Protocol Number: ADCT-402-101

Official Title: Phase 1 Dose-escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-cell Lineage Non Hodgkin Lymphoma (B-NHL)

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A Phase 1 Dose-escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-cell Lineage Non Hodgkin Lymphoma (B-NHL)

PROTOCOL NO.: ADCT-402-101

Sponsor: **ADC Therapeutics SA**

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Sponsor Contact:

[redacted]

Medical Monitor:

[redacted]

Date of Original Protocol: 21 September 2015
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Protocol Amendment 7: 16 October 2017

Confidentiality Statement

Protocol Approval – Sponsor Signatory

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Protocol Amendment 6:	24 July 2017
Protocol Amendment 7:	**16 October 2017**

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 1, Dose-escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-cell Lineage Non Hodgkin Lymphoma (B-NHL)" and the accompanying Investigator Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol, dated 16 October 2017 , the current version of International Council for Harmonisation (ICH) harmonised tripartite guideline E6: Good Clinical Practice and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer 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-402-101**
Title:	A Phase 1, Dose-escalation Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Antitumor Activity of ADCT-402 in Patients with Relapsed or Refractory B-cell Lineage Non Hodgkin Lymphoma (B-NHL)
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 1
Study Sites:	Approximately 11 sites during dose escalation (Part 1) and12 sites during dose expansion (Part 2)
Indication:	Patients with relapsed or refractory B-cell lineage non-Hodgkin Lymphoma (B-NHL) who have failed, or are intolerant to, any established therapy; or for whom no other treatment options are available, in the opinion of the Investigator. The DESC will determine which histologic sub-types will be investigated in Part 2 of the study based on the emerging efficacy and tolerability profile from part 1. B-cell NHL defined as: • Diffuse large B-cell lymphoma (DLBCL) • Follicular lymphoma (FL) • Chronic lymphocytic leukemia (CLL) • Mantle cell lymphoma (MCL) • Marginal Zone B-cell Lymphoma (MZBCL) • Burkitt's lymphoma (BL) • Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia [WM]).
Rationale:	Non-Hodgkin Lymphoma is the seventh most common type of cancer in the U.S., and will account for an estimated 4.3% (n=71,850) of new cancer cases in 2015. It is most commonly a disease of older individuals with approximately 75% of new cases diagnosed in individuals 55 years of age or older (median age at diagnosis = 66 years). Response to initial

treatment generally exceeds 50% and the overall 5-year survival rate in the U.S. is 70%. However, a significant proportion of patients will relapse. The poor prognosis for relapsed patients, especially those with chemo-refractory disease with a short interval between remission and relapse, or those who relapse after high-dose therapy and autologous stem cell transplant (ASCT), highlights the need for new forms of treatment for NHL.

In normal human tissue, expression of cluster of differentiation 19 (CD19) is limited to the developmental stages of the B cell and is lost in terminally differentiated plasma cells. Expression of CD19 is maintained in hematologic B-cell malignancies, including B-NHL.

ADCT-402 is an antibody drug conjugate (ADC) composed of a humanized monoclonal antibody, directed against human CD19, conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin, through a protease-cleavable valine-alanine linker. The PBD dimer cytotoxin (SG3199) attached to the linker is designated as SG3249.

The potential for ADCT-402 in treating B-cell malignancies was tested in mouse xenograft models of human-derived B-cell leukemias and lymphomas. Complete responses were observed in mice after receiving a single low dose of ADCT-402. The efficacy of ADCT-402 in these models is due to targeted delivery of the PBD cytotoxin, SG3199.

ADCT-402 is not pharmacologically cross-reactive (active) in any standard species used for nonclinical safety assessment. In the absence of CD19 target engagement, it was not possible to nonclinically evaluate the safety consequences associated with possible B-cell depletion. However, the impact and overall safety of B-cell depletion has been investigated clinically and nonclinically with other B-cell depleting agents and has been shown to be safe and well tolerated. The safety studies therefore assessed the potential off-target effects of ADCT-402 and the impact of ADCT-402 on the tissues normally associated with antibody clearance.

In rats, ADCT-402 is well tolerated at doses up to 2 mg/kg. A repeat-dose Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys investigated doses from 0.3 to 0.6 mg/kg with the 0.6 mg/kg dose identified as the highest nonsevere toxic dose (HNSTD). Toxicity in the monkey was characterized by reversible dose-dependent skin changes (hyperpigmentation with hyperplasia / hyperkeratosis), reversible dose-dependent anemia associated with some bone marrow hypocellularity, reversible dose-dependent nephropathy and dose-dependent testicular toxicity (atrophy with reduced spermatogenesis, expected to be reversible).

Objectives:

Primary Objectives

- Evaluate the safety and tolerability, and determine, as appropriate, the maximum tolerated dose (MTD) of ADCT-402 in patients with relapsed or refractory B-cell lineage NHL (Part 1).

- Determine the recommended dose(s) of ADCT-402 for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCT-402 in Part 2 (expansion) at the dose level(s) recommended in Part 1.

Secondary Objectives

- Evaluate the clinical activity of ADCT-402 as measured by overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).
- Characterize the pharmacokinetic (PK) profile of ADCT-402 (total antibody; drug to-antibody ratio [DAR] ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) in blood before, during, and after treatment with ADCT-402.

[redacted]

Patient Selection:

Inclusion Criteria

1. Part 1: Male or female patients, ages 18 years or older with pathologically-confirmed relapsed or refractory B-cell lineage NHL who have failed or are intolerant to established therapy, or for whom no other treatment options are available, in the opinion of the Investigator.

Refractory or relapsed B-cell NHL (per World health Organization [WHO] Classification system) defined as:

- Diffuse large B-cell lymphoma (DLBCL),
- Follicular lymphoma (FL),
- Chronic lymphocytic leukemia (CLL),
- Mantle cell lymphoma (MCL),
- Marginal Zone B-cell Lymphoma (MZBCL),

- Burkitt's lymphoma (BL),
- Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia [WM]).

Part 2: Eligible histologic sub-types to be investigated in part 2 of the study will be determinded by the DESC based on evolving efficacy and safety information from Part 1. Patients enrolled in part 2 of the study will have failed or are intolerant to established therapy, or have no other treatment options are available, in the opinion of the Investigator.

The DESC may establish specific patient populations within each hitological subtype to be investigated such as specific prior treatments.

2. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block. An FFPE block from a current biopsy is preferred; however, archival tissue taken at initial diagnosis or 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.

3. Measurable disease, as defined by the 2014 Lugano Classification.

4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.

5. Absolute neutrophil count (ANC) ≥1000/μL.

6. Platelet count of ≥75000/μL.

7. Hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Day 1.

8. Serum/plasma creatinine ≤1.5 mg/dL. If the patient has a creatinine > 1.5mg/dL, a measured creatinine clearance must be >60mL/min as calculated by the Cockcroft and Gault equation.

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

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

11. Negative serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to Day 1 for women of childbearing potential.

12. 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-402. 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-402.

* Women of childbearing potential are defined as sexually mature

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

** Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.
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, in the opinion of the Investigator, have any option for other treatment for B-cell NHL at the current state of disease.

2. Active graft-versus-host disease.

3. Autologous or allogenic transplant within the 60 days prior to the Screening visit.

4. Known history of immunogenicity or hypersensitivity to a CD19 antibody.

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

6. Known history of positive serum human ADA.

7. Active autoimmune disease, motor neuropathy considered of autoimmune origin, and other central nervous system (CNS) autoimmune disease. Known seropositive for human immunodeficiency (HIV) virus, 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. Testing for HCV should be considered if the patient is at risk for having undiagnosed HCV (e.g., history of injection drug use).

8. History of Steven's Johnson's syndrome or toxic epidermal necrolysis syndrome.

9. Pregnant or breastfeeding women.

10. Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure greater than 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.

11. Use of any other experimental medication(s) within 14 days or 5 half-lives but in no case less than 14 days prior to start of study treatment on Cycle 1, Day 1, except if approved by Sponsor.

12. Steroid use equivalent to greater than 20 mg of prednisone within 4 weeks (28 days) prior to Day 1, except for the use of short course systemic corticosteroids (≤ 7 days), with a wash-out period of 1 week prior to start of study treatment on Day 1.

13. Major surgery, chemotherapy, systemic therapy (excluding steroids hydroxyurea steroids, and any targeted small molecules or biologics), or radiotherapy, within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1, Day 1 treatment, except if approved by the Sponsor.

14. Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE] Grade 0 or Grade 1) from acute non hematologic toxicity (except all grades alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to Screening.

15. Congenital long QT syndrome or a corrected QTc interval ≥450 ms at the Screening visit (unless secondary to pacemaker or bundle branch block).

16. Active second primary malignancy other than non-melanoma skin cancers, non-metastatic prostate cancer, *in situ* cervical cancer, ductal or lobular carcinoma *in situ* of the breast, or other malignancy that the Sponsor's medical monitor and Investigator agree and document should not be exclusionary.

17. 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, open-label, dose escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of ADCT-402, used as monotherapy, in patients with relapsed or refractory B-NHL. The study will determine the MTD, as well as evaluate the preliminary activity, PK, pharmacodynamics (PD), and other exploratory assessments of ADCT-402. In Part 1, patients will be assigned to treatment according to a 3+3 dose escalation design (see below) and with oversight by a Dose Escalation Steering Committee (DESC). In Part 2, (expansion), all patients will be assigned to the recommended dose level(s) and schedule(s) of ADCT-402 identified in Part 1.
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), 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 duration of the entire study (Parts 1 and 2) could be approximately 3 years from first patient treated to last patient completed. Patients who discontinue treatment for any reason other than disease progression will continue to be followed approximately every 12 weeks from the last disease assessment until disease progression, or initiation of new anticancer treatment. After documentation of disease progression or start of new treatment, patients will be followed (by telephone contact or chart review) approximately every 12 weeks for up to 12 months after the last dose of study drug to collect survival information. Patients may withdraw from the study at any time and for any reason, without prejudice to their future medical care, by the Investigator or others at the study site.
Efficacy Assessments:	Disease assessments will be conducted 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. If PET-CT is positive, subsequent diagnostic CT and MRI are not needed unless clinically indicated. PET-CT is not required if a PET-CT examination at Screening was negative. For patients who have reduced dosing frequency and are following a 6 week schedule, disease assessments should occur approximately 6 weeks and 12 weeks after Cycle 1 Day 1, and thereafter at least every 12 weeks. It is understood that there will be a ± 6 day window for restaging of these patients. The patient's response to treatment will be determined by the Investigator as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), based on the 2014 Lugano Classification

	Criteria.
Pharmacokinetic and Anti-drug Antibody Assessments:	The PK profile of ADCT-402 (total antibody; DAR ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead SG3199 will be assessed using measures from validated bioanalytical methods . The PK profile will include determination of standard PK parameters (e.g., maximum concentration [C_{max}], time to C_{max} [T_{max}]). The following pharmacodynamic and other exploratory assessments will be performed at various time points in the study: [redacted] • Level of ADAs against ADCT-402 in serum. [redacted] • Serum concentrations of ADCT-402 and free warhead SG3199 will be determined. The QTc interval will also be measured.
Safety Assessments:	Safety will be assessed based on the evaluation of adverse events (AEs), serious AEs (SAEs), treatment discontinuations due to AEs, dose limiting toxicity(s) (DLTs), periodic 12-lead electrocardiogram (ECG) recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, coagulation panel and pregnancy testing (for women of child-bearing potential), biochemistry, and urinalysis test results obtained at various timepoints during the study. Adverse events will be graded according to CTCAE Version 4.0.

