

Protocol Number: ADCT-301-002

**Official Title: A Phase 1, Open-label, Dose-escalation, Multicenter Study to Evaluate the
Tolerability, Safety, Pharmacokinetics, and Activity of ADCT-301 in Patients
with Relapsed or Refractory CD25-positive Acute Myeloid Leukemia or
CD25-positive Acute Lymphoblastic Leukemia**

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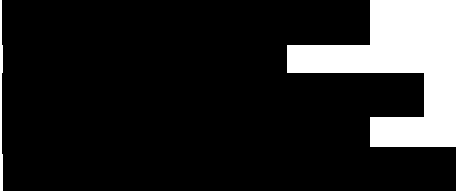
CLINICAL STUDY PROTOCOL


IND: 121912

A Phase 1, Open-label, Dose-escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Activity of ADCT-301 in Patients with Relapsed or Refractory CD25-positive Acute Myeloid Leukemia or CD25-positive Acute Lymphoblastic Leukemia

PROTOCOL NO.: ADCT-301-002

Sponsor: ADC Therapeutics SA


Sponsor Contact:


Medical Monitor:


Date of Original Protocol: 6 July 2015
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Date of Amendment 4: 03 April 2017
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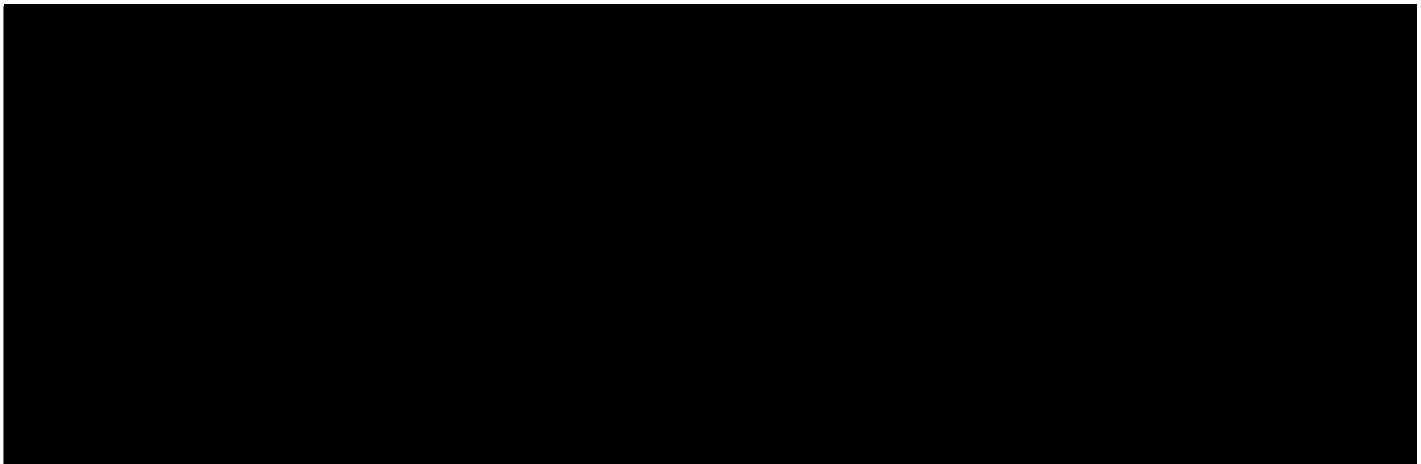
Confidentiality Statement

All financial and nonfinancial support for this study will be provided by ADC Therapeutics SA. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of ADC Therapeutics SA. The study will be conducted according to the International Council for Harmonisation (ICH) harmonised tripartite guideline E6(R1), Good Clinical Practice

Protocol Approval – Sponsor Signatory

Study Title	A Phase 1, Open-label, Dose-escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Activity of ADCT-301 in Patients with Relapsed or Refractory CD25-positive Acute Myeloid Leukemia or CD25-positive Acute Lymphoblastic Leukemia
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Protocol accepted and approved by:



Declaration of Investigator

I have read and understood all sections of the protocol entitled “A Phase 1, Open-label, Dose-escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Activity of ADCT-301 in Patients with Relapsed or Refractory CD25-positive Acute Myeloid Leukemia or CD25-positive Acute Lymphoblastic Leukemia” and the accompanying Investigator Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Protocol Amendment 5, dated 19 January 2018, the International Council for Harmonisation (ICH) harmonised tripartite guideline E6 (R1): Good Clinical Practice and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics SA or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub-Investigator.

