[12, 7, 10, 6]

ADCT-301 binds with picomolar affinity to human CD25. After binding and internalization, ADCT-301 is transported to the lysosomes, where the protease sensitive linker is cleaved and free PBD dimers are released inside the target cell. The released PBD dimers bind into the minor groove of DNA in a sequence-selective manner, and form highly cytotoxic DNA interstrand cross-links. The cross-links formed by PBD dimers are relatively non-distorting of the DNA structure, making them hidden to repair mechanisms, allowing for a longer effective period.

2 Study Rationale and Justification for Dose Level Selection

Study ADCT-301-001 is the first-in-human (FIH) clinical study with ADCT-301.

The potential for ADCT-301 in treating hematological malignancies that demonstrate CD25 over-expression has been shown by complete responses in mouse xenograft models following single, low-dose administration. The efficacy of ADCT-301 in these models is due to targeted delivery of the PBD cytotoxin SG3199.

The safety profiles of monoclonal antibodies directed against CD25 (IL-2Rα), such as Simulect® (basiliximab, Novartis Pharmaceuticals, NJ, USA) and Zenapax® (daclizumab, Roche Pharmaceuticals, NJ, USA) have been well characterized. Both products are indicated for prophylaxis of acute organ transplant rejection in patients receiving renal transplant. The most frequently reported adverse events (AEs) identified in the prescribing information for both products are gastrointestinal disorders, including abdominal pain, constipation, diarrhea, nausea, and vomiting.[8,11]

The safety of ADCT-301 has been assessed in nonclinical testing. In mice, ADCT-301 is well tolerated at doses up to 9 mg/kg. A repeat-dose Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys investigated doses ranging from 0.15 to 0.9 mg/kg. Systemic exposure to total ADCT-301 was consistent with the IV infusion route and increased in a generally dose proportional manner. No marked sex-related differences in exposure were noted. No evidence of accumulation or changes in median time to maximum concentration (T_{max}) and in mean terminal half-life ($T_{1/2}$), clearance (C_L), and volume of distribution (V_z) estimates were observed with increasing dose or on repeat dosing (where total ADCT-301 was sufficiently quantifiable). The average Day 1 ADCT-301 maximum concentration (C_{max}) (N=2 at each dose level) at 0.3 mg/kg, 0.6 mg/kg and 0.9 mg/kg was 4,520 ng/mL, 12,450 ng/mL and 15,950 ng/mL, respectively. The half-life ($T_{1/2}$) of ADCT-301 ranged from 4.25 days to 7.54 days for doses 0.3 mg/kg to 0.9 mg/kg.

Toxicities included body weight loss, nephrotoxicity and cutaneous AEs. The highest non-severe toxic dose was determined to be 0.15 mg/kg. As per guidance from the Food and Drug Administration (FDA), a starting dose of 10 µg/kg (one-sixth of the highest non-severe toxic dose based on body surface area [BSA]) could be proposed for the FIH study. However, based on anomalous exposure data observed on some dosing days at the 0.15 mg/kg dose level (no explanation in the formulation or dosing records), a lower starting dose of 3 µg/kg (Dose Level 1) was chosen for this study to offset any uncertainty associated with the 0.15 mg/kg dose level and to increase the margin of safety.

See the Investigator Brochure for ADCT-301 for additional information, including guidance for the Investigator.

3 Study Objectives

3.1 Primary Objectives

The primary objectives for Part 1 (dose escalation) and Part 2 (expansion) of the study are:

- Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCT-301 in patients with relapsed/refractory lymphoma (Part 1).
- Determine the recommended dose of ADCT-301 for Part 2.
- Evaluate the safety and tolerability of ADCT-301 in Part 2 at the dose level recommended in Part 1.

3.2 Secondary Objectives

The secondary objectives for Part 1 and Part 2 of the study are:

- Evaluate the activity of ADCT-301 measured by overall response rate, duration of response, progression-free survival, and overall survival.
- Characterize the pharmacokinetic (PK) profile of HuMax-TAC (total antibody; drug-to-antibody ratio [DAR] ≥0), PBD-conjugated HuMax-TAC (DAR ≥1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) in blood before, during, and after treatment with ADCT-301.

[redacted]

4 Investigational Plan and Patient Selection

4.1 Study Design

This is a Phase 1, FIH, open-label, dose-escalation (Part 1) and expansion (Part 2) study of ADCT-301 in patients with relapsed and refractory lymphoma. The study will evaluate the safety and tolerability of ADCT-301 as monotherapy, as well as the preliminary activity, PK, pharmacodynamics, and formation of ADAs of ADCT-301 in patients.

For each patient, the study will include a screening period (up to 28 days), a treatment period (until progressive disease, intolerable toxicity, or withdrawal of consent), and a follow-up period to assess disease progression and survival for up to 12 months after the last dose of study drug. The total study duration will be dependent on overall patient tolerability to the study drug and response to treatment. It is anticipated that the entire study (Parts 1 and 2) could last approximately 3 years from first patient treated to last patient completed.

In Part 1, patients will receive ADCT-301 administered as a 1-hour IV infusion on Day 1 of each 3-week (21-day) cycle. If ADCT-301 is well tolerated after the first cycle, the infusion duration may be shortened to 30 minutes for subsequent cycles at the Investigator's discretion.

The first patient at each dose level will be monitored for any AEs for 7 days before proceeding with dosing for the second patient.

The initial dose level for Part 1 will be 3 µg/kg (Dose Level 1). The highest allowed dose will be 300 µg/kg. The MTD will be the highest safe dose that has at least a 60% probability that the dose-limiting toxicity (DLT) rate is < 30%.

After discontinuation of treatment, patients without documented objective disease progression will be followed until progression of disease or initiation of new anticancer therapy for up to 12 months. All patients will be followed for survival (by telephone contact or retrospective chart review) until a new anticancer therapy is initiated or for up to 12 months after treatment discontinuation.

4.1.1 Dose Escalation and Determination of the Maximum Tolerated Dose (Part 1)

Dose escalation will be conducted according to a continual reassessment method (CRM) (Section 13.5). Dose levels from 3 to 300 µg/kg are possible.

However, the final number of doses will be dependent on the emergent toxicity profile and will be decided by a Dose Escalation Steering Committee (DESC) (Section 7.3.1.2). Pharmacokinetic and pharmacodynamic evaluations may also inform decision making.

The DLT observation period for dose escalation will be 1 cycle; however, the adaptive dose-escalation algorithm will incorporate cumulative DLTs occurring through Cycle 3. No intra-patient dose escalation will be allowed during the study. However, once the recommended Part 2 dose(s) is determined, patients receiving lower or higher dose levels of ADCT-301 in Part 1 may be offered continued treatment at the recommended dose.

During Part 1, the DESC may expand enrollment at doses below the current dose level being evaluated as part of the dose escalation process. Additional patients may only be added at a lower dose level provided there is at least 1 patient with documented stable disease. Not more than 10 patients in total can be treated at any dose level unless at least 3 of the 10 patients have documented partial response or better using the 2014 Lugano Classification criteria[2] or other appropriate measures of response (Appendix 13.3).

4.1.2 Dose Expansion (Part 2)

In Part 2 (expansion), patients will be assigned to receive the recommended dose(s) of ADCT-301, as determined by the DESC during Part 1 of the study.

The following dosing regimen(s) may be investigated based on safety and PK emerging information:

- 45 µg/kg every 3 weeks for 3 cycles followed by 30 µg/kg every 3 weeks for patients who have not progressed.
- 45 µg/kg every 3 weeks for 3 cycles followed by 20 µg/kg every 3 weeks for patients who have not progressed.
- 45 µg/kg every 3 weeks for 4 cycles followed by 30 µg/kg every 3 weeks for patients who have not progressed.
- 45 µg/kg every 3 weeks for 4 cycles followed by 20 µg/kg every 3 weeks for patients who have not progressed.

The patient population (e.g., disease subtypes) to be enrolled in Part 2 (expansion) may be refined based on results and observations from Part 1.

4.2 Selection of Study Population

It is estimated that approximately 140 patients (approximately 80 patients in Part 1 and approximately 60 patients in Part 2) will be enrolled at approximately 10 sites in Part 1 and 13 sites in Part 2 of the study. Patients will be assigned to a study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

4.2.1 Inclusion Criteria

1. Male or female age 18 years or older.
2. Refractory or relapsed lymphoma (per WHO Classification system) defined as:
   - Non-Hodgkin lymphoma (NHL): Patients with histologically confirmed NHL (including stage ≥ Ib cutaneous T-cell lymphoma [CTCL]) who have failed or are intolerant to any established therapy known to provide clinical benefit at current state of disease. There is no upper limit to the number of prior therapies.
   - Hodgkin lymphoma: Patients with histologically confirmed classical Hodgkin lymphoma who have failed or are intolerant to brentuximab vedotin. Patients must have received a checkpoint inhibitor. There is no upper limit to the number of prior therapies.
3. Pathologically confirmed relapsed or refractory lymphoma; a biopsy at any relapse is acceptable.
4. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block. An FFPE block from a current biopsy is preferred; however, archival tissue taken at any prior relapse is acceptable. If tissue block is not available, slides from a FFPE block may be acceptable for eligibility upon consultation with the Sponsor.
5. Measurable disease, defined by the 2014 Lugano Classification Criteria (including CTCL patients without evidence of skin disease) (Appendix 13.2). CTCL patients with skin disease and modified Severity-Weighted Assessment Tool (mSWAT) criteria >0, or absolute Sézary count ≥ 1000 cells/μL are eligible (Appendix 13.3).
6. ECOG performance status 0 to 2.
7. Absolute neutrophil count (ANC) ≥1500/μL. Criterion not applicable to adult T cell leukemia/lymphoma (ATLL) patients.
8. Platelet count of ≥75000/μL. Criterion not applicable to ATLL patients.
9. Hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Day 1. Criterion not applicable to ATLL patients.
10. Serum/plasma creatinine ≤1.5 mg/dL, or if the patient has a creatinine > 1.5 mg/dL, a measured creatinine clearance must be > 80 mL/min as calculated by the Cockcroft and Gault equation.[4]

11. Serum/plasma alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase ≤2 times the upper limit of normal (ULN); ≤ 5 times ULN if there is liver or bone involvement.

12. Total serum/plasma bilirubin ≤1.5 times ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 times ULN).

13. Women of childbearing potential must have a negative blood beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to Day 1.

14. Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-301. Men with female partners who are of childbearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-301.

*Defined as: Sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

Defined as: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient. **Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

4.2.2 Exclusion Criteria

1. Patients who have an option for any treatment with proven clinical benefit for their lymphoid malignancy at current state of disease.

2. Active graft-versus-host disease.

3. Autologous or allogenic transplant within the 60 days prior to Cycle 1 Day 1

4. Evidence of myelodysplasia or myeloid leukemia by morphology, immunostains, flow cytometry, or cytogenetics on a bone marrow aspirate or biopsy.

5. Known history of positive serum human ADA or known allergy to any component of ADCT-301.

6. 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]);

7. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome and myasthenia gravis); other central nervous system autoimmune disease (e.g., poliomyelitis, multiple sclerosis).
8. History of recent infection (within 4 weeks of C1D1) considered to be caused by one of the pathogens listed in Section 7.3.4.5: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, Campylobacter jejuni, or enterovirus D68.
9. Known seropositive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HbsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring anti-viral therapy. **Note:** testing is not mandatory to be eligible. If patient is at risk for having undiagnosed HCV (e.g., history of injection drug use), HCV testing should be considered.
10. History of Steven's Johnson's syndrome or toxic epidermal necrolysis syndrome.
11. Pregnant or breastfeeding women.
12. Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure > 115 mm Hg), unstable angina, congestive heart failure (greater than New York Heart Association class II), severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia, poorly controlled diabetes, severe chronic pulmonary disease, coronary angioplasty, or myocardial infarction within 6 months prior to screening, or uncontrolled atrial or ventricular cardiac arrhythmias.
13. Use of any other experimental medication(s) within 14 days or 5 half-lives, but in no case < 14 days prior to the start of study treatment on Cycle 1, Day 1, except if approved by the Sponsor.
14. Major surgery, radiotherapy, chemotherapy, or other anti-neoplastic therapy (including prednisone ≥ 40 mg/day or equivalent) within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1, Day 1 treatment, except if approved by the Sponsor.
15. Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE Version 4.0] Grade 0 or Grade 1) from acute non-hematologic toxicity (except all grades of alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to Screening.
16. Congenital long QT syndrome or a corrected QTc interval ≥ 450 ms at screening (unless secondary to pacemaker or bundle branch block).
17. Active second primary malignancy other than non-melanoma skin cancers, nonmetastatic prostate cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or other malignancy that Sponsor Medical Monitor and Investigator agree, and document should not be exclusionary.

18. 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 Study Procedures

5.1 Procedures by Study Day

The following procedures will be performed during the study.