Definition of DLT	A dose-limiting toxicity (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: • 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. 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 AE (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grades of alopecia). • Grade 3 or higher hypersensitivity reaction (regardless of premedication). • Grade 2 or higher skin ulceration. The DLT period for dose escalation will be 1 cycle.
Investigational Product, Dosage, and Mode of Administration:	ADCT-402 is a sterile formulation containing PBD-conjugated humanized monoclonal IgG1 antibody (DAR ≥1), humanized monoclonal IgG1 antibody (DAR = 0), and SG3249. It is provided pre-formulated in 10 mL glass vials containing approximately 16 mg ADCT-402 per vial (deliverable volume 3.2 mL at 5 mg/mL). Patients will receive a 1-hour intravenous (IV) infusion of ADCT-402, at escalating doses, on Day 1 of each cycle. If ADCT-402 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.

Dose-Escalation Design:

In Part 1, patients will be assigned to treatment with ADCT-402 at escalating doses according to a 3+3 study design. The initial dose of ADCT-402 will be 15 µg/kg (Dose Level 1), and the highest allowed dose will be 300 µg/kg.

Further dose levels and schedules evaluated include the following:

- 120 µg/kg: Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.
- 150 µg/kg: Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.
- 200 µg/kg: Dosing every 6 weeks for 2 cycles. For patients with at least SD 6 weeks after Cycle 2, continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.
- 200 µg/kg: Dosing every 6 weeks. For patients with at least SD 6 weeks after Cycle 1, continue treatment at a reduced dose of 60 µg/kg every 6 weeks beginning 6 weeks after Cycle 1 infusion.

The first patient enrolled into the study at 15 µg/kg (Dose Level 1) must be observed for 7 days for occurrence of AEs prior to treating the second patient in the study. The DLT observation period for dose escalation is 1 cycle.

For each dose level, if none of the first 3 patients at that level experiences a DLT, new patients may be entered at the next higher dose level. If 1 of 3 patients experiences a DLT, up to 3 more patients are to be treated at that same dose level. If none of the additional 3 patients at that dose level experiences a DLT, new patients may then be entered at the next higher dose level. However, if 1 or more of the additional 3 patients experiences a DLT, then no further patients are to be started at that dose level and the preceding dose is identified as the MTD. The MTD is therefore defined as the highest dose level at which none of the first 3 treated patients, or no more than 1 of the first 6 treated patients, experiences a DLT.

The study will be continuously monitored for safety and early stopping for successful identification of the MTD.

Dose-Expansion Design:	In Part 2, (expansion), patients will be assigned to the recommended dose level(s) and schedule(s) of ADCT-402 identified in Part 1 based on evolving safety, efficacy and pharmacokinetic data. The population in Part 2 expansion may be restricted to specific histologies based on both signals of activity and the safety observed in Part 1. Further, dose levels and schedules evaluated in Part 2 may include but are not limited to the following: 90, 120, 150, 200 µg/kg: Dosing every 3 weeks. 120 µg/kg: Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion. 150 µg/kg: Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion. 200 µg/kg: Dosing every 6 weeks for 2 cycles. For patients with at least SD 6 weeks after Cycle 2, continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion. 200 µg/kg: Dosing every 6 weeks. For patients with at least SD 6 weeks after Cycle 1, continue treatment at a reduced dose of 60 µg /kg every 6 weeks beginning 6 weeks after Cycle 1 infusion.
Sample Size:	This is a Phase 1 study with a maximum sample size of up to approximately 200 patients. It is estimated that approximately 90 patients will enroll at 11 sites in Part 1, and approximately 110 patients will enroll at 12 sites in Part 2.

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibody
ADC	antibody drug conjugate
ADL	activities of daily living
AE	adverse event
AI	accumulation index
Ala	alanine
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-last}}$	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
BSA	body surface area
CBC	complete blood count
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
C_L	clearance
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D5W	5% dextrose in water
DAR	drug-to-antibody ratio
DESC	Dose Escalation Steering Committee
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	end of infusion

Abbreviation	Definition
EOT	End of treatment
EWOC	escalation with overdose control
FDA	Food and Drug Administration
FDG	^{18}F-fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
β-HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSTD	highest nonsevere toxic dose
hr	hour
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
INR	international Normalized Ratio
IV	intravenous
IRB	institutional review board
mos	months
MRI	magnetic resonance imaging
MRT	mean residence time
MTD	maximum tolerated dose
NHL	non-Hodgkin Lymphoma
NSAID	non-steroidal anti-inflammatory drug
ORR	overall response rate
OS	overall survival
PABA	para-aminobenzoic acid
PBD	pyrrolobenzodiazepine
PD	progressive disease pharmacodynamics
PEG	polyethylene glycol
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PR	partial response

Abbreviation	Definition
PT	prothrombin time
PTT	partial thromboplastin time
QWBA	Quantitative whole-body autoradiography
q6weeks	Every 6 weeks
RB4v1.2	human monoclonal antibody being studied
SAE	serious adverse event
SAP	statistical analysis plan
SCID	Severely combined immunodeficiency
SD	stable disease
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
Val	valine
V_{ss}	volume of distribution at steady-state
V_Z	volume of distribution
WBC	white blood cell
WHO	World Health Organization
wk	week

1 Introduction and Study Rationale

1.1 Description of ADCT-402

ADCT-402 is an antibody drug conjugate (ADC) composed of a humanized antibody (RB4v1.2) directed against human cluster of differentiation 19 (CD19), attached with a cathepsin-cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin.

The 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-402 is presented in Figure 1.

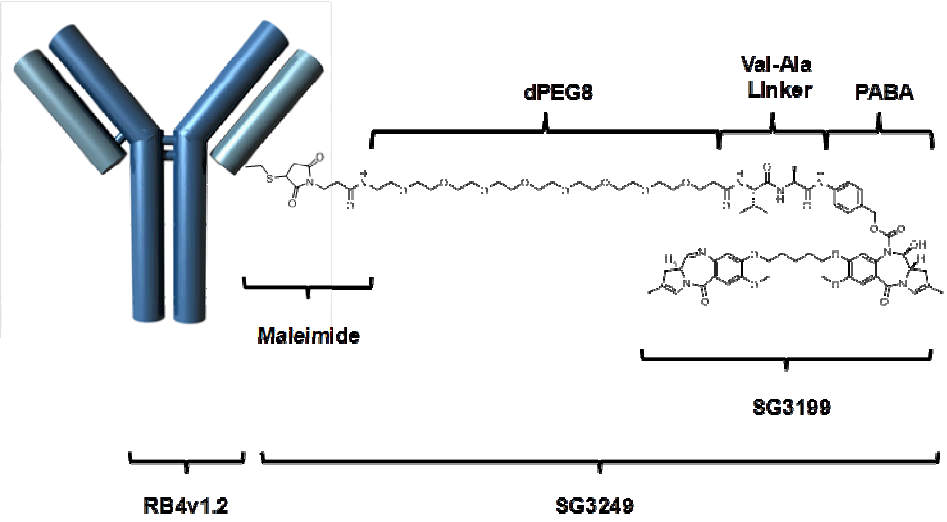


Figure 1 Schematic Representation and Chemical Structure of ADCT-402

Abbreviations: Ala, alanine; PABA, para-aminobenzoic acid; PEG, polyethylene glycol; RB4v1.2, human monoclonal antibody being studied; Val, valine.

The make-up of ADCT-402 includes:

- RB4v1.2: A humanized monoclonal antibody specific for human CD19 of the immunoglobin G1 (IgG1), kappa isotype, generated by the variable domain resurfacing of the murine monoclonal anti-B4 (anti-CD19) antibody (Roguska, 1996).
- 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 (PABA) self-immolative group.

ADCT-402 binds with picomolar affinity to human CD19. After binding and internalization, ADCT-402 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 and form highly cytotoxic DNA interstrand cross-links (Hartley, 2011a). 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 (Adair, 2012) and effectiveness in tumor cell lines resistant to other forms of chemotherapy.

1.2 Study Rationale

Study ADCT-402-101 is the first- clinical study with ADCT-402 in patients with B-cell non-Hodgkin Lymphoma (NHL).

1.2.1 Clinical Background

Non-Hodgkin Lymphoma represents a biologically and clinically diverse group of hematologic malignancies arising from precursor and mature B, T, and natural killer cells. It is the seventh most common type of cancer in the U.S., and will account for an estimated 4.3% (n=71,850) of new cancer cases in 2015. It is most commonly a disease of older individuals with approximately 75% of new cases diagnosed in individuals 55 years of age or older (median age at diagnosis = 66 years) (National Cancer Institute 2015). The two most common types of NHL, diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), together account for more than half of all NHL cases (The Non-Hodgkin's Lymphoma Classification Project, 1997; Swerdlow, 2008).

Combination chemotherapy or chemo-immunotherapy, with or without radiotherapy, is the most common initial treatment for most types of NHL (Ansell, 2015; Evens et al, 2015). Response to initial treatment generally exceeds 50% and the overall 5-year survival rate in the U.S. is 70% (National Cancer Institute 2015). However, a significant proportion of patients will relapse. The current standard of care for relapsed NHL is additional chemotherapy, which can be followed by allogeneic stem cell transplantation (ASCT). The poor prognosis for relapsed patients, especially those with chemo-refractory disease with a short interval between remission and relapse, or those who relapse after high-dose therapy and ASCT, highlights the need for new forms of treatment for NHL (Chao, 2013; Mounier and Gisselbrecht, 2011).