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


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

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	ADCT-301-002
Title:	A Phase 1, Open-label, Dose-escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Activity of ADCT-301 in Patients with Relapsed or Refractory CD25-positive Acute Myeloid Leukemia or CD25-positive Acute Lymphoblastic Leukemia
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 1
Study Sites:	Approximately 10 sites during dose-escalation (Part 1) and 10 sites during dose expansion (Part 2)
Indication:	Patients with relapsed or refractory cluster of differentiation 25 (CD25)-positive acute myeloid leukemia (AML) or CD25-positive acute lymphoblastic leukemia (ALL) who have failed, or are intolerant to, any established therapy known to provide clinical benefit at current state of disease. Patients with myelodysplastic syndrome who have received treatment with hypomethylating agents and subsequently present with CD25+ AML and who failed, or are ineligible for standard induction therapy, are eligible for treatment with ADCT-301.
Rationale:	<p>Acute myeloid leukemia is the most common leukemia in adults and results in the largest number of deaths due to leukemia in the USA. The overall 5-year survival rate for AML is 26%, with younger patients (age <45 years) having a higher survival rate (>50%) compared with older patients (~10% for patients 65-74 years). Cytotoxic induction therapy is associated with high rates of complete response/remission, especially for younger patients who are able to tolerate treatment. However, the majority of patients with AML will eventually relapse or develop refractory disease. More than 6,000 new cases of ALL are diagnosed yearly in the US, with more than half (58%) occurring in patients <20 years of age. Children younger than 15 years have the best prognosis, with an expected 5-year survival rate of 88%, compared with 61% for adolescents and young adults and 40 to 45% for adults >40 years of age. Acute lymphoblastic leukemia in older patients is more often associated with poor prognostic factors, including a higher relapse rate, higher incidence of minimal residual disease (MRD), and poorer tolerance to induction therapy.</p> <p>In normal human tissue, CD25 expression is mainly limited to activated</p>

T- and B-cells. Expression of CD25 by AML and ALL blast cells is associated with adverse outcomes, including induction failure, relapse, and shortened overall survival.

ADCT-301 is an antibody-drug conjugate, composed of the human monoclonal antibody, HuMax[®]-TAC, directed against CD25, and conjugated through a cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. The PBD dimers are highly efficient anti-cancer drugs that bind in the minor groove of DNA and form highly cytotoxic DNA interstrand cross-links. After binding to the cell surface and internalization, ADCT-301 is transported to the lysosomes, where the protease-sensitive linker is cleaved and free PBD dimers are released inside the target cell.

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

The safety of ADCT-301 has been assessed in non-clinical testing. In mice, ADCT-301 is well tolerated at doses up to 9 mg/kg. A repeat-dose Good Laboratory Practice (GLP) toxicology study in cynomolgus monkeys investigated doses ranging from 0.15 to 0.9 mg/kg. Toxicities included body weight loss, nephrotoxicity, and cutaneous adverse events (AEs). The highest non-severe toxic dose was determined to be 0.15 mg/kg.

Objectives:

Primary objectives:

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

- Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCT-301 in patients with CD25-positive relapsed or refractory AML and CD25-positive ALL (Part 1).
- Determine the recommended dose of ADCT-301 for Part 2.
- Evaluate the safety and tolerability of ADCT-301 in Part 2 at the dose level recommended in Part 1.

Secondary objectives:

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

- Evaluate the clinical activity of ADCT-301, based on the patient's response to treatment (complete response [CR], CR with incomplete blood count recover [CRi], partial response [PR], progressive disease [PD], no response [NR]) and determination of the overall duration of response (DOR), overall response rate (ORR), overall survival (OS), and progression-free survival (PFS).