5.1.1 Screening Period (Day –28 to –1)

The following procedures will be performed within 28 days prior to Day 1:

- Signed and dated Institutional Review Board (IRB) /Independent Ethics Committee (IEC) approved informed consent form (ICF) obtained prior to performing any study evaluations. 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 the patient's standard of care.
- Demography.
- Medical history (to include a complete history of all surgeries and significant diagnoses and all cancer treatment [including surgery, radiation therapy, chemotherapy, etc.]) and assessment of cardiac risk factors (e.g., history of angina pectoris, coronary artery disease or cerebrovascular accident, transient ischemic attack, cardiac failure with known ejection fraction < 40%, or cardiac arrhythmia requiring medical therapy).
- Pregnancy test (serum or urine, women of childbearing potential only).
- [redacted]
- Physical examination, including neurological examination and including whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist; however, any unexplained lesion will be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted. The examination must include a determination if the patient has had any 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.
    - Neurological assessment (as part of the physical examination) including strength, sensation, and deep-tendon reflexes throughout; examination does not need to be conducted by neurologist unless there are abnormal findings not explained by previous medical history (e.g., a patient with left sided weakness known to be a result of a previous CVA would not need to see a neurologist as part of this study)

and that could be linked to or may be an early indicator of polyradiculopathy/GBS, such as ascending (bilateral) sensory loss or motor weakness.

- Vital sign measurements.
- Height.
- Weight.
- Eastern Cooperative Oncology Group (ECOG) performance status.
- Disease assessments: Assessed using positron emission tomography - computed tomography (PET-CT) and diagnostic CT of the neck/chest/abdomen/pelvis and other areas of known disease or newly suspected disease with a clinical examination for lymphoma. Contrast should be used unless contraindicated. Magnetic resonance imaging (MRI) is permitted if diagnostic CT is contraindicated. The same assessments methods used at Screening which identify sites of disease should be used uniformly for all subsequent assessments.

  Note: PET-CT is only required at screening for ^{18}F-fluorodeoxyglucose (FDG) avid, nodal lymphomas (defined as per the Lugano Classification criteria as essentially all eligible histologies except small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation). If PET-CT examination is negative at Screening, subsequent PET-CT is not required. If PET-CT is positive, subsequent diagnostic CT and MRI are not needed, unless clinically indicated.
- Hematology.
- Coagulation panel.
- Biochemistry.
- Urinalysis.
- 12-lead electrocardiogram (ECG).
- AEs.
- Concomitant medication use (including prescription or over-the-counter medication, herbal or naturopathic products) within the 14 days prior to Day 1.

5.1.2 Day 1 (± 3 days) of Each Cycle

Day 1 of each cycle occurs on infusion day. The following procedures will be performed prior to ADCT-301 infusion unless otherwise specified:

- Serum or urine pregnancy test (women of childbearing potential, Cycle 1 only) is not required if screening pregnancy test was performed using serum and was done < 7 days before dosing with negative result.
- Physical examination, including neurological examination and including whole body skin assessment, unless a physical examination was performed within 3 days prior to Day 1. The examination must include a determination if the patient has had any 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.
- On Day 1 of Cycle 1, vital signs (arterial blood pressure, heart rate, respiratory rate, temperature) are measured before the start of the infusion, every 30 minutes during the infusion, and at the end of infusion. If no clinically significant changes occur during the first infusion, measurements are required prior to infusion start, hourly during infusion, and end of infusion for all subsequent infusions. For Cycles 1 and 2, patients will be monitored for 4 hours post-infusion with vital signs being measured 1 hour after the end of infusion and at discharge.

  Note: Timing of measurements is ± approximately 5 minutes.
- Weight, unless an assessment was performed within 3 days prior to Day 1.
- ECOG performance status, unless an assessment was performed within 3 days prior to Day 1.
- Disease assessments:
  - To be performed within 6 days prior to Day 1 of Cycles 3 and 5 and thereafter every third cycle (i.e., Cycles 8, 11, 14, etc.), until disease progression or more frequently, if clinically indicated.
  - The same methods used at Screening which identify sites of disease should be used uniformly for all subsequent assessments.

    Note: The results of the disease assessment are to be available to the Investigator prior to administration of study drug.

    Note: if PET-CT examination is negative at Screening, subsequent PET-CT is not required. For CTCL patients with disease limited to the skin, disease assessments after screening will be performed using mSWAT; radiological imaging after screening for CTCL patients with disease limited to the skin is not required unless clinically indicated.

- Hematology, coagulation panel, and biochemistry parameters will be measured prior to dosing unless the last sample was collected:
  - <24 hours before the start of ADCT 301 infusion on Day 1 of Cycle 1, or
  - <72 hours before the start of ADCT-301 infusion on Day 1 of Cycle 2 and subsequent cycles.
- Urinalysis and sample collection for additional renal function studies will be done prior to dosing unless the last sample was collected:
  - <24 hours before the start of ADCT 301 infusion on Day 1 of Cycle 1, or
  - <72 hours before the start of ADCT-301 infusion on Day 1 of Cycle 2 and subsequent cycles.
- 12-lead ECG (see Section 7.3.5 for timing of serial ECG measurements).
- Sample collection for central laboratory assessment of PK, [redacted], ADA, (for additional sample collections following dosing, see Appendix 13.1.2).
- Sample collection and shipment for PBMC subset analysis (Cycles 1 and 2, for additional sample collections following dosing see Appendix 13.1.2; only in Study Part 2).
- Sample collection for [redacted], Cycles 1 and 2.
- Sample collection for [redacted], Cycles 1 and 3.
- AEs.
- Concomitant medication use.
- Premedication administration, if applicable (Section 6.2).
- ADCT-301 administration.

5.1.3 Day 8 (± 1 day) of Each Cycle

- Physical examination, including neurological examination and including whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist; however, any unexplained lesion will be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted (Cycles 1 and 2). The examination must include a determination if the patient has had any 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.
- Weight
- Vital signs.

- Hematology.
- Biochemistry.
- Urinalysis.
- Additional renal function studies.
- PK blood sample collection (Cycles 1 and 2).
- Sample collection and shipment for PBMC subset analysis (Cycles 1 and 2, for additional sample collections following dosing see Appendix 13.1.2; only in Study Part 2).
- AEs.
- Concomitant medication use.

5.1.4 Day 15 (± 1 day)

- Physical examination, including neurological examination and including whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist; however, any unexplained lesion will be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted (Cycles 1 and 2). The examination must include a determination if the patient has had any 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.
- Weight
- Vital signs (Cycles 1 and 2).
- Hematology.
- Biochemistry.
- Urinalysis.
- Additional renal function studies.
- Sample collection for analysis of PK.
- Sample collection and shipment for PBMC subset analysis (Cycles 1 and 2, for additional sample collections following dosing see Appendix 13.1.2; only in Study Part 2).
- AEs.
- Concomitant medication use.

5.1.5 End of Treatment Visit

The following procedures will be performed as soon as possible after decision to discontinue the study drug and prior to initiation of anticancer treatment:

- Serum or urine pregnancy test.
- Physical examination, including neurological examination and including whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist; however, any unexplained lesion will be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted. The examination must include a determination if the patient has had any 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.
- Vital sign measurements.
- ECOG performance status.
- Weight
- Disease assessments:
  - Patients who already have documented objective disease progression do not need to have assessments repeated.
  - Patients who do not already have documented objective disease progression will have assessments performed at the end of treatment visit if the most recent disease assessment was > 9 weeks prior to the end of treatment visit.
- Hematology.
- Coagulation panel.
- Biochemistry.
- Urinalysis.
- Additional renal function studies.
- 12-lead ECG.
- Sample collection for central laboratory assessment of PK, [redacted], ADA, and [redacted]
- Sample collection and shipment for PBMC subset analysis (only in Study Part 2).
- AE collection (collected until 84 days [12 weeks] after last dose of study drug).
- Concomitant medication use.

5.1.6 Long-term Follow-up

Patients who discontinue treatment for any reason other than objective disease progression will continue to be followed with scans approximately every 12 weeks from the last tumor assessment until disease progression, or initiation of new anticancer treatment. If a patient discontinues treatment for a hematopoietic stem cell transplant, the frequency of imaging will be as per the transplant center standard of care.

After documentation of disease progression or start of new anticancer treatment, patients will be contacted by telephone approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.

Blood Sample Collection and Adverse Event Monitoring During Long-Term Follow-up

For all patients, PK and ADA blood sample collection will be performed 12 weeks (± 1 week) following the last dose of ADCT-301, unless a new anticancer treatment has been initiated.

Patients who test positive for ADAs may be requested to supply additional ADA samples.

For all patients, collection of AEs and SAEs will continue for 12 weeks after the last dose of study drug or initiation of new anticancer treatment (see Section 7.3.2.2).

5.2 Withdrawal of Patients from the Study

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent through the completion of the follow-up period or withdrawal of consent.

5.2.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from treatment at any time and for any reason without prejudice to their future medical care by the Investigator or others at the study site. A patient may be withdrawn from treatment for any of the following reasons:

- Objective disease progression.
- Clinical progression.
- AE.
- Withdrawal of consent.
- Major protocol deviation.
- Required treatment delay > 21 days (except in case of potential patient benefit, which must be approved by the Sponsor).
- Non-compliance, including lost to follow-up.
- Pregnancy

- Other (e.g., development of contraindications with use of the study drug).
- The Investigator determines if it is in the best interest of the patient to discontinue the patient's participation in the study.
- Discontinuation of the study by the Sponsor.
- Death.

5.2.2 Handling of Withdrawals

Upon occurrence of a serious or intolerable AE, the Investigator will confer with the Sponsor. If a patient discontinues because of an AE, then the event will be followed until it is resolved. When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the Investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end of treatment assessments. Patients who fail to return for final assessments will be contacted by the site. Following a minimum of two documented unsuccessful telephone calls, a registered letter will be sent to the patient in a final attempt to ensure protocol compliance.

5.2.3 Patient Replacements

Patients in Part 1 who discontinue treatment for any reason without a DLT AE before completion of the first treatment cycle will be replaced. No other patients will be replaced.

6 Study Treatments

6.1 Method of Assigning Patients to Treatment Groups

This is an open-label study that will be conducted in 2 parts. In both parts, ADCT-301 will be administered on Day 1 of each cycle. The duration of each cycle will be 21 days (3 weeks).

In Part 1, dose escalation will begin with the 3 µg/kg dose starting dose (Dose Level 1). The maximum dose will be 300 µg/kg. Patients will be assigned to the appropriate dose level according to the CRM design (Section 13.5) and judgment of the DESC.

In expansion (Part 2), all patients will be assigned to the dose level of ADCT-301 as identified in Part 1 by the DESC.

6.2 Prophylactic Treatments for Hypersensitivity

If Grade 2 or higher infusion-related hypersensitivity reactions are observed in a patient at any time during the study, this patient must receive prophylactic treatment with all subsequent dosing, as described below or as per the institution's standard of care, to reduce the risk of hypersensitivity reactions:

- Patient will be instructed to take 20 mg of dexamethasone orally at 12 hours and 6 hours before the start of ADCT-301 infusion on Day 1 of each cycle. When necessary, 12 and 6 hours before the first infusion may be defined as "immediately before sleeping" and "immediately after waking up."
- Patient will be given 50 mg of diphenhydramine hydrochloride intravenously 30 minutes before the start of the ADCT-301 infusion on Day 1 of each cycle.
- Patient will be given 50 mg of ranitidine intravenously 30 minutes before the start of ADCT-301 infusion on Day 1 of each cycle.
- For 2 days after administration of ADCT-301, dexamethasone 4 mg (twice per day) will be taken orally by the patient.

Other doses and other medications for prophylaxis and treatment of hypersensitivity or infusion reactions may be administered according to standard treatment center protocols. Medications for the treatment of severe hypersensitivity reactions including anaphylaxis should be available for immediate use.

If a Grade 1 or Grade 2 hypersensitivity occurs in a patient, the following medications should be administered for 48 hours after ADCT-301 infusion:

- Ranitidine 150 mg orally given 2 times per day
- Diphenhydramine hydrochloride 50 mg orally given 3 times per day

If a Grade 3 or higher hypersensitivity occurs, the patient should be discontinued from the study and must be treated immediately with hydrocortisone 20 mg administered intravenously and/or other appropriate medications. In case of life-threatening symptoms (e.g., arrhythmia, hypotension, respiratory distress, seizures, shock, stridor, unconsciousness, wheezing), epinephrine 0.2 to 0.5 mL of 1:1000 dilution should be administered subcutaneously or intramuscularly, repeating every 5 minutes to a total dose of 1 mg. In these cases, patients must be carefully observed after the treatment. Additional therapy per institution standard of care should also be followed.

6.3 Treatments Administered

Part 1 of the study will investigate ADCT-301 administration every 3 weeks. In Part 2, all patients will be assigned to the dose level identified in Part 1 by the DESC. ADCT-301 will be administered on Day 1 of each cycle as a 1-hour IV infusion. If ADCT-301 is well tolerated after the first cycle, the infusion duration may be shortened as a 30 minutes IV infusion for subsequent cycles, at the Investigator's discretion.