1.2.2 Biology of CD19

Human CD19 is a 95 kilodalton (kDa) type I transmembrane glycoprotein belonging to the immunoglobulin Ig super family (Carter and Barrington, 2004; Tedder, 2009). In normal human tissue, expression of CD19 is restricted to the various stages of B cell development, from early pre B stage to mature B cells, but is lost in terminally differentiated plasma cells (Haas and Tedder, 2005; Scheuermann and Racila, 1995). Once bound to an antibody, CD19 is rapidly internalized by the cell (Gerber, 2009; Blanc, 2011). It is not shed into the circulation to the extent observed with other CD antigens[1] (Cooper, 2004), therefore low to no levels of soluble CD19 are present to compete with binding at the target tissue.

Expression of CD19 is maintained in B-cell malignancies, including DLBCL, Burkitt's lymphoma, and FL. Additionally, CD19 expression is maintained in B-cell tumors which have

[1] Note: A report of soluble CD19 detected in the cerebrospinal fluid of patients with certain types of B-cell lymphoma was recently published (Muniz, 2014).

lost expression of CD20 after anti-CD20 monoclonal antibody treatment (Anderson, 1984, Scheuermann and Racila, 1995; Wang, 2012).

1.2.3 Nonclinical Efficacy and Safety of ADCT-402

The potential for ADCT-402 in treating B-cell hematologic malignancies expressing CD19 has been shown by complete responses in mouse xenograft models of human-derived B-cell leukemias and lymphomas following single, low-dose administration. The efficacy of ADCT-402 in these models is due to targeted delivery [redacted]

ADCT-402 is not pharmacologically cross-reactive (active) in any standard species used for nonclinical safety assessment (Blanc, 2011). In the absence of CD19 target engagement in the rat and monkey, it is not possible to evaluate the safety consequences associated with likely B-cell depletion. However, the impact and overall safety of B-cell depletion has been investigated clinically and nonclinically with other B-cell deleting agents and been shown to be safe and well tolerated (Kimby, 2005; Chen and Cohen, 2012).

Therefore, the safety studies performed assess the potential off-target effects of ADCT-402 and the impact of ADCT-402 on the tissues associated with 'normal' antibody clearance. In rats, ADCT-402 is well tolerated at doses up to 2 mg/kg. [redacted]

As per guidance from the Food and Drug Administration (FDA), the starting dose of ADCT-402 chosen for this study is 15 µg/kg.

See the Investigator Brochure for ADCT-402 for additional information, including guidance for the Investigator.

1.2.4 Safety of Commercially Available Antibodies Directed against CD19

Although several antibodies targeted against CD19 are currently in clinical development with different manufacturers (Jabbour, 2015), only one is commercially available in the U.S. Blinatumomab (Blincyto™, Amgen, Thousand Oaks, CA) is a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative, relapsed or refractory B-ALL. The antibody binds to CD19 on B-lineage cells and to CD3 on T cells. The most commonly reported adverse reactions reported with its use include pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, and constipation (Amgen, 2014).

2 Study Objectives

2.1 Primary Objectives

- Evaluate the safety and tolerability, and determine, as appropriate, the maximum tolerated dose (MTD) of ADCT-402 in patients with relapsed or refractory B-cell lineage NHL in Part 1.
- Determine the recommended dose(s) of ADCT-402 for Part 2 (expansion).
- Evaluate the safety and tolerability of ADCT-402 in Part 2 (expansion) at the dose level(s) recommended in Part 1.

2.2 Secondary Objectives

- Evaluate the clinical activity of ADCT-402 as measured by overall response rate (ORR), duration of response (DOR), overall survival (OS), and progression-free survival (PFS).
- Characterize the pharmacokinetic (PK) profile of ADCT-402 (total antibody; drug to-antibody ratio [DAR] ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) to ADCT-402 in blood before, during, and after treatment with ADCT-402.

3 Investigational Plan and Patient Selection

3.1 Study Design

This is a Phase 1, open-label, dose escalation (Part 1) and expansion (Part 2) study of the safety and tolerability of ADCT-402, used as monotherapy, in patients with relapsed or refractory B-cell NHL. The study will determine the MTD, as well as evaluate the preliminary activity, PK, pharmacodynamics, and other exploratory assessments of ADCT-402.

Patients will receive a 1-hour intravenous (IV) infusion of ADCT-402, at escalating doses, on Day 1 of each cycle. If ADCT-402 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.

For each patient, the study will include a screening period (up to 28 days), a treatment period (until withdrawal, Section 4.2), 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 depend on overall patient tolerability to the study drug and response to treatment. It is anticipated that the duration of the entire study (Parts 1 and 2) could be approximately 3 years from first patient treated to last patient completed.

Part 1

In Part 1, patients will be assigned to treatment according to a 3+3 dose escalation design (Section 3.2) and oversight of a Dose Escalation Steering Committee (DESC) (Section 6.3.1.1).

During the conduct of Part 1, and prior to implementation of Amendment 5, alternative dosing schedules are being evaluated at the discretion of the DESC as described below:.

- 120 µg/kg: Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.
- 150 µg/kg: Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.
- 200 µg/kg: Dosing every 6 weeks for 2 cycles. For patients with at least SD 6 weeks after Cycle 2, continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.
- 200 µg/kg: Dosing every 6 weeks. For patients with at least SD 6 weeks after Cycle 1, continue treatment at a reduced dose of 60 µg /kg every 6 weeks beginning 6 weeks after Cycle 1 infusion.

Changes described in part 2 resulted from requests based on DESC decisions.

Part 2

In Part 2, (expansion), patients will be assigned to the recommended dose level(s) and schedule(s) of ADCT-402 identified in Part 1 based on evolving safety, efficacy and pharmacokinetic data.

The *population* in Part 2 expansion may be restricted to specific histologies based on both signals of activity and the safety observed in Part 1.

Further, *dose levels and schedules* evaluated in Part 2 may include but are not limited to the following:

A. **90, 120, 150, and/or 200 µg/kg:** Dosing every 3 weeks.

B. **120 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

C. **150 µg/kg:** Dosing every 3 weeks for 2 cycles. Patients with at least SD after the second cycle continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

D. **200 µg/kg:** Dosing every 6 weeks for 2 cycles. For patients with at least SD 6 weeks after Cycle 2, continue treatment at a reduced dose of 60 µg/kg q6weeks, beginning 6 weeks after Cycle 2 infusion.

E. **200 µg/kg:** Dosing every 6 weeks. For patients with at least SD 6 weeks after Cycle 1, continue treatment at a reduced dose of 60 µg /kg every 6 weeks beginning 6 weeks after Cycle 1 infusion.

The continuation of each patient's treatment will be based on an independent verification of local response assessments, unless otherwise approved by the sponsor.

The DESC will determine and document the dose levels, schedules, and disease subtypes to be evaluated in Part 2. These determinations by the DESC will be provided in writing.

Based on emerging safety and efficacy profile, the DESC may add additional cohorts to part 2 of the study with the same or different dosing regimens and for the same or different B-cell NHL histologies. The dose will not exceed the highest dose tested in part 1 at which 3 patients cleared the DLT observation period.

Patients who discontinue treatment for any reason other than disease progression will continue to be followed approximately every 12 weeks from the last disease assessment until disease progression, or initiation of new anticancer treatment.

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

3.2 Dose Escalation

In Part 1, dose escalation will be conducted according to a 3+3 design (Figure 2). The initial dose of ADCT-402 will be 15 µg/kg (Dose Level 1), and the highest allowed dose will be 300 µg/kg. The potential dose levels are described in Table 1.

Table 1. Planned Dose Levels for ADCT-402

Dose Level	Dose of ADCT-402	Dose Level	Dose of ADCT-402
1	15 µg/kg	**6**	150 µg/kg
2	30 µg/kg	**7**	200 µg/kg
3	60 µg/kg	**8**	250 µg/kg
4	90 µg/kg	**9**	300 µg/kg
5	120 µg/kg		

The dose-limiting toxicity (DLT, Section 6.3.1) observation period for dose escalation is 1 cycle. The first patient enrolled into the study at 15 µg/kg (Dose Level 1) must be observed for 7 days for occurrence of AEs prior to treating the second patient in the study. Patients will be entered sequentially to each dose level.

For each dose level, if none of the first 3 patients at that level experiences a DLT, new patients may be entered at the next higher dose level. If 1 of 3 patients experiences a DLT, up to 3 more patients are to be treated at that same dose level. If none of the additional 3 patients at that dose level experiences a DLT, new patients may then be entered at the next higher dose level. However, if 1 or more of the additional 3 patients experiences a DLT, then no further patients are to be started at that dose level and the preceding dose is identified as the MTD. The MTD is therefore defined as the highest dose level at which none of the first 3 treated patients, or no more than 1 of the first 6 treated patients, experiences a DLT.

No intra-patient dose escalation is allowed.

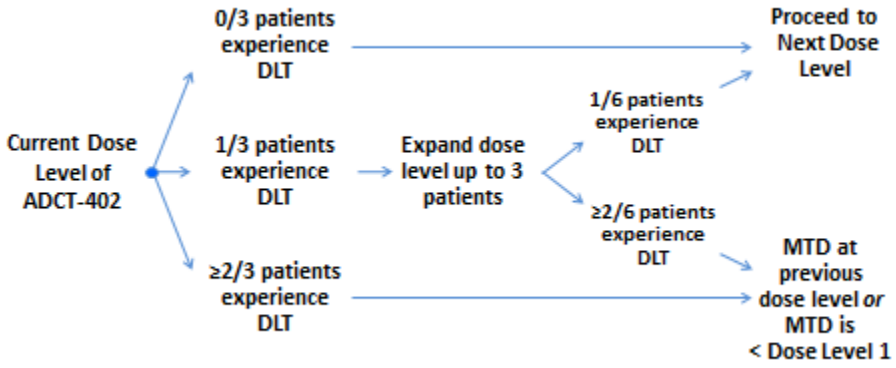


Figure 2. Schematic Representation for Dose Escalation (3+3) Design

Abbreviations: DLT, dose-limiting toxicity; MTD, maximum tolerated dose; <, less than; ≥ greater than or equal to.

The number of dose levels will depend on the emergent toxicity profile of ADCT-402 and will be decided by the DESC (Section 6.3.1.1); PK, and PD evaluations may also inform decision making.

The trial will be continuously monitored for safety. If the maximum allowed dose (300 µg/kg) is reached and the MTD is not identified, no further dose escalation will be allowed pending a safety analysis and review and accordingly, an amendment to the protocol.

During Part 1, the DESC may expand enrollment at any dose level in which 3 patients have completed the DLT observation period if at least 1 patient in the study has achieved a partial response (PR, Section 6.1) or better, or if further evaluation of PK or PD data is deemed necessary to characterize pharmacology in humans. No more than 10 patients in total can be treated at any dose level unless ≥3 of the 10 patients have achieved a PR or better.

During dose expansion (part 2), patients will be monitored for safety using the same DLT criteria employed during dose-escalation. If during the treatment period, > 30% of patients experience safety events that would meet the criteria that define a DLT in the dose-escalation phase of the study, enrollment in the expansion cohort(s) may be paused and the study data reviewed to determine whether additional monitoring or other action (such as alternate dose levels) should be evaluated prior to further enrollment.

3.3 Selection of Study Population

This is a Phase 1 study with a sample size of up to 200 patients. It is estimated that approximately 90 patients will enroll at 11 sites in Part 1, and approximately 110 patients will enroll at 12 sites in Part 2. Patients will be assigned to a study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

3.3.1 Inclusion Criteria

1. Part 1: Male or female patients, ages 18 years or older with pathologically-confirmed relapsed or refractory B-cell lineage NHL who have failed or are intolerant to established therapy, or for whom no other treatment options are available, in the opinion of the Investigator.

Refractory or relapsed B-cell NHL (per WHO Classification system; Swerdlow, 2008) defined as:

- Diffuse large B-cell lymphoma (DLBCL),
- Follicular lymphoma (FL),
- Chronic lymphocytic leukemia (CLL),
- Mantle cell lymphoma (MCL),
- Marginal Zone B-cell Lymphoma (MZBCL),
- Burkitt's lymphoma (BL),
- Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia [WM]).

Part 2:

Eligible histologic sub-types to be investigated in part 2 of the study will be determined by the DESC based on evolving efficacy and safety information from Part 1. Patients enrolled in part 2 of the study will have failed or are intolerant to established therapy, or have no other treatment options are available, in the opinion of the Investigator.

2. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block. An FFPE block from a current biopsy is preferred; however, archival tissue taken at initial diagnosis or 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 (Section 6.4).
3. Measurable disease, as defined by the 2014 Lugano Classification (Appendix 12.2).
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2.
5. Absolute neutrophil count (ANC) ≥1000/µL.
6. Platelet count of ≥75000/µL.
7. Hemoglobin ≥9.0 g/dL without transfusion within the 2 weeks prior to Day 1.
8. Serum/plasma creatinine ≤1.5 mg/dL. If the patient has a creatinine > 1.5mg/dL, a measured creatinine clearance must be >60mL/min as calculated by the Cockcroft and Gault equation (Cockcroft and Gault 1976).
9. Serum/plasma alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤2 times the upper limit of normal (ULN); ≤ 5 times ULN if there is liver or bone involvement.
10. Total serum/plasma bilirubin ≤1.5 times ULN (patients with known Gilbert's syndrome may have a total bilirubin up to ≤3 times ULN).
11. Negative blood or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test within 7 days prior to Day 1 for women of childbearing potential.
12. 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-402. 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-402.

    * Women of childbearing potential are defined as sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

    ** Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective forms of birth control include: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the

preferred and usual lifestyle of the patient. 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.

3.3.2 Exclusion Criteria

1. Patients who, in the opinion of the Investigator, have any option for other treatment for B-cell NHL at the current state of disease.
2. Active graft-versus-host disease.
3. Autologous or allogenic transplant within the 60 days prior to the Screening visit.
4. Known history of immunogenicity or hypersensitivity to a CD19 antibody.
5. Evidence of myelodysplasia or myeloid leukemia by morphology, immunostains, flow cytometry, or cytogenetics on a bone marrow aspirate or biopsy.
6. Known history of positive serum human ADA.
7. Active autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]); motor neuropathy considered of autoimmune origin (e.g., Guillain-Barré syndrome and myasthenia gravis); other CNS autoimmune disease (e.g., poliomyelitis, multiple sclerosis). Known seropositive for human immunodeficiency (HIV) virus, 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. Testing for HCV should be considered if the patient is at risk for having undiagnosed HCV (e.g., history of injection drug use).
8. History of Steven's Johnson's syndrome or toxic epidermal necrolysis syndrome.
9. Pregnant or breastfeeding women.
10. Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure greater than 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.
11. Use of any other experimental medication(s) within 14 days or 5 half-lives but in no case less than 14 days prior to start of study treatment on Cycle 1, Day 1.
12. Steroid use equivalent to greater than 20 mg of prednisone within 4 weeks (28 days) prior to Day 1, except for the use of short course systemic corticosteroids (≤ 7 days), with a wash-out period of 1 week prior to start of study treatment on Day 1.

13. Major surgery, chemotherapy, systemic therapy (excluding steroids; and any targeted small molecules or biologics),), radiotherapy, within 14 days or 5 half-lives (whichever is shorter) prior to Cycle 1, Day 1 treatment, except if approved by the Sponsor.

14. Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE] Grade 0 or Grade 1) from acute non hematologic toxicity (except all grades alopecia or grade 2 or lower neuropathy), due to previous therapy, prior to Screening.

15. Congenital long QT syndrome, or a corrected QTc interval of ≥450 ms, at the Screening visit (unless secondary to pacemaker or bundle branch block).

16. 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 the Sponsor's medical monitor and Investigator agree and document should not be exclusionary.

17. 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.

4 Study Procedures

4.1 Procedures by Study Day

The following procedures will be performed during the study. Timings for sample collections and procedures are provided in Appendix 12.1.

4.1.1 Screening Period (Day –28 to –1)

The following procedures will be performed within 28 days prior to the Day 1 visit of Cycle 1, unless otherwise specified:

- A 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.
- Demographic characteristics.
- Medical history (to include a complete history of all surgeries and significant diagnoses and all cancer treatment [including surgery, radiation therapy, chemotherapy, etc.]).
- Blood or urine β-HCG pregnancy testing (women of childbearing potential only).
- Physical examination including whole body skin assessment. The whole body skin assessment does not have to be performed by a dermatologist. However, any unexplained lesion is to be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted.
- Vital signs (arterial blood pressure, heart rate, respiratory rate, body temperature), height and weight measurements.
- ECOG performance status.

- Disease assessment: 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 18F-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, and urinalysis parameters.
- 12-lead electrocardiogram (ECG).
- Collection of adverse event (AE) information.
- Collection of information on medications used (including prescription or over-the-counter medication, herbal or naturopathic products) within the 14 days prior to the Day 1 visit.

4.1.2 Day 1 of Each Cycle

The following procedures will be performed prior to ADCT-402 infusion (unless otherwise indicated) at each cycle, unless otherwise specified.

- Blood or urine β-HCG pregnancy test required if the pregnancy test was obtained >7 days prior to Day 1 (every other cycle).
- Physical examination including whole body skin assessment, unless an assessment was performed within 3 days prior to Day 1.
- Vital signs: On Day 1 of Cycles 1 and 2, vital signs are to be measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of infusion. If no clinically significant changes occur during Cycles 1 and 2, vital sign measurements are to be obtained prior to infusion start and end of infusion for all subsequent infusions. If clinically significant changes in vital signs are observed at Cycle 1 and/or 2 infusion, that patient will be required to have vital signs measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of the ADCT-402 infusion for all subsequent cycles.
- Weight.
- ECOG performance status.
- Samples for hematology, coagulation panel, biochemistry parameters, will be measured prior to dosing unless the last sample was collected:
  - <24 hours before the start of ADCT-402 infusion on Day 1 of Cycle 1, or
  - <72 hours before the start of ADCT-402 infusion on Day 1 of Cycle 2 and subsequent cycles.

- Sample collection for additional renal function studies.
- Sample collection for urinalysis

  Prior to dosing unless the last sample was collected:
  - <24 hours before the start of ADCT-402 infusion on Day 1 of Cycle 1, or
  - <72 hours before the start of ADCT-402 infusion on Day 1 of Cycle 2 and subsequent cycles.
- Disease assessment:

  Patients Initially Treated Every 3 weeks

  - To be conducted 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.
  - Patients who initially follow a three-week dose schedule and then transition to a six-week schedule following Cycle 2 should have disease assessments ~6 weeks after Cycle 1 Day 1, and ~12 weeks after Cycle 1 Day 1, and thereafter at least every 12 weeks.

  Patients Initially Treated Every 6 weeks

  - For patients who have reduced dosing frequency and are following a 6 week schedule, disease assessments should occur approximately 6 weeks and 12 weeks after Cycle 1 Day 1, and thereafter at least every 12 weeks. It is understood that there will be a ± 6 day window for restaging of these patients.
  - For patients in Part 2: Treatment continuation will require independent verification of the local response assessment unless otherwise approved by the sponsor.

  In case of dose delays, please refer to Section 6.1 for the frequency of disease assessments.

  The same methods used at Screening which identify sites of disease should be used uniformly for all subsequent assessments. If PET-CT is positive, subsequent diagnostic CT and MRI are not needed unless clinically indicated.

  If PET-CT examination is negative at Screening, subsequent PET-CT is not required.
- 12-lead ECG (Cycles 1 and 2) before the start of the ADCT-402 infusion, within 30 minutes of the end of infusion, and at 3 hours (± 30 minutes) and 24 (± 2.4) hours after the end of infusion. For Cycle 3 and subsequent cycles, a 12-lead ECG is to be performed before the start of ADCT-402 infusion.
- Sample collection for central laboratory analysis of ADA (all cycles).
- Sample collection (Cycles 1 and 2) for central laboratory analysis of PK parameters before the start of the ADCT-402 infusion, at the end of the infusion, and at 1, 3, and 6 hours after the end of the ADCT-402 infusion. For Cycle 3 and subsequent cycles, samples will be collected before the start of the ADCT-402 infusion and at the end of the infusion.

[redacted]

- Collection of AE information.
- Collection of concomitant medication information.
- Premedication administration, if applicable (Section 5.2).
- ADCT-402 administration.

4.1.3 Day 2 (Cycles 1 and 2)

The following procedures will be performed 24 hours (± 10%) after the end of the ADCT-402 infusion:

- 12-lead ECG.
- Vital signs
- Sample collection for central laboratory analysis of PK parameters.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.4 Day 3 (Cycles 1 and 2)

The following procedures will be performed 48 hours (± 10%) after the end of the ADCT-402 infusion:

- Vital signs.
- Sample collection for central laboratory analysis of PK parameters.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.5 Day 5 (Cycles 1 and 2)

The following procedures will be performed 96 hours (± 1 day) after the end of the ADCT-402 infusion:

- Sample collection for central laboratory analysis of PK parameters.
- Vital signs.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.6 Day 8 (± 2 days) of Each Cycle

- Physical examination (Cycles 1 and 2) including whole body skin assessment.