Variation in infusion times due to minor differences in IV bag overfill/ underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviations. Prophylactic antiemetic medications, electrolyte supplementation, and other standard supportive care measures may be administered according to standard treatment center protocols.

Although the study patient population has a low risk for development of tumor lysis syndrome (TLS) compared to patients with acute disease,[1] patients should be observed for development of TLS and treated according to standard treatment center protocols.

Because of non-clinical observations related to nephropathy and adrenal gland changes, adequate patient hydration (e.g., 8 to 10 glasses of water or equivalent per day) is recommended for patients receiving ADCT-301.

Available pre-clinical data on ADCT-301 does not suggest a photosensitivity concern, based on the lack of any signals in the rat and monkey toxicology studies with ADCT-301 and the non-clinical experience with SG3199, including a QWBA study indicating no specific accumulation to melanin containing tissues, skin or eyes.

However, skin rash has been reported in the ADCT-301 program, as well as with another investigational agent containing the same pyrollobenzodiazepine warhead.[3] The rash has been limited to areas at risk for sun exposure; it is therefore recommended that precautions are taken to avoid prolonged exposure of skin to direct sunlight.

6.4 Dose Delays and Modifications

The Investigator may suspend ADCT-301 dosing for up to 21 days for any patient who experiences a protocol-defined DLT during any treatment cycle.

At the discretion of the Investigator, the dose may also be delayed for up to 21 days for any other toxicity of any grade.

Resumption of dosing with ADCT-301 after any suspension, even when longer than 21 days, is at the discretion of the Investigator, in consultation with the Sponsor, based on assessment of the patient's clinical condition and whether or not the patient is deriving potential clinical benefit from treatment with ADCT-301. Following recovery to Grade 1 or baseline, treatment may resume at the Investigator's discretion.

Patients who resume treatment following a dose delay may, at the discretion of the Investigator, have their dose reduced by 1 dose level in either part of the study. If toxicity reoccurs at a severity that would mandate a dose delay, then the dose may be further reduced 1 dose level. If toxicity reoccurs at such level, then the patient is to be discontinued from treatment. Dose re-escalation is allowed at the investigator's discretion, at maximum to the dose level the patient was initially assigned to.

Patients experiencing certain types of infection during the course of participation in this clinical study also must delay further dosing, as stipulated in Section 7.3.4.5.

Patients experiencing any autoimmune toxicities (e.g. endocrinopathies) ≥ Grade 1 need to be followed at least weekly to quickly detect deterioration and modify dosing as per DLT criteria (can be done by telephone unless symptoms worsen).

Patients experiencing the following significant toxicities will be immediately and permanently withdrawn from treatment with ADCT-301:

- Any patient who experiences a Grade 3 or higher hypersensitivity reaction, regardless of premedication, during any cycle of treatment per CTCAE definitions (Appendix 13.4).
- Any patient who experiences a recurrent Grade 3 or 4 toxicity excluding hematological toxicity.
- Any patient who requires a dosing delay > 21 consecutive days from the planned Day 1 dosing at any time during treatment (except in case of potential patient benefit, which must be approved by the Sponsor).

Neurological toxicities: dose delay/permanent discontinuation

Patients experiencing any new neurological toxicities ≥ 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 ADCT-301 needs to be delayed until polyradiculopathy/GBS is ruled out. Should further clinical, radiologic, or laboratory evidence support the diagnosis of polyradiculopathy/GBS with the level 1 of diagnostic certainty (Appendix 13.6), treatment with ADCT-301 must be stopped and patient must be permanently discontinued.

Patients with Grade ≥ 3 neurologic toxicities defined as peripheral sensory and peripheral motor neuropathies must be permanently discontinued.

Other new neurological findings not explained by previous medical history 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).

6.5 Study Stopping Rules

The study will be paused if any of the following circumstances occur:

- ≥ 30% of patients experience a specific Grade 4 or higher non-hematologic treatment-emergent AE.
- if any patient in Part 1 or Part 2 experiences a CTCAE Grade 5 AE, or 2 non-hematologic CTCAE Grade 4 AEs that are not attributable to the underlying disease, and for which relationship to ADCT-301 cannot be ruled out, within 30 days of their last dose of ADCT-301.

Furthermore, the Sponsor will notify regulatory agencies within 48 hours of being made aware of any new confirmed cases of GBS/polyradiculopathy to discuss, if appropriate, and determine whether or not the benefit-risk ratio has changed and dosing of additional patients and/or dosing of ongoing patients must be stopped. IRBs/IECs will be informed about the outcome of the assessment as appropriate.

6.6 Identity of Investigational Product

ADC Therapeutics will provide and distribute adequate supplies of ADCT-301 to the study sites. The following drug supplies will be used in the study:

Product	Supplied As:
ADCT-301	10 mL glass vial at a deliverable volume of 5.4 mL at 6 mg/mL (equivalent to 30 mg ADCT-301)

6.6.1 ADCT-301 Drug Product

ADCT-301 is a sterile formulation containing PBD-conjugated HuMax-TAC (DAR ≥1), HuMax-TAC (DAR = 0), and SG3249. It is provided pre-formulated in 10 mL glass vials containing approximately 30 mg ADCT-301 per vial (deliverable volume 5.4 mL at 6 mg/mL).

6.7 Management of Clinical Supplies

6.7.1 Study Drug Packaging and Storage

ADCT-301 will be supplied in a labeled 10 mL stoppered glass vial and shipped by Fisher Clinical Services to the investigational site. Once the package arrives, the receiving site pharmacy will complete the enclosed procedures to acknowledge receipt.

All study drugs must be stored in a secure area (e.g., a locked cabinet). ADCT-301 should be protected from light and stored frozen (–65°C or below). ADCT-301 should be thawed under ambient conditions. After the vials have been completely thawed, they should be gently mixed by swirling to ensure homogeneity and visually inspected before use. The appropriate quantity of ADCT-301 will be removed from the vial with a syringe and diluted into a 50 mL IV bag containing 5% dextrose in water (D5W). The amount of the product to be diluted will depend on the dose level and the mass of the patient. Once the ADCT-301 has been transferred, the bag should be mixed to ensure homogeneity of the dosing solution. The contents of the IV bag will then be administered to the patient with a dosing pump per institutional guidelines for intravenous fluid (IVF) administration.

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

6.7.2 Study Drug Accountability

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

6.8 Overdose Management

An overdose is any dose of study treatment given to a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor. There are no data available to determine what effects and whether effects of an overdose can be reversed. Symptomatic treatment and standard supportive care measures for the management of this toxicity should be applied.

6.9 Treatment Compliance

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

6.10 Concomitant Treatment

All medications used within 14 days prior to Day 1 and during the treatment period are to be recorded in the eCRF. Concomitant medication information will be collected for 30 days following the patient's last dose of ADCT-301. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

6.10.1 Prohibited During Study

- Other anticancer therapy, with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Radiation therapy is prohibited during the first cycle of therapy. After the first cycle, radiation is permitted for palliative use only if documented radiographic disease progression is ruled out first.
- Other investigational agents.
- Chronic treatment with prednisone ≥40 mg/day or equivalent.
- Live vaccines.

6.10.2 Permitted During Study

After confirmation and documentation of eligibility, supportive care treatments (transfusions, etc.) can be prescribed as medically appropriate. Note: hematopoietic growth factors are permitted per American Society of Clinical Oncology guidelines; however, prophylactic use of growth factors is not allowed during the first treatment cycle.

If Grade 2 or higher infusion-related hypersensitivity reactions are observed in a patient at any time during the study, this patient must receive prophylactic treatment with all subsequent dosing as per Section 6.2.

Concomitant steroid use is permitted as follows:

- Replacement doses of steroids for patients with adrenal insufficiency
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)

Patients scheduled to receive ADCT-301 are to be administered prophylactic steroid treatment as follows, unless contraindicated:

Dexamethasone 4 mg PO BID

- Day -1 (day prior to dosing – if possible)
- Day 1 (day of dosing; give at least 2 hours prior to administration when not given the day before; otherwise any time prior to administration)
- Day 2 (day after dosing)

Note: prophylaxis for hypersensitivity will supersede stipulations on dexamethasone prophylaxis.

In addition, spironolactone, at standard doses, may be instituted at any time for patients with weight gain greater than 1 kg (2.2 pounds) from Cycle 1 Day 1, new or worsening edema, and/or new or worsening pleural effusion. The dose of spironolactone should be titrated as clinically indicated. Additional diuretic support may be added if there is further increase in weight, edema or pleural effusion.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator.

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

It is recommended starting management of polyradiculopathy/GBS with either intravenous immunoglobulin (IVIg) 0.4 g/kg/day for 5 days or plasma exchange (PLEX) once the diagnosis of polyradiculopathy/GBS has been considered by a neurologist; this would be at CTCAE Grade 2 symptoms for neuropathy or Score 1 as per GBS disability scale (Appendix 13.7).

Diagnostic workup should include:

- Neurology consultation
- MRI spine with and without contrast to rule out compressive lesion and evaluate for nerve root enhancement or thickening
- Electrodiagnostic studies (nerve conduction studies)
- Pulmonary function tests
- Lumbar puncture: CSF typically has albuminocytologic dissociation with protein elevation disproportionate to WBC—although note that CSF WBC 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[14]
- Admission to inpatient unit with capability for rapid transfer to ICU-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

7 Study Assessments and Procedures

Patients will undergo the procedures at the time points specified in schedule of events (Appendix 13.1).

7.1 Efficacy Assessments

Disease assessments will occur every other cycle for the first 2 evaluations (6 weeks [end of Cycle 2 ±1 week] and 12 weeks [end of Cycle 4 ±1 week]), and every third cycle (every 9 weeks [e.g., end of Cycles 7, 10, 13, etc., ±1 week]) thereafter until progression or more frequently, if clinically indicated. Assessments may be performed within ± 1 week of the required timepoint and response assessment must be available prior to initiation of dosing at the subsequent cycle.

In case of dose delays, disease assessment should be maintained at the frequencies defined above and response assessment is required prior to resumption of ADCT-301 dosing (only if the interval from last scan is ≥ 6/9 weeks, as applicable) to rule out disease progression.

Tumor response will be determined by the Investigator, based on the 2014 Lugano Classification Criteria (Appendix 13.2) and Global Response Score Grading Scales for CTCL (Appendix 13.3). Images will be obtained according to local site imaging requirements. Images will be required to be submitted for a central/independent review for Part 2. Submission instructions for the central/independent review will be provided in a separate manual.

7.2 Pharmacokinetic and Pharmacodynamic Assessments

Blood samples (5 mL draw) will be collected for PK assessment processed according to the instructions provided by the bioanalytical laboratory to the clinical sites. The concentration versus time profile of total antibody HuMax-TAC, PBD-conjugated HuMax-TAC and free warhead SG3199 in serum will be determined centrally in Cycles 1 and 2.

In Cycles 1 and 2, whole blood samples for analysis of PK parameters will be collected at the following times: before the start of the ADCT-301 infusion, end of the infusion, and at 1, 3, 6, 24, 48, 96, 168 (Day 8), and 336 hours (Day 15) after the end of the ADCT-301 infusion (Appendix 13.1.2). In all subsequent cycles, PK blood samples will be collected before the start of the ADCT-301 infusion, at end of the infusion, at End of Treatment (EOT), and 12 weeks following the last ADCT-301 infusion. Additional PK/biomarker blood samples will be collected, at the discretion of the Investigator, during any visit where toxicity is observed. All PK samples will be evaluable as long as the actual collection times are recorded.

Please see Appendix 13.1.2 for details on timing windows for blood sample collection for all PK and pharmacodynamic assessments.

Antidrug (ADCT-301) antibodies will be measured centrally at the following times in serum: before the start of each ADCT-301 infusion, at EOT, at 12 weeks following the last ADCT-301 infusion, and optionally in PK samples if needed.

[redacted]

7.3 Safety and Tolerability Assessments

Safety will be assessed based on AEs, SAEs, treatment discontinuations due to AEs, DLTs, hematology, biochemistry, coagulation panel, pregnancy testing (for women of child-bearing potential) and urinalysis test results. Adverse events will be graded according to CTCAE Version 4.0. Additional safety assessments include periodic 12-lead ECG recordings, physical examination, vital sign measurements, and ECOG performance status. A schedule of all assessments, including safety, is provided in Appendix 13.1.1.