- Weight
- Vital signs.
- Hematology and biochemistry parameters.
- Urinalysis and sample collection for additional renal function studies.
- Sample collection for central laboratory analysis of PK parameters (Cycles 1-4).
- Collection of AE information.
- Collection of concomitant medication information.

4.1.7 Day 15 (± 2 days) of Cycles 1 and 2

The Day 15 visit will be conducted during Cycles 1 and 2 only; the following procedures will be performed at this visit:

- Physical examination including whole body skin assessment.
- Weight.
- Vital signs.
- Hematology and biochemistry parameters.
- Urinalysis and sample collection for additional renal function studies.
- Sample collection for central laboratory analysis of PK parameters.
- Collection of AE information.
- Collection of concomitant medication information.

4.1.8 Day 28 (± 3 days)

For patients who have transitioned to a reduced dosing frequency (see Section 3.1) this visit will be required for Safety/PK Monitoring. Assessments required for Safety/PK Monitoring are indicated below. For patients in Part 1 this visit will be done approximately 21 days after infusion.

- Physical examination
- Vital signs
- Weight
- ECOG
- 12-lead ECG
- Sample collection for hematology, coagulation panel, and biochemistry parameters
- Sample collection for urinalysis

- Sample collection for additional renal function studies.
- Sample collection for central laboratory analysis of PK parameters and ADA.
- Collection of AE information
- Collection of concomitant medication information

4.1.9 End of Treatment Visit

The following procedures will be performed within 30 days after study treatment discontinuation and prior to initiation of new anticancer treatment:

- Physical examination including whole body skin assessment.
- Weight and vital signs.
- ECOG performance status.
- 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.
- Blood or urine pregnancy test
- Hematology, coagulation panel, and biochemistry parameters.
- Urinalysis and sample collection for additional renal function studies.
- 12-lead ECG.
- Sample collection for central laboratory analysis of PK parameters and ADA.
- [redacted]
- Collection of AE information
- Collection of concomitant medication information.

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

4.1.10 12-week Follow-up Visit

Each patient will have a blood sample taken for assessment of PK and ADA at 12 (±1) weeks after their last dose of ADCT-402, unless a new anticancer treatment has been initiated.

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

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 6.3.2.2).

4.1.11 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 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.

4.2 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.

4.2.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study 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 with ADCT-402 for any of the following reasons:

- Disease 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).
- Following a dose delay due to toxicity, if the same toxicity recurs after second dose reduction, study drug must be discontinued permanently.
- Non-compliance, including lost to follow-up.
- Pregnancy.
- Other (e.g., development of contraindications with use of the study drug).
- The Investigator determines that it is in the best interest of the patient to discontinue the patient's participation in the study.
- Discontinuation of the study by the Sponsor.

- Death.

Patients experiencing other significant toxicities must be immediately and permanently withdrawn from treatment with ADCT-402 as follows:

- Any patient who experiences a Grade 3 or higher hypersensitivity (Appendix 12.3) reaction, regardless of premedication, during any cycle of treatment.
- 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).

4.2.2 Handling of Withdrawals

The Investigator will confer with the Sponsor if a patient experiences a serious or intolerable AE. If a patient discontinues from the study because of an AE, the patient will be 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 (Section 6.3.2.6).

For each patient who discontinues study treatment and withdraws from the study, the Investigator will record the reason(s) for discontinuation on the relevant page of the electronic case report form (eCRF). Whenever possible, each patient who discontinues study treatment will undergo an EOT visit and all EOT assessments (Section 4.1.9). Patients who fail to return for final assessments are to be contacted by the investigative site. Following a minimum of 2 documented unsuccessful telephone calls, the investigative site will send a registered letter to the patient in a final attempt to ensure protocol compliance.

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

4.2.3 Patient Replacements

Any patient in Part 1 who discontinues before completion of the first treatment cycle, for any reason other than a DLT, is to be replaced.

5 Study Treatments

5.1 Method of Assigning Patients to Treatment Groups

In Part 1 (dose escalation), patients will receive an IV infusion of ADCT-402 on Day 1 of each 3-week (21-day) cycle. The first patient receiving the first dose of ADCT-402 in the study must be observed for 7 days for occurrence of AEs prior to treating a second patient. The dose escalation procedure is described in Section 3.2. If the highest allowed dose (300 µg/kg) is reached and the MTD is not identified, no further dose escalation will be allowed, pending a safety analysis and an amendment to the protocol.

In Part 2 (expansion), patients will be assigned to the recommended dose level(s) and schedule(s) of ADCT-402 identified in Part 1 by the DESC. Once the recommended Part 2 dose(s) and schedule(s) is/are determined, patients receiving lower or higher dose levels of ADCT-402 may be offered continued treatment at the recommended dose(s) and schedule(s).

5.2 Prophylactic Treatments for Hypersensitivity

If 1 patient experiences a Grade 2 or higher (Appendix 12.3) infusion-related hypersensitivity reaction at any time during Part 1 (dose escalation), all subsequent patients must receive prophylactic treatment, as described below or as per the institution's standard of care, to reduce the risk of hypersensitivity reactions.

- On Day 1 of each cycle, patients will be instructed to take 20 mg orally of dexamethasone at 12 and 6 hours before the start of ADCT-402 infusion. When necessary, 12 and 6 hours before the first infusion may be defined as "immediately before sleeping" and "immediately after waking up".
- On Day 1 of each cycle, patients will be given 50 mg IV of diphenhydramine hydrochloride at 30 minutes before the start of ADCT-402 infusion.
- On Day 1 of each cycle, patients will be given 50 mg of ranitidine (or equivalent) IV at 30 minutes before the start of ADCT-402 infusion.
- For 2 days following administration of ADCT-402 on Day 1, all patients are to take dexamethasone 4 mg orally, twice per day.

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 patient experiences a Grade 1 or 2 hypersensitivity reaction (Appendix 12.3), the following medications (or equivalent) should be administered for 48 hours after ADCT-402 infusion:

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

Any patient who experiences a Grade 3 or higher hypersensitivity (Appendix 12.3) reaction should be discontinued from the study and immediately treated according to institutional

standard of care and determined by the treating investigator. These patients must be carefully observed after the treatment. Additional therapy, as per the institution's standard of care, should also be followed.

5.3 Treatments Administered

In Part 1 (dose escalation), each patient will be assigned a dose level and schedule as described in Section 3.1 and Section 3.2. In Part 2 (expansion), all patients will be assigned to the recommended dose level(s) and schedule(s) of ADCT-402 identified in Part 1 by the DESC.

ADCT-402 will be administered on Day 1 of each cycle as a 1-hour IV infusion. If ADCT-402 is well tolerated after the first cycle, the infusion duration may be shortened to 30 minutes for subsequent cycles, on an individual patient basis, at the Investigator's discretion. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

Prophylactic antiemetic medications, electrolyte supplementation, and other standard supportive care measures may also be administered according to standard treatment center protocols, or as in Section 5.2 and Section 5.9.2.

Although the study patient population has a low risk for development of tumor lysis syndrome (TLS) compared to patients with acute disease (Cairo, 2010), patients should be observed for development of TLS and treated according to standard treatment center protocols.

Because of non-clinical observations related to nephropathy, adequate patient hydration (e.g., 8 to 10 glasses of water or equivalent per day) is recommended for patients receiving ADCT-402.

Additionally, because new or worsening edema and / or new or worsening pleural effusion have been observed, patients are advised to monitor their weight on a daily basis (Section 6.3.8 and 5.9.2)

As non-clinical testing indicates testicular toxicity (atrophy with reduced spermatogenesis), male patients are advised to consider cryopreservation of sperm prior to treatment with ADCT-402, where applicable.

Available pre-clinical data on ADCT-402 does not suggest a photosensitivity concern, based on the lack of any signals in the rat and monkey toxicology studies with ADCT-40 [redacted]

However, skin rash has been reported in the ADTC 402-101 study, as well as with another investigational agent containing the same pyrollobenzodiazepine warhead (Rudin, 2016). 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.

5.4 Dose Delays and Modifications

The Investigator may suspend ADCT-402 dosing for up to 21 days for any patient who experiences a protocol-defined DLT after Cycle 1 (the defined DLT observation period). At the discretion of the Investigator, the dose may also be delayed for up to 21 days for any toxicity that does not meet DLT criteria. Resumption of dosing with ADCT-402 after suspension is at the discretion of the Investigator, based on assessment of the patient's clinical condition and whether or not the patient is deriving potential clinical benefit from treatment with ADCT-402. Following recovery to Grade 1 or to baseline grade, treatment with ADCT-402 may resume at the Investigator's discretion.

Patients who resume treatment following a dose delay may, at the discretion of the DESC, have their dose of study drug reduced by 50%. If toxicity occurs again at the reduced dose, the patient will be discontinued from the study.

During part 2, dose delay due to toxicity may extend beyond 21 days 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-402. When dosing is resumed, the dose may be decreased by 50% at the discretion of the Investigator, in consultation with the Sponsor.

If the dose is reduced and the toxicity recurs, the dose will be further reduced by 50%.

If toxicity recurs after second dose reduction, study drug must be discontinued permanently.

If dose is held for six weeks or more, restaging scans must be done prior to restarting dosing to rule out disease progression.

5.5 Identity of Investigational Product

ADC Therapeutics will provide and distribute adequate supplies of ADCT-402 to the study sites. The following drug supplies will be used in the study:

Product	Supplied As:
ADCT-402	10-mL single-use glass vial with overfill to allow for up to 3.2 mL to deliver a total of 16 mg per vial (overfill deliverable volume 3.5 mL at 5 mg/mL). (equivalent to 16 mg ADCT-402)

5.5.1 ADCT-402 Drug Product

ADCT-402 is a sterile formulation containing PBD-conjugated RB4v1.2 (DAR ≥1), RB4v1.2 (DAR = 0), and SG3249. It is provided pre-formulated in 10-mL glass vials containing approximately 16 mg ADCT-402 per vial (deliverable volume 3.2 mL at 5 mg/mL).

5.6 Management of Clinical Supplies

5.6.1 Study Drug Packaging and Storage

ADCT-402 will be supplied in a labeled 10-mL stoppered glass vial shipped 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-402 should be protected from light and stored frozen (–65°C or below). ADCT-402 should be thawed under ambient conditions.

5.6.2 Study Drug Preparation and Administration

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-402 will be removed from the vial with a syringe and diluted into a 50 mL IV bag containing 5% dextrose in water (D5W)/Glucose. The amount of the product to be diluted will depend on the dose level and the body mass of the patient. Once the ADCT-402 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.

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

5.6.3 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.

5.7 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 the effects of overdose are and whether they can be reversed. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

5.8 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.

5.9 Concomitant Treatment

All medications used within 14 days prior to Day 1 and during the treatment period are recorded in the eCRF. 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.

5.9.1 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 corticosteroids (prednisone ≥12.5 mg/day or dexamethasone ≥2 mg/day, excluding inhaled steroids).
- Live vaccines.

5.9.2 Permitted During Study

After confirmation and documentation of eligibility, supportive care treatments (transfusions, etc.) can be prescribed as medically appropriate.

Hematopoietic growth factors are permitted as per American Society of Clinical Oncology guidelines (Smith, 2006); however, prophylactic use of growth factors is not allowed during the first treatment cycle.

If a Grade 2 or higher infusion-related hypersensitivity (Appendix 12.3) reaction is observed in 1 patient at any time during Part 1 of the study, all subsequent patients must receive prophylactic treatment (Section 5.2).

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)

During Part 1, the DESC agreed to evaluate the potential for the addition of dexamethasone to mitigate toxicity. The recommendation was communicated (February 2017) as follows:

Dexamethasone 8 mg PO BID

- Day -1 (day prior to dosing) [if possible]
- Day 1 (day of dosing, pre-dose)
- Day 2 (day after dosing)

It is further recommended that patients in Part 2 have receive dexamethasone as follows:

- Dexamethasone 4 mg PO BID the day before IP administration (if possible), the day of IP administration (given at least 2 hours prior to IP administration, if not given the day before),

and the day after IP administration (Week 1/Day 1 of each cycle only, regardless of treatment schedule).

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 may 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 Study Assessments and Procedures

Patients will undergo the procedures at the time points specified in schedule of events (Appendix 12.1).

6.1 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.

Patients Initially Treated Every 3 weeks

- To be conducted 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.

Patients who initially follow a three week dose schedule and then transition to a six week schedule following cycle 2 should have disease assessments ~6 weeks after Cycle 1 Day 1, ~12 weeks after Cycle 1 Day 1, and thereafter at least every 12 weeks.

Patients Initially Treated Every 6 weeks

- For patients who have reduced dosing frequency and are following a 6 week schedule, disease assessments should occur approximately 6 weeks and 12 weeks after Cycle 1 Day 1, and thereafter at least every 12 weeks. It is understood that there will be a ± 6 day window for restaging of these patients.

For patients in Part 2: Treatment continuation will require independent verification of the local response assessment unless otherwise approved by the sponsor.

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-402 dosing (only if the interval from last scan is ≥ 6/9/12 weeks, as applicable) to rule out disease progression.

The patient's response to treatment will be determined by the Investigator as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), based on the 2014 Lugano Classification Criteria (Appendix 12.2). Images will be obtained according to local site imaging requirements and may be required to be submitted for a central/independent review. Submission instructions for the central/independent review will be provided in a separate manual.

6.2 Pharmacokinetic and Pharmacodynamic Assessments

Blood (5-mL draw) samples will be collected for assessment and will be processed according to the instructions provided by the bioanalytical laboratory to the study sites. All PK and

pharmacodynamic assessments will be conducted using measures from validated bioanalytical methods. Timing and timing windows for sample collection are shown in Appendix 12.1.

6.2.1 Pharmacokinetic Assessments

The PK profile of ADCT-402 (total antibody; DAR ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead SG3199 will be assessed by a central laboratory. Additional PK blood samples will be collected, at the discretion of the Investigator, during any visit where toxicity is observed. A PK and ADA sample will also be collected concurrently with any other blood draw to assess safety (e.g., Unscheduled Visit), if possible. All PK samples will be evaluable as long as actual collection times are recorded.

To understand the metabolic disposition of ADCT-402 in humans, samples remaining after PK analysis is complete may be pooled among patients for potential metabolite identification.

The PK profile will include determination of: maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$), area under the concentration-time curve (AUC) 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 (λ_z), terminal half-life ($T_{1/2}$), clearance (CL), and volume of distribution (V_z).

6.2.2 Pharmacodynamic and Other Assessments

The following pharmacodynamic/exploratory assessments will be performed at varying timepoints in the study:

[redacted]

- Level of ADAs against ADCT-402 in serum.

[redacted]

6.3 Safety and Tolerability Assessments

Safety will be assessed based on AEs, SAEs, periodic 12-lead ECG recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, coagulation panel, biochemistry, pregnancy testing (for women of child-bearing potential) and urinalysis test results. Adverse events will be graded according to CTCAE version 4.0. A schedule of safety assessments is provided in Appendix 12.1.

6.3.1 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:
  - 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.
- 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 AE (including nausea, vomiting, diarrhea, and electrolyte imbalances lasting more than 48 hours despite optimal therapy; excluding all grade ofalopecia).
  - Grade 3 or higher hypersensitivity (Appendix 12.3) reaction (regardless of premedication).
  - Grade 2 or higher skin ulceration.

The DLT period for dose escalation will be 1 cycle.

6.3.1.1 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.
- Determine dose levels to be administered and the MTD based on assessment of safety findings and determination of DLTs.
- 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.

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

6.3.2 Adverse Events

6.3.2.1 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 ICF signature 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, are life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, the event may jeopardize the patient or may require medical or surgical intervention to prevent any 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.

6.3.2.2 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 more than 84 days after the last dose of study drug do not need to be reported unless the Investigator considers them related to study drug.

At every study visit, patients will be asked a standard nonleading 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.

6.3.2.3 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.

Any AE that meets SAE criteria (Section 6.3.2.1) 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]

6.3.2.4 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 shown in Table 2.

Table 2. Definition of Severity Grades for Common Terminology Criteria for Adverse Events (CTCAE)

Grade	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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.

6.3.2.5 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).

6.3.2.6 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.

6.3.3 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 6.3.2.3, 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 that is brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study treatment must be promptly reported (Section 6.3.2.3).

6.3.4 Clinical Laboratory Analyses

Samples will be collected at the time points specified in Appendix 12.1.

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

6.3.4.1 Hematology

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

6.3.4.2 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. Biochemistry will also include creatinine clearance (Cockcroft and Gault, 1976) on Day 1 of each cycle.

6.3.4.3 Urinalysis

Urinalysis includes pH, specific gravity, protein, glucose, bilirubin, nitrites and occult blood. The urinalysis may be performed by dipstick.

6.3.4.4 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 laboratory manual).

6.3.5 Electrocardiograms

A 12-lead electrocardiogram is to be performed at the time points shown in Appendix 12.1.

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.

During Part 1, measurement of the QTc interval may be obtained according to the formula used by the institution, however, the Fridericia formula is preferred (Fridericia, 1920). During Part 2, the Fridericia formula should be used for all patients.

The same formula used to confirm eligibility must be applied within a patient for the duration of the study.

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

6.3.7 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.

6.3.8 Weight

If possible, patients are advised to monitor their weight daily starting cyle 1 day 1 and inform their investigator if their weight increases more than 1 kg (2.2 pounds) from Cycle 1 Day 1.

6.3.9 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 12.1) using the ECOG performance status grades (Table 3; Oken, 1982).

Table 3. Definition of Eastern Cooperative Oncology Group (ECOG) Performance Status Grades

Grade	Definition
0	Fully active, able to carry on all predisease 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

As per Oken, 1982.

6.4 Sample Handling, Storage and Shipment

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

For the tissue sample provided at screening, blocks and slides should be packed in ice or cold packs prior to priority overnight shipping. If available, a copy of the original pathology report containing the histopathological diagnosis should accompany each specimen. Refer to the Laboratory Manual for further information. Desired specimen characteristics are:

- Tissues fixed in neutral buffered formalin (NBF);
- Blocks preferable to slides;
- If slides are supplied, sections must be:
  - Mounted on positively charged slides of the correct type,
  - Transferred to the slide in a water bath (not by tape),
  - Not have been baked,
  - Not be paraffin coated (the slide containing the mounted specimen should not have been dipped in paraffin),
  - Stored at 4°C in an airtight container prior to shipment.

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

For PK and ADA, 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 should be clearly labeled with the following information: study number, study center number, patient number, tube identification, and the scheduled sampling time 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. Samples may be retained at the central laboratory for up to 5 years after the end of the study, and may be used for additional analyses. Samples will not be destroyed until 5 years after the end of the study, or unless a specific authorization is given by ADC Therapeutics.

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

[redacted]

Each sample tube should be clearly labeled with the following information: Study number, study center number, patient number, tube identification, and the scheduled sampling time by day (and hour, when necessary).

7 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).

7.1 Safety Endpoints

Safety will be assessed based on AEs, SAEs, treatment discontinuations due to AEs, DLTs, periodic 12-lead ECG recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, coagulation panel, biochemistry, and urinalysis test results.

7.2 Primary Endpoints

7.2.1 Primary Endpoints

- Assessment of DLTs (Section 6.3.1) and determination of the MTD (Section 3.2) for ADCT-402 during Part 1.
- Determination of the recommended dose of ADCT-402 for Part 2 by the DESC.
- Assessment of safety parameters for Part 1 and Part 2 (Section 6.3).

7.2.2 Secondary Endpoints

- Determination of DOR, ORR, OS, and PFS (Section 7.6.2).
- Determination of PK parameters (Section 7.6.3) for ADCT-402 (total antibody; DAR ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead SG3199.
- Measurement of ADAs to ADCT-402 before, during, and after treatment with ADCT-402 (Section 7.6.3).

7.3 Sample Size Calculations

This is a Phase 1 study with a maximum total sample size of 200 patients. It is expected that Part 1 will enroll up to 90 patients and Part 2 will enroll up to 110 patients.

Patients will be enrolled in Part 2 of the study in cohorts of approximately 10 to 20.

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.

7.4 Analysis Sets

Five analysis sets will be used in this study:

- The Safety analysis set will consist of all patients who receive study drug
- The DLT-evaluable analysis set will consist of all patients in Part 1 who receive study drug and excludes patients who discontinue study drug during Cycle 1 without experiencing a DLT.
- The Efficacy analysis set will consist of all patients with valid baseline data who receive 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.
- The PK analysis set will consist of all patients who receive study drug and have sufficient concentration data for PK analysis.
- The Pharmacodynamic analysis set will consist of all patients who receive study drug and have sufficient concentration data for analysis.

[redacted]

7.5 Description of Subgroups to be Analyzed

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

7.6 Statistical Analysis Methodology

7.6.1 Safety Analyses

7.6.1.1 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 + 84 days. 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.