7.3.1 Dose-Limiting Toxicities and Dose-Escalation Scheme

7.3.1.1 Definition of Dose-Limiting Toxicities

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

- A hematologic DLT is defined as (not applicable for ATLL patients):
  - Grade 3 or 4 febrile neutropenia or neutropenic infection.
  - Grade 4 neutropenia lasting > 7 days.
  - Grade 4 thrombocytopenia.
  - Grade 3 thrombocytopenia with clinically significant bleeding, or Grade 3 thrombocytopenia requiring a platelet transfusion.
  - Grade 4 anemia.
- For ATLL patients, a hematologic DLT is defined as:
  - Any Grade 4 neutropenia lasting ≥ 42 days from the start of the cycle in the absence of evidence of residual leukemia.
  - Grade 3 or higher event of thrombocytopenia or a Grade 4 anemia, with a hypocellular bone marrow lasting for ≥ 42 days from the start of the cycle, in the absence of evidence of residual leukemia (i.e., with <5% malignant cells).
- A non-hematologic DLT is defined as:
  - Grade 4 tumor lysis syndrome (Grade 3 TLS will not constitute DLT unless it leads to irreversible end-organ damage).
  - Grade 3 or higher (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting ≥ 48 hours despite optimal therapy [excluding all grades of alopecia]).
  - Grade 3 or higher hypersensitivity reaction (regardless of premedication) (Appendix 13.4).
  - Skin ulceration ≥ Grade 2.
  - Peripheral sensory or motor neuropathy ≥ Grade 2.

Note: The DLT period for dose escalation will be 1 cycle; however, the adaptive dose-escalation algorithm will incorporate cumulative DLTs occurring through Cycle 3.

7.3.1.2 Safety Oversight by the Dose Escalation Steering Committee

A DESC will be responsible for safety monitoring and overall supervision of the study. Membership of the DESC will include:

- Medical monitor(s)/Pharmacovigilance representative(s) (Sponsor and/or designee)
- Investigator(s) from each participating site
- Biostatistician(s)
- Ad-hoc members (e.g., project manager, study coordinators, regulatory representatives, etc.)

In general, the DESC will make any substantial decisions regarding the conduct of the study, such as:

- Monitor the safety of the study and review its progress at monthly intervals or more frequent intervals as required.
- In accordance with the CRM (Appendix 13.5), determine dose levels to be administered and the MTD based on assessment of safety findings and determination of DLTs.
- While the DESC cannot dictate dose level(s) higher than those prescribed by the CRM, the medical judgment of the DESC will supersede the statistical parameters of the CRM.
- Approve any amendments or administrative changes to the protocol, when required.

Each DESC meeting and the decisions made will be documented in writing and provided to all participating DESC members and Investigators. Meeting documents may be submitted to IRBs/IECs or competent authorities according to institutional or local requirements.

Dose escalation will be conducted according to a CRM, as described in Appendix 13.5.

The first patient at each new dose will be monitored for any AEs for 7 days before proceeding with dosing for second patient.

During dose escalation, the DESC may expand enrollment at doses below the current dose level being evaluated as part of the dose escalation process. Patients may only be added to the lower doses provided there is at least 1 patient with an efficacy evaluation showing stable disease. No more than 10 patients in total can be treated at any dose level unless at least 3 of the 10 patients have documented partial response or better using the 2014 Lugano Classification criteria[2] or other appropriate measures of response (Appendix 13.3).

The DESC will be maintained during Part 2 (expansion) of the study to continue to monitor and evaluate patient safety.

7.3.2 Adverse Events

7.3.2.1 Definitions of Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the Investigator at any time after the patient signs the ICF if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

A serious adverse event (SAE) is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Hospitalization for elective procedures or for protocol compliance is not considered an SAE.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.2 Eliciting and Documenting Adverse Events

All AEs will be assessed from the time the patient signs the ICF until 84 days (12 weeks) after the last dose of study drug, or initiation of new anticancer treatment.

Any SAEs that occur > 84 days (12 weeks) after the last dose of study drug do not need to be reported unless the Investigator considers the event to be related to study drug.

At every study visit, patients will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., clinically significant changes in laboratory values, physical examination, ECG changes, etc.) or identified from review of other documents that are relevant to patient safety.

7.3.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, dose, event terminology, date of onset, CTCAE Version 4.0 assessment of severity and relationship to study drug, date of resolution of the event, seriousness, any required treatment or evaluations, and outcome. With the exception of disease progression, AEs resulting from concurrent illnesses, reactions to concurrent illnesses, and reactions to concurrent medications also must be reported. All AEs will be followed to adequate resolution. CTCAE Version 4.0 will be used to grade all AEs. The CTCAE includes 5 grades (1 to 5), with Grade 5 being death.

Any AE that meets SAE criteria (Section 7.3.2.1) must be reported to the contract research organization (CRO) immediately (i.e., within 24 hours after the time site personnel first learn about the event). The following contact information is to be used for SAE reporting:

[redacted]

7.3.2.4 Assessment of Severity

Adverse events are graded according to CTCAE Version 4.0. For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5 as follows:

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 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 Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

7.3.2.5 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the eCRF. All adverse events, regardless of assessment of causality, are reported in the eCRF.

All SAEs considered at least possibly related to the study drug will be considered unexpected; and therefore, reported as Suspected Unexpected Serious Adverse Reactions (SUSARs).

7.3.2.6 Follow-up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

7.3.3 Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical study Pregnancy Report Form. To ensure patient safety, each pregnancy must be reported as described for reported AEs in Section 7.3.2.3, upon learning of its occurrence. 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 was discontinued from the study. The outcome of the pregnancy will be reported on the Pregnancy Outcome Form. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study treatment must be promptly reported (Section 7.3.2.3).

7.3.4 Clinical Laboratory Analyses

Samples will be collected at the time points specified in Appendix 13.1.

Any clinically significant abnormal laboratory test results are to be recorded as AEs or SAEs per CTCAE Version 4.0.

7.3.4.1 Hematology

Complete blood count (CBC) includes WBC with a 5-part differential, platelet count, hemoglobin, hematocrit, and ANC. Coagulation panel includes prothrombin time (PT) expressed in seconds, International Normalized Ratio (INR), and partial thromboplastin time (PTT). Patients taking coumarin-derivative anticoagulants should be monitored closely and their anticoagulant dose adjusted as needed.

7.3.4.2 Biochemistry

Biochemistry includes alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin, sodium, potassium, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, chloride, creatinine, creatine phosphokinase, total protein, albumin, glucose, triglycerides, total cholesterol, phosphorus, and lactate dehydrogenase. At Day 1 of each cycle, biochemistry will include creatinine clearance (calculated using the Cockcroft and Gault 1976 formula).

7.3.4.3 Urinalysis

Urinalysis analytes will include pH, protein, specific gravity, glucose, ketones, bilirubin, nitrites, and occult blood. The urinalysis may be performed using a urine dipstick.

7.3.4.4 Additional Renal Function Studies

Urine will be collected for testing of biomarkers suggestive of potential renal injury (aquaporin-2, calbindin D28, and clusterin). Analysis of this additional urine sample will be performed at a central laboratory (instructions provided in the Laboratory Manual).

7.3.4.5 Additional Microbiological Serological studies

Patients will be regularly examined and asked whether they have been suffering from 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 below, appropriate microbiological workup must be conducted. Should such workup indicate that infection was indeed caused by one of these microorganisms, re-dosing must be delayed so that there is at least a four-week window between symptom resolution and the next dose of ADCT-301.

Pathogens of interest are: HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, Campylobacter jejuni, and enterovirus D68.

7.3.5 Electrocardiograms

On Day 1 of Cycles 1 and 2, a 12-lead ECG will be performed before the start of the ADCT-301 infusion, at completion of infusion and at 3 hours and 24 hours (Day 2) after the end of infusion. ECGs should occur within 10% of nominal time (e.g., 3 hours ± 18 minutes). Any abnormalities, including those that worsen from baseline, believed to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

Measurement of the QTc interval may be obtained according to the formula used by the institution, however, the Fridericia formula is preferred.[5] The same formula used to confirm eligibility must be applied within a patient for the duration of the study.

7.3.6 Physical Examination

Physical examinations will include a complete review of body systems, including whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist; however, any unexplained lesion will be referred to a dermatologist for further evaluation and biopsy if clinically warranted. Physical examination will also include a neurological examination of strength, sensation, and deep tendon reflexes; unexpected findings will be referred to a neurologist for further evaluation. Height will be measured at the Screening Visit (Day –28 to –1) and patients are advised to monitor their weight on a daily basis because new or worsening edema and / or new or worsening pleural effusion have been observed. Patients should inform their Investigator if their weight increases by more than 1 kg (2.2 pounds) after Cycle 1 Day 1.

The examination must include a determination if the patient has had any 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.

Any clinically significant abnormalities, including those that worsen from baseline, are to be recorded as AEs or SAEs.

7.3.7 Vital Sign Measurements

Vital sign measurements will include arterial blood pressure, heart rate, respiratory rate, and temperature. Any clinically significant abnormalities, including those that worsen from baseline, are to be recorded as AEs or SAEs.

7.3.8 Eastern Cooperative Oncology Group Performance Status

The patient's performance status will be assessed according to the time points in the schedule of events (Appendix 13.1) using the ECOG performance status grades[9] below:

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

7.4 Sample Handling, Storage, and Shipment

Detailed instructions for central laboratory sample collection, labeling, processing, storage, and shipping will be provided to the site in the central Laboratory Manual.

During the study, whole blood samples will be collected for PK, ADA, pharmacodynamics [redacted] PBMC subset analysis), and safety analyses (clinical chemistry, [redacted], and hematology).

For PK, ADA, [redacted] blood samples are to be collected and processed on site according to the Laboratory Manual. The resulting serum samples should be aliquoted and stored frozen at ≤ -70°C until shipment. Each sample tube must be clearly labeled with the following information: study number, study center number, patient number, tube identification, and the sample collection time point (by day and hour), when necessary.

Serum and urine samples are to be packed in sufficient dry ice and shipped from the study center to the central laboratory. Once labeled, samples should be stored at ≤ -70°C until shipment. Samples should be shipped according to the sample shipment schedule provided

in Laboratory Manual. [redacted]

The clinical chemistry and hematology samples, which should not be frozen, are transferred at ambient temperature to local laboratories.

For the PBMC subset analysis, whole blood is to be collected and shipped as per the central Laboratory Manual directly to the testing laboratory for immediate processing.

8 Statistical and Analytical Plan

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

8.1 Safety Endpoints

Safety will be assessed based on AEs, SAEs (graded using CTCAE v4.0), treatment discontinuations due to AEs, DLTs, hematology, coagulation panel, biochemistry, pregnancy testing (for women of child-bearing potential) and urinalysis test results. Additional safety assessments include periodic 12-lead ECG recordings, physical examinations, vital sign measurements, and ECOG performance status. A schedule of the safety assessments is provided in Appendix 13.1.1.

8.2 Study Endpoints

8.2.1 Primary Endpoints

The primary objectives for Part 1 (dose escalation) and Part 2 (expansion) of the study are:

- Determine the safety of ADCT-301 by assessing DLTs and determining the MTD in Part 1 (dose-escalation).
- Determine the recommended dose of ADCT-301 for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCT-301 in patients with relapsed/refractory lymphoma in Part 2 (expansion).

8.2.2 Secondary Endpoints

The following secondary endpoints will be determined in Part 1 and Part 2:

- Evaluate response to ADCT-301 using the Lugano Classification Criteria (2014) (Appendix 13.2) and Global Response Score Grading Scales for CTCL (Appendix13.3) through the evaluation of complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD).
- Characterize PK profile of HuMax-TAC (total antibody; drug-to-antibody ratio [DAR] ≥ 0), PBD-conjugated HuMax-TAC (DAR ≥ 1), and free warhead SG3199 (see Section 8.6.3).
- Determine anti-drug antibodies ADAs in blood before, during, and after treatment with ADCT-301.

[redacted]

8.3 Sample Size Calculations

This is a Phase 1 study with a total sample size of approximately 140 patients. It is expected that Part 1 will enroll approximately 80 patients, and Part 2 will enroll approximately 60 patients (Section 4.1.1 and Section 4.1.2).

Simulations were performed assuming scenarios with different dose-toxicity relationships to evaluate the sample size for Part 1.

Patients will be enrolled in Part 2 of the study in cohorts of approximately 10. The cohorts will be enrolled at the dose level recommended in Part 1.

The DESC will make recommendations with regard to the intended differences between these cohorts, e.g. tumor subtypes, dosing regimen or dose levels, as well as the number of these cohorts, taking into account the limit on the overall number of patients as specified above and safety/efficacy data observed up to that decision point.

8.4 Analysis Sets

Five analysis sets will be used in this study:

- The Safety analysis set consists of all patients who receive study drug
- The DLT-evaluable analysis set consists of all patients in Part 1 who receive study drug and excludes patients who discontinue from the study during the first 21-day cycle without experiencing a DLT.
- The Efficacy analysis set will consist of all patients with valid baseline data who receive at least 2 doses of study drug or who have documented progression of disease at any time after the first dose of study drug. Patients who do not have a post baseline assessment due to early clinical progression, toxicity, or death will also be included.
- The PK analysis set consists of all patients who receive study drug and have sufficient concentration data for PK analysis.

- The pharmacodynamic analysis set consists of all patients who receive study drug and have sufficient concentration data for pharmacodynamic analysis.

8.5 Description of Subgroups to be Analyzed

Subgroup analyses, if planned, will be described in the SAP.