7.6.1.2 Clinical Laboratory Results

Clinical hematology, coagulation panel, 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.

7.6.1.3 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.

7.6.2 Efficacy Analysis

7.6.2.1 Overall Response Rate

Overall response rate will be defined as the proportion of patients with a best overall response of CR or PR at the time each patient discontinues ADCT-402. Percentage of ORR with its 95% confidence interval (CI) will be presented.

7.6.2.2 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 (Appendix 12.2). For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. In addition, patients with disease progression or death after an extended loss to follow-up will be censored at the date of the last valid disease assessment prior to the extended loss to follow-up. The data will be analyzed by Kaplan-Meier method. The median duration of response and 95% CI will be presented. Further details will be outlined in the SAP.

7.6.2.3 Overall Survival

Overall survival will be defined as the time from the beginning of study drug 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. The data will be analyzed by Kaplan-Meier method. The median survival time and 95% CI will be presented. Further details will be outlined in the SAP.

7.6.2.4 Progression-Free Survival

Progression-free survival will be defined among the efficacy population (Section 7.4) 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 (Appendix 12.2). For patients whose disease has not progressed or who have not died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. In addition, patients with disease progression or who have died after an extended loss to follow-up by the investigative site will be censored at the date of the last disease assessment prior to the extended loss to follow-up. The data will be analyzed by Kaplan-Meier method. The median PFS time and 95% CI will be presented. Further details will be outlined in the SAP.

7.6.3 Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic endpoints for RB4v1.2, PBD-conjugated RB4v1.2, and free warhead SG31999 will be evaluated for all patients using noncompartmental analysis. Data for PK parameters will be summarized in tables and individual data will be listed.

[redacted]

7.6.4 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.

7.7 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.

7.7.1 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.

8 Ethics

8.1 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.

8.2 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.

8.3 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 [redacted]

9 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.

9.1 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.

9.2 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.

9.3 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 time line 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).

9.4 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.
- Curriculum vitae for the Investigator and each sub-Investigator listed on Form FDA 1572.
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. 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.

9.5 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.

9.6 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.

9.7 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.

9.8 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 Study Management

10.1 Monitoring

10.1.1 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.

10.1.2 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.

10.2 Management of Protocol Amendments and Deviations

10.2.1 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.

10.2.2 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.

10.3 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).

10.4 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 access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

11 Reference List

Adair JR, Howard PW, Hartley JA, Williams DG, and Chester KA (2012). Antibody-drug conjugates - a perfect synergy. *Expert Opin Biol Ther* 12(9):1191-1206.

Amgen, Thousand Oaks, California USA (2014). Prescribing information for blinatumomab (Blincyto™), Accessed on 21 May 2015 at http://pi.amgen.com/united_states/blincyto/blincyto_pi_hcp_english.pdf.

Anderson KC, Bates MP, Slaughenhoupt BL, Pinkus GS, Schlossman SF, and Nadler LM (1984). Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. *Blood* 63(June):1424-1433.

Ansell SM (2015). Non-hodgkin lymphoma: diagnosis and treatment. *Mayo Clin Proc* 90(8):1152-1163.

Blanc V, Bousseau A, Caron A, Carrez C, Lutz RJ, and Lambert JM (2011). SAR3419: an anti-CD19-maytansinoid immunoconjugate for the treatment of B-cell malignancies. *Clin Cancer Res* 17(20):6448-6458.

Cairo MS. Coiffier B, Reiter A, and Younes A, on behalf of the TLS Expert Panel (2010). Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haem* 149:578–586.

Carter RH and Barrington RA (2004). Signaling by the CD19/CD21 complex on B cells. *Curr Dir Autoimmun* 7:4–32.

Chao MP (2013). Treatment challenges in the management of relapsed or refractory non-Hodgkin's lymphoma – novel and emerging therapies. *Cancer Manag Res* 5: 251–269. Published online 2013 Aug 23. doi:10.2147/CMAR.S34273

Chen DR and Cohen PL (2012). Living life without B cells: is repeated B-cell depletion a safe and effective long-term treatment plan for rheumatoid arthritis? *Int J Clin Rheumtol* **7**(2):159-166.

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

Cockcroft DW and Gault MH, (1976). Prediction of creatinine clearance from serum creatinine. *Nephron* 16(1):31-41.

Cooper LJ, Al-Kadhimi Z, DiGiusto D, Kalos M, Colcher D, Raubitschek A, et al (2004). Development and application of CD19-specific T cells for adoptive immunotherapy of B cell malignancies. *Blood Cells Mol Dis* 33(1):83-89.

Evens AM, Winter JN, Gordon LI, Chiu BCH, Tsang R, and Rosen ST (2015). Non-hodgkin lymphoma. Accessed 2 Aug 2015 on Cancer Network at http://www.cancernetwork.com.

Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Act Med Scand 1920, 53:469–486. Translation published in 2003 in Annals Noninvasive Electrocardiology 8(4):343-351.

Gerber HP, Kung-Sutherland M, Stone I, Morris-Tilden C, Miyamoto J, McCormick R, et. al. (2009). Potent antitumor activity of the anti-CD19 auristatin antibody drug conjugate hBU12-vcMMAE against rituximab-sensitive and -resistant lymphomas. *Blood* 113(18):4352-4361.

Haas KM and Tedder TF (2005). Role of the CD19 and CD21/35 receptor complex in innate immunity, host defense and autoimmunity. *Adv Exp Med Biol* 560:125–139.

Hartley JA (2011a). The development of pyrrolobenzodiazepines as antitumour agents. *Expert Opin Investig Drugs* 20(6): 733-744.

Hartley JM, Spanswick VJ, and Hartley JA (2011b). Measurement of DNA damage in individual cells using the single cell gel electrophoresis (comet) assay. *Methods Mol Biol* 731:309-320.

Jabbour E, O'Brien S, Ravandi F, and Kantarjian H (2015). Monoclonal antibodies in acute lymphoblastic leukemia. *Blood* 125(26):4010-4015.

Kimby E (2005). Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 31(6):456-473.

Mounier N and Gisselbrecht C (2011). Stem cell transplantation for diffuse large B-cell lymphoma patients in the rituximab era. *Curr Opin Oncol* 23(2):209-213.

Muniz C, Martin-Martin L, Lopez A, Sanchez-Gonzalez B, Salar A, Almeida J, et. al. (2014). Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome. *Blood* 123(12): 1864-1869.

National Cancer Institute (2015). SEER Stat Fact Sheets: Non-Hodgkin Lymphoma. Accessed at http://seer.cancer.gov/statfacts/html/nhl.html.

The Non-Hodgkin's Lymphoma Classification Project (1997). A clinical evaluation of the international lymphoma study group classification of Non-Hodgkin's Lymphoma. *Blood* 89(11):3909-3918.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP (1982). Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 5(6):649-55.

Roguska MA, Pedersen JT, Henry AH, Searle SM, Roja CM, Avery B, et. al. (1996). A comparison of two murine monoclonal antibodies humanized by CDR-grafting and variable domain resurfacing. *Protein Eng* 9(10):895-904.

Rudin CM, Pietanza MC, Bauer TM, Spigel DR, Ready N, Morgansztern D, et al. Safety and efficacy of single-agent rovolpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC). J Clin Oncol 34 (2016) (suppl: abstr LBA8505).

Scheuermann RH and Racila E (1995). CD19 antigen in leukemia and lymphoma diagnosis and immunotherapy. *Leuk Lymphoma* 18(5-6):385-397.

Smith TJ (Chair), Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et. al. (2006). 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Onc* 24(19):3187-3286.

Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et. al. editors (2008). *WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues,* 4th ed., Lynon, France.

Tedder TF (2009). CD19: a promising B cell target for rheumatoid arthritis(2009). *Nat Rev Rheumatol* 5:572–577; doi:10.1038/nrrheum.2009.184.

Wang K, Wei G, and Liu D (2012). CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. *Exp Hematol Oncol* 1(1):36.

Wu J, Clingen PH, Spanswick VJ, Melinas-Gomez M, Meyer T, Puzanov I, et. al. (2012). g-H2AX foci formation as a pharmacodynamic marker of DNA damage produced by DNA cross-linking agents: results from 2 phase I clinical trials of SJG-136 (SG2000). *Clinl Can Res*, published online December 18, 2012; DOI: 10.1158/1078-0432.CCR-12-2529.

12 Appendices

12.1 Appendix: Schedule of Events

Timings for study procedures are shown in Section 12.1.1 of this Appendix. Timings for sample collections for assessments of ECG, PK, PD, and exploratory parameters are shown in Section 12.1.2 of this Appendix.

12.1.1 Schedule of Study Procedures

Procedure	Screen	Cycle 1						Cycle 2					
	Day –28 to –1	Day 1	Day 2[1]	Days 3 and 5[2]	Day 8 (±2 days)	Day 15 (±2 days)	Day 28[3] (± 2 days)	Day 1 (±3 days)	Day 2[1]	Days 3 and 5[2]	Day 8 (±2 days)	Day 15 (±2 days)	Day 28[3]4[3] (±2 days)
Informed consent	X												
Demography	X												
Medical history[4]	X												
Blood or urine β-HCG	X	X[5]											
Physical examination[6]	X	X			X	X	X	X			X	X	X
Vital signs[7]	X	X[8]	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Weight	X	X			X	X	X	X			X	X	X
ECOG performance status	X	X					X	X					X
[redacted]	[redacted]												
Disease assessment[10]	X[11]							X					
Hematology[12]	X	X[13]			X	X	X	X[13]			X	X	X
Coagulation Panel[14]	X	X[13]					X	X[13]					X
Biochemistry[15]	X	X[13]			X	X	X	X[13]			X	X	X
Urinalysis [16]	X	X[13]			X	X	X	X[13]			X	X	X
Additional renal function studies[17]		X			X	X	X	X			X	X	X
12-lead ECG[18]	X	X	X				X	X	X				X
Sample for PK assessments[19]		X	X	X	X	X	X	X	X	X	X	X	X
Sample for ADA assessment[19]		X					X	X					X
[redacted]		[redacted]						[redacted]					
Concomitant medications[21]	X	X	X	X	X	X	X	X			X	X	X
Premedication[22]		X						X					
ADCT-402 administration[23]		X						X					
Adverse events[24]	X	X	X	X	X	X	X	X			X	X	X
Survival information													
New anticancer treatment information													

Procedure	Cycles 3 until Progression/ Discontinuation			EOT	12-Week Follow-up Visit[26]	Long-term Follow-up
	Day 1 (±3 days)	Day 8[27] (±2 days)	Day 28[3] (±3 days)	Within 30 days[25]		
Informed consent						
Demography						
Medical history[4]						
Blood or urine β-HCG[5]	X			X		
Physical examination[6]	X			X		
Vital signs[7]	X[8]	X	X	X		
Height						
Weight	X	X	X	X		
ECOG performance status	X		X	X		
Tumor tissue collection						
Disease assessment	X			X		X
Hematology[12]	X	X	X	X		
Coagulation Panel[14]	X		X	X		
Biochemistry[15]	X	X	X	X		
Urinalysis[16]	X	X	X	X		
Additional renal function studies[17]	X	X	X	X		
12-lead ECG[18]	X		X	X		
Sample for PK assessments[19]	X	X[28]	X	X	X[29]	
Sample for ADA assessment	X		X	X	X[29]	
[redacted]				[redacted]		
Concomitant medications[21]	X	X	X	X		
Premedication[22]	X					
ADCT-402 administration[23]	X					
Adverse events	X	X	X	X[24]		
Survival information					X	X
New anticancer treatment information					X	X

Abbreviations: ADA, anti-drug antibody; [redacted]; ECG, electrocardiogram; EOI, end of ADCT-402 infusion; EOT, end of treatment; ECOG, Eastern Cooperative Oncology Group; HCG, human chorionic gonadotropin; PK, pharmacokinetics; [redacted]

Day 2 to occur 24 hours (±10%) after EOI.

Day 3 to occur 48 (±10%) hours after EOI. Day 5 to occur 96 hours (±1 day) after EOI.

For patients who have transitioned to a reduced dosing frequency based on response (see Section 3.1) this visit will be required for Safety/PK Monitoring. For patients in Part 1, this visit will be done approximately 21 days after infusion.

Medical history to include a complete history of all surgeries, significant diagnoses, and all cancer treatments.

Blood or urine pregnancy test for women of childbearing potential. Not to be repeated at Cycle 1 Day 1 if negative screening β-HCG pregnancy test was obtained within 7 days prior to Cycle 1, Day 1. Pregnancy test Day 1 (every 6 weeks) and at EOT.

Physical examination to include whole body skin assessment. Whole body skin assessment does not have to be performed by a dermatologist. Any unexplained lesion is to be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted. Does not have to be done on Cycle 1, Day 1 if last performed within 3 days prior to dosing with ADCT-402.

Vital signs to include arterial blood pressure, heart rate, respiratory rate, and body temperature. Vital signs window is ±15 minutes.

Vital signs**:** On Day 1 of Cycles 1 and 2, vital signs are to be measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of infusion. If no clinically significant changes occur during Cycles 1 and 2, vital sign measurements are to be obtained prior to infusion start and end of infusion for all subsequent infusions. If clinically significant changes in vital signs are observed at Cycle 1 and/or 2 infusion, that patient will be required to have vital signs measured before the start of the ADCT-402 infusion, every 30 minutes during the infusion, at the end of infusion, and at 1, 3, and 6 hours after the end of the ADCT-402 infusion for all subsequent cycles.

[redacted]

Modification to a patient's treatment schedule will be based on an independent review of images unless otherwise approved by the sponsor. Therefore, the decision to delay treatment and/or reduce dose based on response will require independent verification of the local response assessment (see Section 6.1). Refer to Sections 4.1.2 and 6.1 for timing of tumor assessments for patients who have reduced dosing frequency.

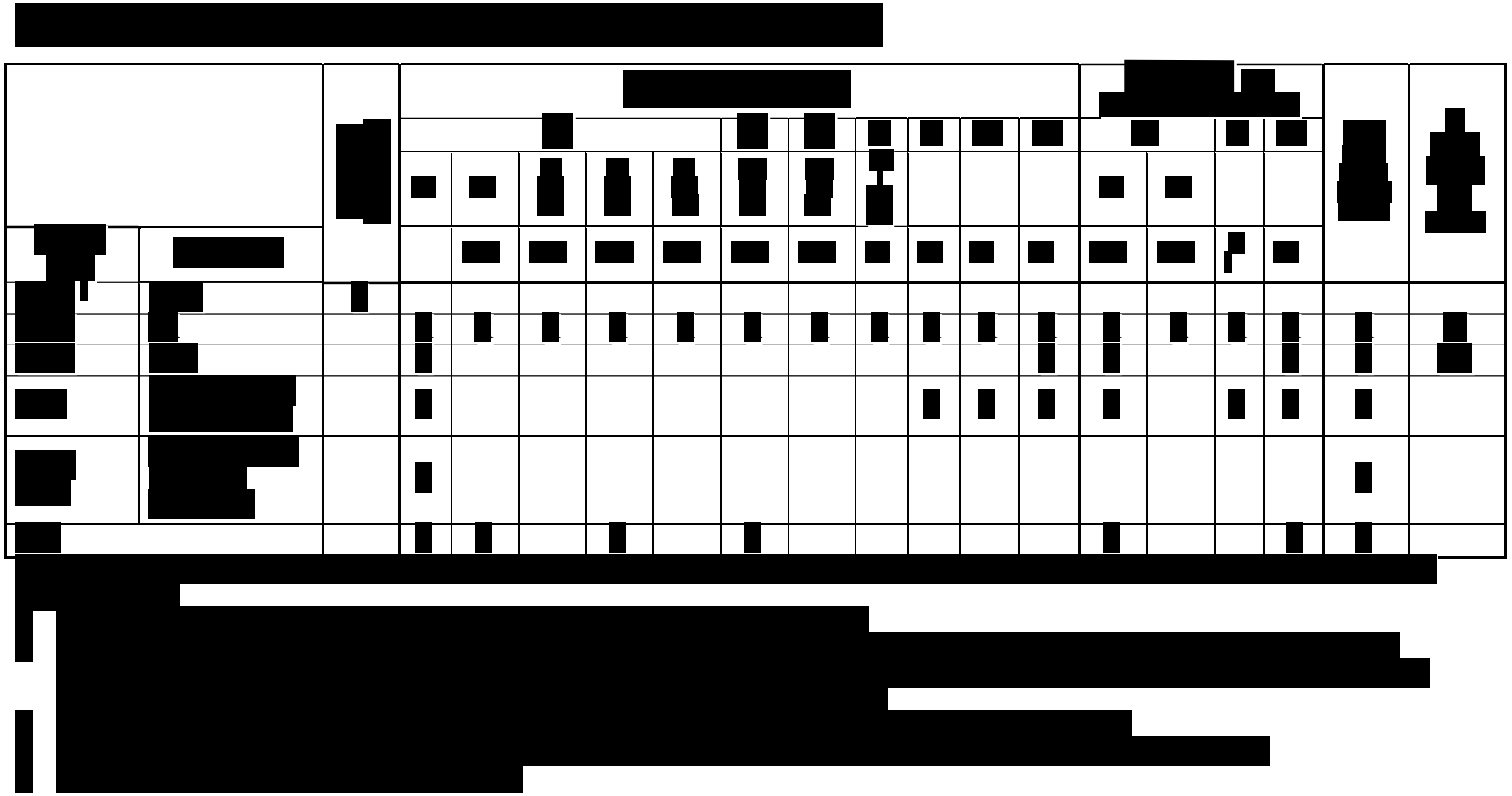
Assessment of Disease at Screening

- 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. If PET-CT is positive, subsequent diagnostic CT and MRI are not needed unless clinically indicated
- PET-CT only required at Screening for 18F-fluorodeoxyglucose (FDG) avid, nodal lymphomas (defined as per the Lugano Classification criteria as essentially all eligible histologies except small lymphocytic lymphoma, lymphoplasmacytic lymphoma/WM, 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.

Hematology: CBC to include WBC with 3- or 5-part differential, platelet count, hemoglobin, hematocrit, and ANC.

Samples for hematology, coagulation panel, biochemistry, urinalysis, and additional renal function studies will be collected:
<24 hours before the start of ADCT 402 infusion on Day 1 of Cycle 1, or
<72 hours before the start of ADCT-402 infusion on Day 1 of Cycle 2 and subsequent cycles.

14 The coagulation panel must include partial thromboplastin time (PTT) and International Normalized Ratio (INR); prothrombin time (PT) is optional.
15 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 formula [Cockcroft and Gault, 1976]).
16 Urinalysis to include, pH, specific gravity, protein, glucose, ketones, nitrates, occult blood and bilirubin. The urinalysis can be done by dipstick.
17 Urine to be collected for testing of biomarkers suggestive of potential renal injury (aquaporin-2, calbindin D28, and clusterin).
18 12-lead ECG to be performed on Day 1 of Cycles 1 and 2, a 12-lead ECG is to be performed before the start of the ADCT 402 infusion, within 30 minutes of the end of infusion, and 3 (± 30 minutes) and 24 (± 2.4) hours after the end of infusion.
19 See Section 12.1.2 of this Appendix for sample timing.
[redacted]
21 Concomitant medications to include prescription or over-the-counter medication, herbal or naturopathic products within the 14 days prior to the Cycle 1, Day 1 visit and during the study.
22 Premedication to be performed if grade 2 or higher infusion-related hypersensitivity reactions are observed in 1 patient at any time during Part 1 of the study, all subsequent patients must receive prophylactic treatment on Day 1 of each cycle thereafter to reduce the risk of hypersensitivity reaction.
23 ADCT-402: Patients will receive a 1-hour IV infusion at escalating doses, on Day 1 of each 3-week (21-day) cycle. If ADCT-402 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. Variations in infusion times due to minor differences in IV bag overfill/under fill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.
24 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. 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 End of Treatment to occur within 30 days after last dose of ADCT-402 and prior to the initiation of new anticancer treatment. When EOT coincides with a scheduled visit, the scheduled visit will become EOT.
26 Follow-up to occur 12 (±1) weeks after last dose of ADCT-402.
27 After completion of 6 treatment cycles (e.g., 6 infusions), the Day 8 visit is not required unless clinically indicated.
28 PK sample collection on Day 8 Cycles 1-4. Refer to Section 6.1, Efficacy Assessments.
29 Sample for assessment of PK and ADA to be obtained 12 weeks (± 1 week) after last dose of ADCT-402, unless a new anticancer treatment has been initiated.



12.2 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
Nonmeasured lesion	• Not applicable	• Absent/normal, regressed, but no increase
Organ enlargement	• Not applicable	• Spleen must have regressed by >50% in length beyond normal
New lesions	• None	• None

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

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

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

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

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

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 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 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, ListerTA. 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

12.3 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.					

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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
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.					

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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 6 to 21 days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort, and dyspnea.					
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.