8.6 Statistical Analysis Methodology

8.6.1 Efficacy Analysis

8.6.1.1 Overall Response Rate

Overall response rate is defined as the proportion of patients with best overall response of PR or CR at the time each patient discontinues treatment with ADCT-301 (Appendix 13.2, Appendix 13.3).

8.6.1.2 Duration of Response

Duration of response 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 as assessed by the Investigator using the 2014 Lugano Classification for response for Hodgkin and Non-Hodgkin Lymphoma[2] (Appendix 13.2) or Global Response Score criteria for disease progression for CTCL (Appendix 13.3). For patients who have not progressed or who have died at the time of the analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, patients with disease progression or death after an extended loss to follow-up will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up. Further details on censoring rules will be outlined in the SAP.

8.6.1.3 Overall Survival

Overall survival will be defined as the time from the beginning of ADCT-301 treatment until death due to any cause. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. Further details on censoring rules will be outlined in the SAP.

8.6.1.4 Progression-Free Survival

Progression-free survival will be defined as the time from first dose of study drug until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of radiological disease progression as assessed by the Investigator using the 2014 Lugano Classification for response for Hodgkin and Non-Hodgkin Lymphoma[2] (Appendix 13.2) or Global Response Score criteria for disease

progression for CTCL (Appendix 13.3). Patients with stable disease / without disease progression, or patients with death after an extended loss to follow-up, will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up. Further details on censoring rules will be outlined in the SAP.

8.6.2 Safety Analyses

8.6.2.1 Analyses of Adverse Events

An AE will be considered to be a TEAE if it begins or worsens on or after first dose date and before last dose date until 84 days (12 weeks). Planned summaries of TEAEs are detailed in the statistical analysis plan and will include:

- All TEAEs.
- All serious TEAEs.
- All treatment-related TEAEs.
- All treatment-related serious TEAEs.
- All TEAEs resulting in study drug discontinuation.
- All DLTs.
- Other AE analyses of interest will be specified in the SAP.

The incidence of deaths and the primary cause of death will be summarized.

8.6.2.2 Clinical Laboratory Results

Clinical hematology, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Numeric hematology and biochemistry results will be summarized using change from baseline. All results will be summarized using shift from baseline. Shifts for clinical laboratory results that can be graded according to CTCAE Version 4.0 will be summarized by CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

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

8.6.2.3 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 treatment. All data will be listed. Further details will be provided in the SAP.

8.6.3 Pharmacokinetic and Pharmacodynamic Analyses

In Cycles 1 and 2, whole blood for PK samples will be collected at the following times: before the start of the ADCT-301 infusion, at the end of infusion and at 1, 3, 6, 24, 48, 96, 168 (Day 8) and 336 hours (Day 15) after the end of the ADCT-301 infusion. In all subsequent cycles PK blood samples will be collected before the start of the ADCT-301 infusion, at end of infusion, at EOT, and finally 12 weeks following the last ADCT-301 infusion.

PK endpoints for HuMax-TAC, PBD-conjugated HuMax-TAC, and free warhead SG3199 will be evaluated for all patients using noncompartmental analysis and may include: maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$), area under the concentration-time curve from time zero to the end of the dosing interval ($AUC_{0\text{-}\tau}$), area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}\infty}$), accumulation index (AI), volume of distribution at steady-state (V_{ss}), mean residence time (MRT), terminal elimination phase rate constant (λz), apparent terminal half-life, C_L, and Vz.

Data for PK parameters will be summarized in tables and individual data will be listed.

In addition, pharmacodynamic and ADA analyses will be performed to include:

- PBMC subset analysis in Part 2 of the study by flow cytometry in whole blood

8.6.4 Study Drug Exposure

Study drug exposure will be summarized by dose level and overall. Duration of treatment, total number of cycles dosed, and total dose received will be summarized. The number of patients dosed by cycle will also be summarized using frequency counts and percentages.

Duration of treatment will be calculated as date of last dose of study drug – date of first dose of study drug + 1.

8.7 Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of a qualified Investigator and appropriate study site, review of protocol procedures with the Investigator and associated personnel before the study and periodic monitoring visits by the clinical research associate. Written instructions will be provided for collection, preparation, and shipment of blood and plasma samples.

The eCRFs will be provided to the clinical contact and the clinical research associate will review them with site personnel.

The clinical research associate will review eCRFs for accuracy and completeness by remote monitoring, during on-site monitoring visits, and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After entry of the data into the clinical study database they will be verified for accuracy.

8.7.1 Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, and patient diaries.

Investigative site personnel will enter patient data into Medidata Rave. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse events will be coded using the Medical Dictionary for Regulatory Activities Version 16.0. Concomitant medications will be coded using WHO Drug Dictionary 01 June 2013.

After database lock, each study site will receive information about all of their site-specific eCRF data as entered into electronic data capture system for the study, including full discrepancy and audit history. Additionally, a copy of all of the study site's data from the study 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.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB)/independent ethics committee (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 to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with the current version of ICH harmonised tripartite guideline E6: Good Clinical Practice (GCP) 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 at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

9.2 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, ICH GCP, and all applicable regulations.

9.3 Patient Information and Consent

A written informed consent in compliance with IRB/IEC and local regulations shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all patients on-study must sign the revised form, unless otherwise indicated by the IRB/IEC (local or global, as applicable). In such case, the reason for not re-consenting the patient should be documented.

Before recruitment and enrollment, each prospective patient or his or her legal guardian 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/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study and that additional [redacted]

10 Investigator's Obligations

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

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

The Investigator and all employees and coworkers involved with this study 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.

10.2 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 required under 21 CFR 54 and local regulations. In addition, the Investigator must provide to the Sponsor a commitment to 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.

Neither the Sponsor nor the CRO is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor the CRO is financially responsible for further treatment of the patient's disease.

10.3 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with the current version of ICH E6 8.2, Title 21 of the CFR, and local regulations by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original Investigator-signed Investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 (where applicable)
- Curriculum vitae for the Investigator and each sub-Investigator listed on Form FDA 1572 (where applicable)
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian

10.4 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of the current version of ICH E6. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

10.5 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with the current version of ICH E6 and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs to the Sponsor according to the timeline and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

The Sponsor will ensure that all relevant safety information (SAEs and SUSARSs) is reported to the FDA and competent authorities of EU Member States, and to the IEC, in accordance with current legislation (US 21CFR.316 and EU Directive 2001/20/EC).

10.7 Investigator's Final Report

Upon completion of the study, where applicable, the Investigator should provide the IRB/IEC with a summary of the study outcome and the Sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, 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.

10.9 Publications

Data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for coordination of these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

11.1 Monitoring

11.1.1 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and written contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.2 Inspection of Records

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 audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any change in the study plan requires a protocol amendment. An Investigator may not make any changes to the study without IRB/IEC and Sponsor approval, except those necessary to remove an apparent immediate hazard to the patient. A protocol change intended to eliminate an apparent immediate hazard to patient(s) may be implemented immediately, but the circumstances of the change must be documented and submitted to the IRB/IEC and to the Sponsor for further evaluation. If the protocol is in need of substantial changes, the Sponsor will amend the protocol and seek approval from the appropriate regulatory authority(ies) before implementation. 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.

11.2.2 Protocol Deviations

The Investigator will make every attempt to avoid deviations from the protocol, except in medical emergencies. In the event of a medical emergency, the Medical Monitor must be notified as soon as possible. The Investigator will inform the governing IRB/IEC of all protocol changes issued by the Sponsor in accordance with the IRB/IEC's established procedure.

11.3 Study Termination

The Sponsor has every intention of completing the study; however, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit to the study site (includes any end of treatment visit to the site and any visit to the site to obtain confirmatory scan of response).

11.4 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s).

An Investigator will be identified to act as the signatory for the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

12 Reference List

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13 Appendices

13.1 Appendix: Schedule of Events

The Schedule of Events for study procedures is shown in Section 13.1.1 of this Appendix. Timings for sample collections for assessments of PK, ADA, [redacted], and [redacted] are shown in Section 13.1.2.

13.1.1 Schedule of Study Procedures

Procedure	Screening	Cycle 1			Cycle 2			Cycles 3 until Progression/ Discontinuation		End of Treatment[1]	Long-term Follow-up (up to 12 mos)
	Day –28 to –1	Day 1 (±3 days)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day)		
Informed consent	X										
Demography	X										
Medical and cancer history[2]	X										
Pregnancy test (β-HCG, serum or urine)	X	X[3]								X	
Tumor tissue collection[4]	X										
Physical examination, including neurological examination and whole body skin assessment[5]	X	X[6]	X	X	X[6]	X	X	X[6]		X	
Vital signs	X	X[7]	X	X	X[7]	X	X	X[7]	X	X	
Height	X										
Weight	X	X[6]	X	X	X[6]	X	X	X[6]	X	X	
ECOG Performance status	X	X[6]			X[6]			X[6]		X	
Disease assessment[8]	X							X[9]		X[10]	X[11]
Hematology[12]	X	X[13]	X	X	X[13]	X	X	X[13]	X	X	
Coagulation Panel[14]	X	X[13]			X[13]			X[13]		X	
Biochemistry[15]	X	X[13]	X	X	X[13]	X	X	X[13]	X	X	
Urinalysis [16]	X	X[13]	X	X	X[13]	X	X	X[13]	X	X	
Additional renal function studies[17]		X[13]	X	X	X[13]	X	X	X[13]	X	X	
12-lead ECG	X	X[18]			X[18]			X		X	
Sample collection for Pharmacokinetic assessments[19]		X	X	X	X	X	X	X		X	X[20]
[redacted]		[redacted]			[redacted]			[redacted]		[redacted]	

Procedure	Screening	Cycle 1			Cycle 2			Cycles 3 until Progression/ Discontinuation		End of Treatment[1]	Long-term Follow-up (up to 12 mos)
	Day –28 to –1	Day 1 (±3 days)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day)	Day 15 (±1 day)	Day 1 (±3 days)	Day 8 (±1 day)		
Sample collection for anti-drug antibody assessment[19]		X			X			X		X	X[20]
Sample collection and shipment for PBMC analysis[21]		X	X	X	X	X	X			X	
[redacted]		[redacted]			[redacted]					[redacted]	
[redacted]		[redacted]						[redacted]			
ADCT-301 administration[22]		X			X			X			
Prophylactic administrations[23]		X			X			X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X[24]
Concomitant medications[25]	X	X	X	X	X	X	X	X	X	X	
Survival information											X[26]
New anti-cancer treatment information											X[27]

Abbreviations: ANC, absolute neutrophil count; b-HCG, beta human chorionic gonadotropin; CBC, complete blood count; CT, computed tomography; CTCL, cutaneous T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ECG, electrocardiogram; FDG, 18F-fluorodeoxyglucose; [redacted]; INR, International Normalized Ratio; mos, months; MRI, magnetic resonance imaging; mSWAT, modified Severity-Weighted Assessment Tool; NHL, non-Hodgkin lymphoma; PBMC, peripheral blood mononuclear cells; PET-CT, positron emission tomography- computed tomography; PT, prothrombin time; PTT, Partial prothrombin time; WBC, white blood cell

1 As soon as possible after decision to discontinue the study drug AND prior to initiation of anticancer treatment.
2 To include a complete history of all surgeries, significant diagnoses, all cancer treatments, and assessment of cardiac risk factors.
3 For women of childbearing potential. Not required if negative screening serum beta-human chorionic gonadotropin pregnancy (β-HCG) test was obtained within 7 days prior to Day 1, Cycle 1.

4 Collection of tumor tissue (formalin-fixed paraffin embedded block) for retrospective testing of [redacted] protein expression by immunochemistry at a central laboratory. Tissue from a recent biopsy is preferred, if available, and/or if patient provides consent for biopsy during screening. Archival tissue taken at any prior relapse is acceptable.

5 Physical examination, including neurological examination and whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist. Any unexplained lesion to be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted. The examination must include a determination if the patient has had any 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.

6 Not to be repeated on Day 1, Cycle 1 if last performed within 3 days prior to dosing.

7 On Day 1 of Cycle 1, vital signs (arterial blood pressure, heart rate, respiratory rate, temperature) are measured before the start of the infusion, every 30 minutes during the infusion, and at the end of infusion (± 15 minutes). If no clinically significant changes occur during the first infusion, measurements are required prior to infusion start, hourly during infusion, and end of infusion for all subsequent infusions.
For Cycles 1 and 2, patients will be monitored for 4 hours post-infusion with vital signs being measured 1 hour after the end of infusion and at discharge (± 15 minutes).

8 Screening tumor assessments: PET-CT and diagnostic CT of the neck/chest/abdomen/pelvis and other areas of known disease or newly suspected disease with a clinical examination for lymphoma. Contrast should be used unless contraindicated. Magnetic resonance imaging (MRI) is permitted if diagnostic CT is contraindicated. The same assessment methods used at Screening should be used for all subsequent assessments. Note: PET-CT is only required at screening for FDG-avid, nodal lymphomas (defined as per the Lugano Classification criteria as essentially all eligible histologies except small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there is a suspicion of aggressive transformation. If PET-CT examination is negative at Screening, subsequent PET-CT is not required. If PET-CT is positive, subsequent diagnostic CT and MRI are not needed, unless clinically indicated. In case of dose delays, response assessment is required prior to resumption of ADCT-301 dosing (only if the interval from last scan is ≥ 6/9 weeks, as applicable) to rule out disease progression.
For CTCL patients with disease limited to the skin, disease assessments after screening will be performed using mSWAT; radiological imaging after screening for CTCL patients with disease limited to the skin is not required unless clinically indicated.

9 Disease assessments will be performed within 6 days prior to Day 1 of Cycles 3 and 5 and thereafter every third cycle (i.e., Cycles 8, 11, 14, etc.) until disease progression or more frequently, if clinically indicated. The same assessment methods used at Screening which identify sites of disease should be used uniformly for all subsequent assessments

10 Patients who already have documented objective disease progression do not need to have assessments repeated. Patients who do not already have documented objective disease progression will have assessments performed if the most recent disease assessment was greater than 9 weeks prior to the end of treatment visit.

11 Patients who discontinue treatment for any reason other than objective disease progression will continue to be followed with scans approximately every 12 weeks from the last tumor assessment until disease progression, or initiation of new anticancer treatment. If patient discontinues treatment for a hematopoietic stem cell transplant, the frequency of imaging will be as per the transplant center standard of care.

12 Hematology: complete blood count (CBC) to include WBC with 5-part differential, platelet count, hemoglobin, hematocrit, and ANC.

13 Sample collection to occur prior to dosing on Day 1 unless the last sample was collected: <24 hours before the start of ADCT 301 infusion on Day 1 of Cycle 1, or <72 hours before the start of ADCT-301 infusion on Day 1 of Cycle 2 and subsequent cycles.

14 Coagulation panel includes prothrombin time (PT) expressed in seconds, International Normalized Ratio (INR), and partial thromboplastin time (PTT).
15 Biochemistry: alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin, sodium, potassium, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, chloride, creatinine, creatine phosphokinase, total protein, albumin, glucose, triglycerides, total cholesterol, phosphorus, and lactate dehydrogenase. At Day 1 of each cycle, biochemistry will include creatinine clearance (calculated using the Cockcroft and Gault 1976 formula).
16 Urinalysis will include pH, specific gravity, protein, occult blood, glucose, ketones, nitrites and bilirubin. The urinalysis may be performed using a urine dipstick.
17 Urine to be collected for testing of biomarkers suggestive of potential renal injury (aquaporin-2, calbindin D28, and clusterin).
18 On Day 1 of Cycles 1 and 2, a 12-lead ECG is to be performed before the start of the ADCT-301 infusion, at completion of infusion, and at 3 hours and 24 hours (Day 2) after the end of infusion. ECGs should occur within 10% of nominal time (e.g., 3 hours ± 18 minutes).
19 See Section 13.1.2 of this Appendix for timing.
20 Sample for assessment to be obtained 12 weeks (± 1 week) after last dose of ADCT-301, unless a new anticancer treatment has been initiated.
21 Sampling for peripheral blood mononuclear cell (PBMC) subset analysis by Flow Cytometry in Cycles 1 and 2, and at EOT; only in Part 2. See Section 13.1.2 of this Appendix for sample timing.
22 Patients to receive ADCT-301 intravenously over 1 hours (± 15 minutes). If ADCT-301 is well tolerated after the first cycle, the infusion duration may be shortened to a 30-minutes intravenous infusion for subsequent cycles at the Investigator's discretion. The IP administration window is ± 15 minutes.
23 Dexamethasone prophylaxis (4 mg BID on Day -1, Day 1, and Day 2) should be administered, unless contraindicated. If Grade 2 or higher infusion-related hypersensitivity reactions are observed in a patient at any time during the study, this patient must receive prophylactic treatment with all subsequent dosing to reduce the risk of hypersensitivity reaction. Prophylaxis for hypersensitivity will supersede stipulations on dexamethasone prophylaxis
24 For all patients, collection of AEs and SAEs will continue for 12 weeks (84 days) after the last dose of study drug or initiation of new anticancer treatment. Any SAEs that occur more than 84 days after the last dose of study drug do not need to be reported unless the Investigator considers the event to be related to study drug.
25 To include prescription or over-the-counter medication, herbal or naturopathic products within the 14 days prior to Day 1, throughout the study, and for 30 days after last dose of study drug.
26 After documentation of disease progression or start of new anti-cancer treatment, patients will be contacted by telephone approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information.
27 Information on anti-cancer treatment initiated after discontinuation of ADCT-301 to be recorded in the eCRF.

13.1.2 Timing of ECG and Sample Collection for PK, ADA, [redacted] and PBMCs

Assessment	Cycles 1 and 2										Cycle 3 – Progression		EOT	Follow up 3 mos after last infusion (±7 days)
	Day 1					Day 2	Day 3	Day 5	Day 8	Day 15	Day 1			
	Before start infusion	EOI (±10%)*	1 hr after EOI (±10%)	3 hrs after EOI (± 10%)	6 hrs after EOI (± 10%)	24 hrs after EOI (± 10%)	48 hrs after EOI (± 10%)	96 hrs after EOI (±1 day)	168 hrs after EOI (±2 days)	336 hrs after EOI (±2 days)	Before start infusion (± 10%)	EOI (±10%)		
PK	X	X	X	X	X	X	X	X	X	X	X	X	X	X[1]
ADA[2]	X										X		X	X[1]
sCD25	X										X		X	
[redacted]														
[redacted]														
PBMC subsets (Study Part 2 only)	X			X			X	X	X	X			X	
ECG	X	X		X		X					X		X	

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; EOT, end of treatment; [redacted]; hr, hour(s); mos, months; PK, pharmacokinetics; [redacted] PBMC, peripheral blood mononuclear cells.
Note: No sample collections for PK, ADA, [redacted], links at the screening visit.
* Samples to be collected within 10% of nominal time point (e.g., 1 hr ± 6 min, 48 hrs ± 4.8 hrs) for first 48 hours.

[1] Sample to be obtained at Follow-up, unless a new anticancer treatment has been initiated.
[2] Patients who test positive for ADAs may be requested to supply additional ADA samples.

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

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

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

Response / Site	PET-CT-Based Response	CT-Based Response
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
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	• No 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 update 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

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

Response / Site	PET-CT-Based Response	CT-Based Response
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
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 two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as

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

Response / Site	PET-CT-Based Response	CT-Based Response

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 BD, Fisher RI, Barrington SF, Cavalli F, Schwartz H, Lister TA. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin lymphoma: The Lugano classification. J Clin Onc 2014, 32(27):3059-3068

13.3 Appendix: Global Response Score Grading Scales for Modified Severity-weighted Assessment Tool (mSWAT) for CTCL

13.3.1 Skin Scoring

13.3.1.1 Total Body Surface Area (TBSA) Involvement by Skin Disease

The body is divided into 12 regions with pre-assigned percentage (%) total body surface area (TBSA) based on the burn literature. The extent of skin disease in each region is quantified by using the patient's palm to measure the %TBSA involvement within region: patient's palm with 4 fingers (excluding the thumb) is 1% of TBSA. Patient's palm without fingers is 0.5% of TBSA. The patient's palm with 4 fingers is traced on a transparency sheet at the baseline visit, using a permanent marker that will not rub off or smear. The transparency of the patient's palm should be used in all mSWAT assessments during the course of the clinical study. The transparency will be labeled with the patient's study ID number kept in the patient's study file on site. Using the baseline visit transparency of the patient's palm, the Investigator will measure and record the %TBSA for each lesion type within each of the 12 regions.

13.3.1.2 Severity Weighting Factor

The severity weighting factors will be the following:

- 1= patch (flat erythema or erythema with mild infiltration)
- 2=plaque (elevated erythema or erythema with moderate infiltration)
- 4= tumor or ulceration (erythema with fissuring, ulceration or tumor)

Patch is defined as abnormal skin not elevated from normal skin. A plaque is defined as abnormal skin elevated from normal skin by < 5 mm. A plaque elevated ≥ 5 mm is a tumor.

13.3.1.3 Calculating Skin Scores

The sum of %TBSA by lesion is derived by summing the %TBSA from all regions affected by the lesion. The sum of %TBSA across lesion types (patches, plaques and tumors) within each region cannot exceed the %TBSA for the region. For example, the %TBSA for the head region is 7%. The sum of %TBSA across lesion types from head can only range from 0-7%. The skin score subtotal by lesion type are derived by multiplying the sum of %TBSA for patches from all regions by 1, sum of %TBS of plaques from all regions by 2, and the sum of %TBSA of tumors or ulcers from all regions by 4. The skin score total is derived from summing the skin score subtotals for patches, plaques and tumors or ulcers. The skin score total is dimensionless with a scale of 0 to 400.

%TBSA for Each Lesion Type Within Each of the 12 Regions

Region	Percentage TBSA for the region	Percentage TBSA patch (or flat erythema)	Percentage TBSA plaque (or elevated/indurated erythema)	Percentage TBSA tumor/ulceration (or erythema w/fissuring, ulceration
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper Arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower Leg	14			
Feet	7			
%BSA by category	100			
Severity Weighting factor		×1	×2	×4
Skin Score subtotal				

Abbreviations: TBSA, total body surface area; BSA, body surface area

13.3.1.4 Response Definitions

Responses will be determined by the criteria described in the table below. Progression of disease while on treatment should be confirmed by a second assessment 1 to 4 weeks later so that patients who experience a temporary flare of disease due to skin infection or other intercurrent illnesses are not removed from the study prematurely.

Response	Description
Skin	
Complete Response (CR)	No evidence of disease; 100% clearance of skin lesions.
Partial Response (PR)	≥50% decrease in skin scores compared to baseline and improvement is maintained for a minimum of 4 weeks
Stable Disease (SD)	< 50% decrease in skin scores compared to baseline
Progressive Disease (PD)	≥ 25% increase in skin scores compared to baseline while the patient is actively taking the study drug, *or* new tumor(s) ≥ 1 cm diameter in skin disease only patient, *or* ≥ 50% increase in the sum of the products of the greatest diameters of pathologically positive lymph nodes (should be documented by biopsy) compared to baseline while the patient is actively taking the study drug.
Relapse	Any disease recurrence in those with complete response.
Lymph Nodes (peripheral and central)	
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction > 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or >1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain criteria for CR, PR, or PD
PD	≥ 50% increase in SPD from baseline of lymph nodes *or* Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically *or* Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically.
Viscera	
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain criteria for CR, PR, or PD

Response	Description
PD	>50% increase in size (SPD) of any organs involved at baseline *or* New organ involvement *or* Loss of response: >50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR.
Blood	
CR (a)	B_0: Absence of significant blood involvement, <5% of peripheral blood lymphocytes are atypical (Sézary) cells
PR (b)	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD	B0 to B2 or >50% increase from Baseline and at least 5,000 neoplastic cells/μL, or >50% increase from nadir and at least 5,000 neoplastic cells/μL for those with OR who were originally B2 at baseline.
Relapse	Increase of neoplastic blood lymphocytes to ≥ B1 in those with CR

SPD = sum of the maximum linear dimension (major axis) x longest perpendicular dimension (minor axis)

13.3.2 Global Response Score

The individual component scores for skin, nodes, blood, and viscera are incorporated into the definition of the Global Response Score (see table below).

Global Score	Definition	Skin	Nodes	Blood	Viscera
Complete Response (CR)	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/noninvolved (NI)		
Partial Response (PR)	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
Stable Disease (SD)	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
Progressive Disease (PD)	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

References:

Olsen EA, S Whittaker, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical end points and response criteria in mycosis fungoides and Sézary Syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Onc 2011; 29(18):2598-2607.

Stevens SR, Ke MS, Parry EJ, Mark J, Cooper KD. Quantifying skin disease burden in mycosis fungoides-type cutaneous T-cell lymphomas: the severity-weighted assessment tool (SWAT). Arch Dermatol 2002; 138:42-48.

13.4 Appendix: CTCAE Immune System Hypersensitivity Grades

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Definition: A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, intravenous fluids); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or intravenous fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately 66 to 21 days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort, and dyspnea.					

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

Abbreviations: ADL, Activities of daily living; NSAIDs, non-steroidal anti-inflammatory drugs.
Adapted from CTCAE 4.0 – June 14, 2010, Immune system disorders.

13.5 Appendix: Dose Escalation Scheme Report

13.5.1 Overview

A primary objective of the dose escalation portion of the study is to estimate an MTD. The MTD will be the highest safe dose that has at least a 60% probability that the dose limiting toxicity (DLT) rate is < 30%. The DLT observation period is 1 cycle.

Dose escalation will begin with the 3 μg/kg starting dose (Dose Level 1). There will be 33 dose levels including all dose levels from:

- 0.003 to 0.02 mg/kg in increments of 0.001
- 0.02 to 0.05 mg/kg in increments of 0.005
- 0.05 to 0.10 mg/kg in increments of 0.01
- 0.10 to 0.30 mg/kg in increments of 0.05

Dose escalation will be conducted according to a continual reassessment method (CRM). Non-DLT toxicity events (i.e. Grade 2 or higher toxicities) will inform the probability of DLT at each dose level. Dose escalation is also conducted according to a set of rules that govern entry into the study and assignment of dose level. These rules allow that untried dose levels may be skipped. The trial is continuously monitored for safety and early stopping for successfully identifying the MTD.

13.5.2 Continual Reassessment Method

Dose escalation in this study will be conducted using the CRM. For each dose, *d = 1,….,33*, we model the ordinal outcome of no toxicity event, non-DLT (i.e. Grade 2) toxicity event, or a DLT.

We model the log odds of a DLT,

$$\theta_d = \log\left(\frac{\pi_{DLT}}{1-\pi_{DLT}}\right)$$

with a two-parameter model

$$\theta_d = \alpha + \beta d$$

We model the log odd-odds of a non-DLT toxicity

$$\rho_d = \log\left(\frac{\pi_{grade2}}{1-\pi_{grade2}}\right)$$

as related to DLTs by including an additive term, γ, which must be > 0,

$$\rho_d = (\alpha + \gamma) + \beta d.$$

We place the following independent prior distributions on the parameters.

$$\alpha \sim N(-3, 6^2)$$

$$\beta \sim N(8, 20^2)$$

$$\gamma \sim N^{+}(3, 6^2)$$

This parameterization imposes that Grade 2 or higher toxicities (which include DLTs) will occur more frequently than DLTs. We use "pseudo-prior" weighting to impose a prior expectation of the rate of DLTs that helps shape the correlation of the parameters. We assume one observation each of three doses. We place one observation with 0% DLT on the 0.003 mg/kg dose, with 30% DLT on the on the 0.10 mg/kg dose, and with 60% DLT on the 0.20 mg/kg dose.

After each patient is treated and assessed for non-DLT toxicity or DLT, the distributions of all parameters are updated and the MTD is estimated based on the posterior probability of DLT at each dose.

Additionally, we define a dose as safe if there is at least a 60% probability that the DLT rate is < 30%,

$$\Pr(\pi_d < 30\%) > 60\%.$$

Patients cannot be assigned to a dose that is not safe by this definition.

13.5.3 Dose Escalation Rules

Dose escalation begins with enrollment of patients on the 0.003 mg/kg dose. The queue refers to the number of patients that have been allocated to doses, but have not yet completed the observation period. For safety purposes we want to keep the queue size moderate to prevent large numbers of patients being enrolled at any one time. Until 4 patients have complete DLT information the queue maximum is 2. After 4 patients have complete DLT information, the queue increases to 3. Patients cannot be enrolled for dose escalation if the queue maximum has been reached.

13.5.3.1 Starting Dose and Entry into the Study

Dose escalation begins with enrollment of patients on the 0.003 mg/kg dose (dose escalation will be conducted according to a CRM, as described in Appendix 13.5).

The queue refers to the number of patients that have been allocated to doses, but have not yet completed the observation period. For safety purposes we want to keep the queue size moderate to prevent large numbers of patients being enrolled at any one time. Until 4 patients have complete DLT information the queue maximum is 2. After 4 patients have complete DLT information the queue increases to 3. Patients cannot be enrolled for dose escalation if the queue maximum has been reached.

13.5.3.2 Assignment of Dose Level

The dose-toxicity model will be used to assign patients to doses. However, assignment of dose level is also governed by rules that govern the speed of dose escalation and rules that determine if untried dose levels may be skipped.

There must be complete DLT information through the first cycle (3 weeks) on at least 2 patients in order to escalate. When the dose is escalated, the dose level may increase by 100% as long as no toxicity events are observed. Once a non-DLT toxicity is observed, the dose may only be increased by 67%; and once a DLT is observed, the dose may only increase by 50%. In addition, the dose may never increase by more than 100% or by more than an absolute value of 1) 0.02 mg/kg at dose levels below 0.10 or 2) 0.10 mg/kg for dose levels between 0.10 and 0.30.

The increase in dose level is always constrained by the dose-toxicity model. The dose may never escalate to a dose that is considered unsafe.

13.5.4 Interim Monitoring

The trial is continuously monitored for safety and for success in identifying the MTD. If dose escalation is not stopped for either safety or success in identifying the MTD it will continue to enroll to the maximum sample size.

13.5.4.1 Safety Monitoring

The lowest dose (0.003 mg/kg) will be considered unsafe if it has a probability < 25% of a DLT rate < 30%. The trial will stop, and no MTD found, if the lowest dose is considered unsafe (hence all doses are considered unsafe).

13.5.4.2 Success in Identifying the MTD

Dose escalation may be stopped early when sufficient information around the MTD has been obtained. We characterize this by having a sufficient number of patients at and around the MTD. We require at least 3 patients with complete information at the MTD and at least 6 patients with complete information within a certain interval around the MTD. If the MTD is 0.010 mg/kg or lower, we require 6 patients at the MTD. If the MTD is 0.011 mg/kg or greater, we require a total of 6 patients between the MTD and the dose level below.

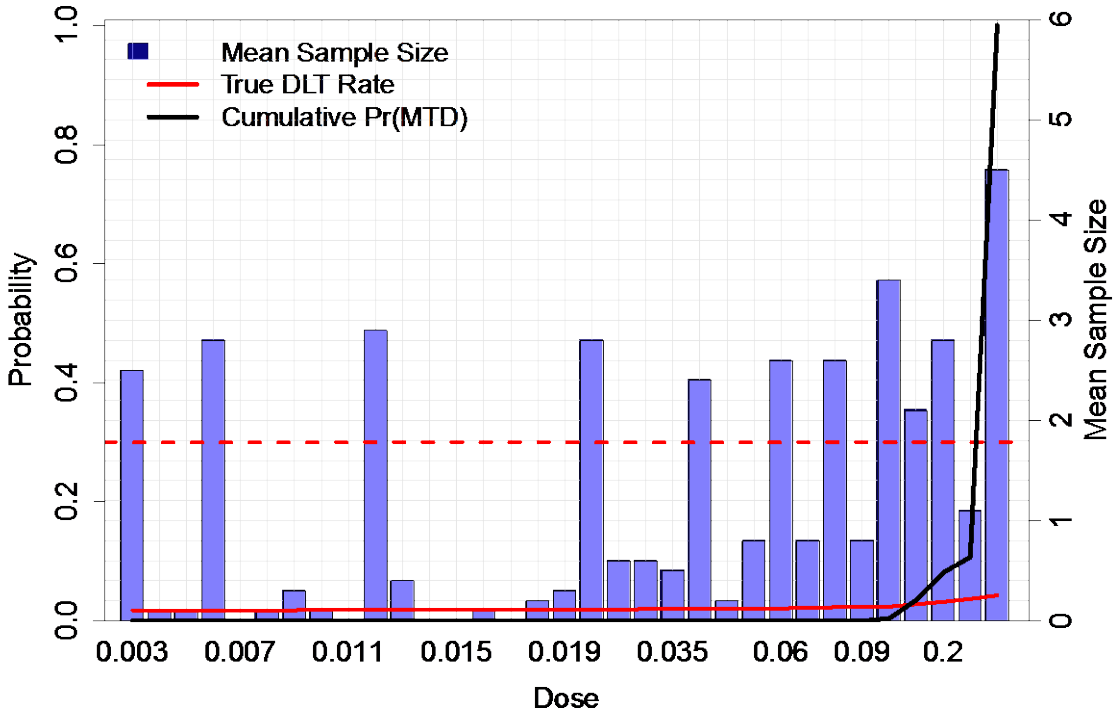
13.5.5 Operating Characteristics

To evaluate how the dose escalation design performs, we simulated the study considering different dose-toxicity scenarios. We show operating characteristics of the trial based on 1,000 simulations per scenario. For each scenario we plot the mean sample size and cumulative probability of MTD across the 33 dose levels including all dose levels from:

- 0.003 to 0.02 mg/kg in increments of 0.001
- 0.02 to 0.05 mg/kg in increments of 0.005
- 0.05 to 0.10 mg/kg in increments of 0.01
- 0.10 to 0.30 mg/kg in increments of 0.05

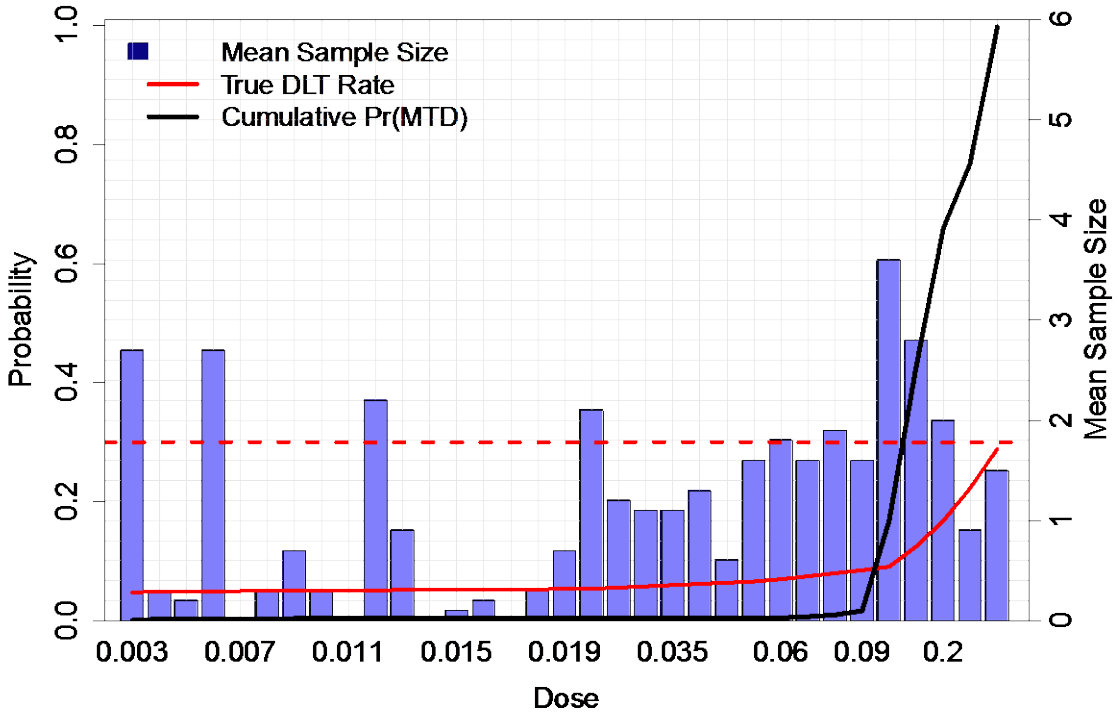
The true DLT scenario is shown for reference along with a line indicating a 30% DLT rate. We further summarize the performance of the dose escalation design by showing the mean sample size and the 10%, 20%, 50%, 80%, and 90% quantiles of the cumulative MTD curve.

13.5.5.1 All Doses Safe



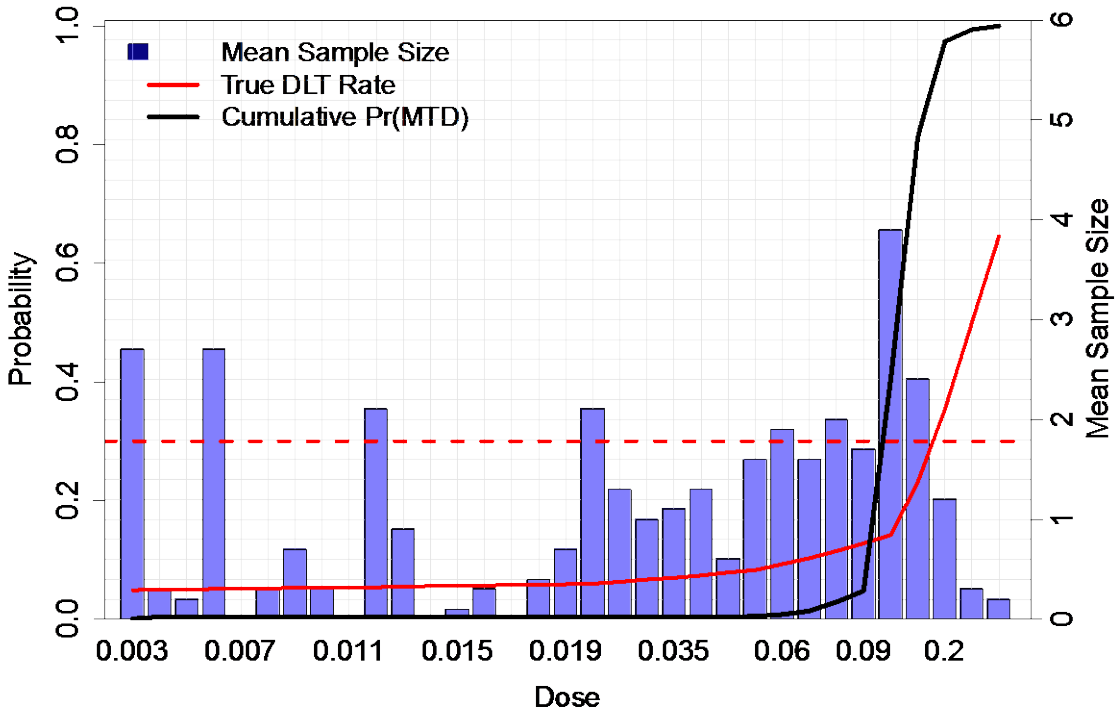
		Quantile of Cumulative MTD Selection				
True MTD	**Mean N**	**10%**	**20%**	**50%**	**80%**	**90%**
0.3	38	0.25	0.30	0.30	0.30	0.30

13.5.5.2 MTD is the Highest Dose (0.30 mg/kg)



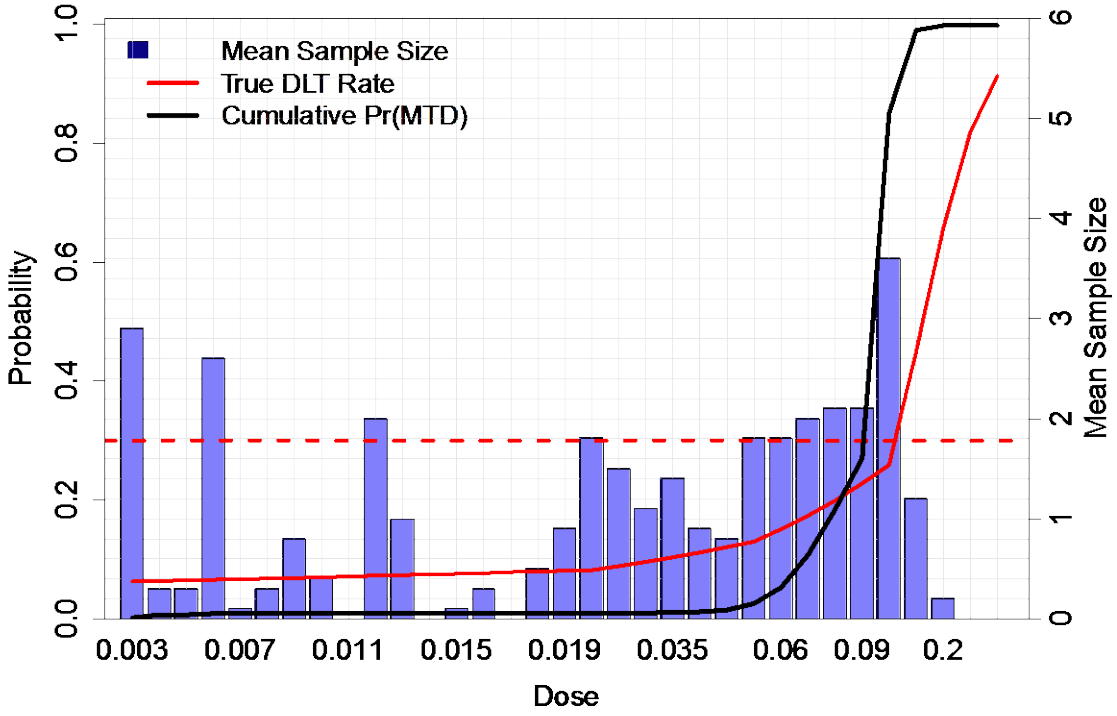
		Quantile of Cumulative MTD Selection				
True MTD	**Mean N**	**10%**	**20%**	**50%**	**80%**	**90%**
0.30	38.3	0.10	0.15	0.20	0.30	0.30

13.5.5.3 MTD is a Middle Dose (0.15 mg/kg)



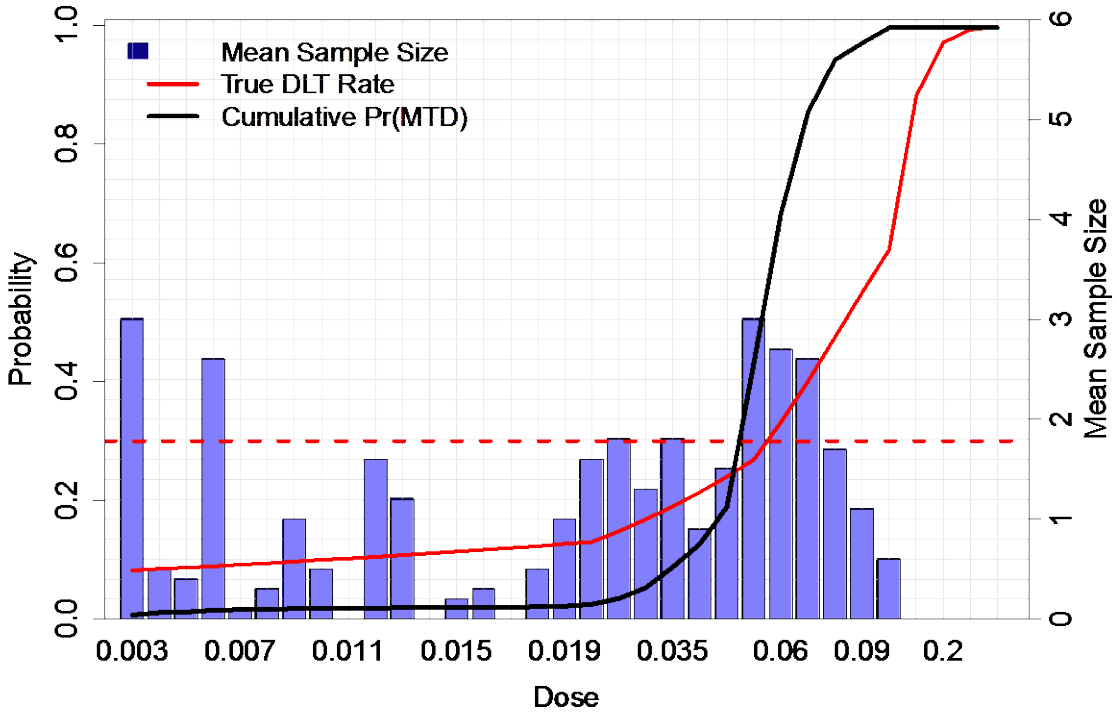
		Quantile of Cumulative MTD Selection				
True MTD	**Mean N**	**10%**	**20%**	**50%**	**80%**	**90%**
0.15	35.6	0.10	0.10	0.15	0.15	0.20

13.5.5.4 MTD is a Middle Dose (0.10 mg/kg)



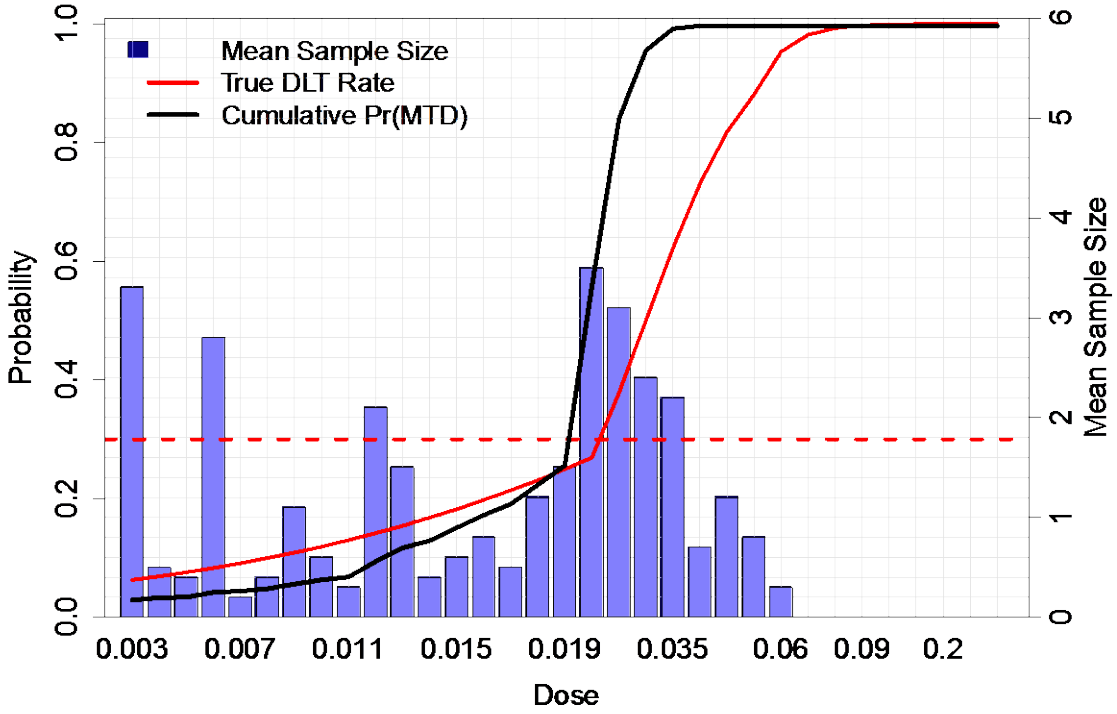
		Quantile of Cumulative MTD Selection				
True MTD	**Mean N**	**10%**	**20%**	**50%**	**80%**	**90%**
0.1	34.9	0.07	0.09	0.10	0.10	0.15

13.5.5.5 MTD is a Low Dose (0.05 mg/kg)



		Quantile of Cumulative MTD Selection				
True MTD	**Mean N**	**10%**	**20%**	**50%**	**80%**	**90%**
0.05	34.2	0.04	0.05	0.06	0.07	0.08

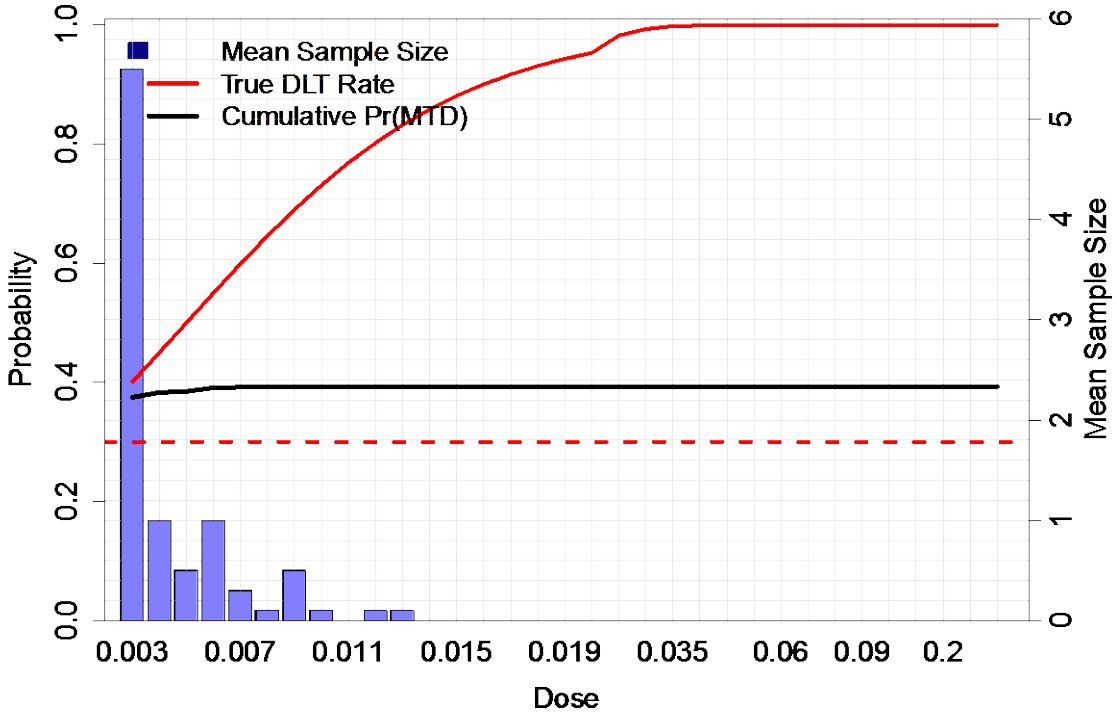
13.5.5.6 MTD is a Low Dose (0.02 mg/kg)



		Quantile of Cumulative MTD Selection				
True MTD	**Mean N**	**10%**	**20%**	**50%**	**80%**	**90%**
0.02	32.6	0.013	0.018	0.020	0.025	0.03

13.5.5.7 No Doses Safe

In this scenario, there is a 61% probability of stopping early for safety. The lowest dose is selected as the MTD with 37% probability.



13.6 Appendix: Clinical Case Definitions: Level 1 of Diagnostic Certainty for Guillain-Barré Syndrome

- 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[13]

[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.

13.7 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 (5m across an open space) but incapable of manual work/running
3	Able to walk with a stick, appliance, or support (5m 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]