- Characterize the pharmacokinetic (PK) profile of ADCT-301 (total antibody, drug-to-antibody ratio [DAR] ≥ 0), PBD-conjugated antibody (DAR ≥ 1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) to ADCT-301 in blood before, during, and after treatment with ADCT-301.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Patient Selection:

Inclusion Criteria:

1. Male or female age 18 years or older.
2. Patients with:
 - Relapsed or refractory CD25-positive* AML** who have failed, or are intolerant to, any established therapy known to provide clinical benefit at current state of disease.
 - Myelodysplastic syndrome who have received treatment with hypomethylating agents and subsequently present with CD25-positive* AML and who failed, or are ineligible for standard induction therapy.
 - Relapsed or refractory CD25-positive* ALL** 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.

Note: *CD25-positive is defined as determination of CD25 expression by $\geq 5\%$ of blast cells within bone marrow (aspirate or biopsy), assessed at an approved clinical laboratory. **Diagnosis and classification as per World Health Organization (WHO) classification of acute leukemias.³⁴

3. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.
4. Serum/plasma creatinine ≤ 1.5 mg/dL, or if the patient has a serum/plasma creatinine > 1.5 mg/dL, creatinine clearance must be > 60 mL/min/1.73 m², as calculated by the Cockcroft and Gault equation.⁹
5. Serum/plasma 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.
6. Total serum/plasma bilirubin ≤ 1.5 times the ULN. Patients with known Gilbert's syndrome may have a total bilirubin up to ≤ 3 times ULN.
7. Women of child-bearing potential must have a negative urine or serum beta-human chorionic gonadotropin (β -HCG) pregnancy test within 7 days prior to the Day 1 visit.
8. Women of child-bearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-301. Men with female partners who are of child-bearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-301.

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

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

9. WBC count value of <15,000 cells/ μ L prior to C1D1.

Exclusion Criteria:

1. Patients who have an option for any treatment with proven clinical benefit for CD25-positive AML or CD25-positive ALL at current state of disease.
2. Known active central nervous system (CNS) leukemia, defined as morphologic evidence of leukemic blasts in the cerebrospinal fluid (CSF), use of CNS-directed intrathecal treatment for active disease within 28 days prior to Screening, or symptomatic CNS leukemia (i.e., cranial nerve palsies or other significant neurologic dysfunction) within 28 days prior to Screening.

Note: Patients may have a history of CNS leukemic involvement if they have received prior treatment for CNS involvement and no evidence of active disease (defined as ≥ 2 consecutive spinal fluid assessments with no evidence of disease) is present at Screening. Prophylactic intrathecal chemotherapy is not a criterion for exclusion.

3. Active graft-versus-host disease.
4. Autologous or allogenic transplant within the 60 days prior to Screening.
5. Known history of immunogenicity or hypersensitivity to a CD25 antibody.
6. Known history of positive serum human ADA, or known allergy to any component of ADCT-301.
7. History of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]).
8. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome and myasthenia gravis); other CNS autoimmune disease (e.g., poliomyelitis, multiple sclerosis).
9. History of recent infection (within 4 weeks of C1D1) considered to be caused by one of the pathogens listed in [section 7.3.4.5](#): HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, Campylobacter jejuni, or enterovirus D68.

10. Known seropositive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring anti-viral therapy.
Note: Testing is not mandatory to be eligible. Testing for HCV should be considered if the patient is at risk for having undiagnosed HCV (e.g., history of injection drug use).
11. History of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome.
12. Pregnant or breastfeeding women.
13. Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure >115 mm Hg), unstable angina, congestive heart failure (greater than New York Heart Association class II), severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, poorly controlled diabetes, severe chronic pulmonary disease, coronary angioplasty, myocardial infarction within 6 months prior to Screening, or uncontrolled atrial or ventricular cardiac arrhythmias.
14. Use of any other experimental medication(s) within 14 days or 5 half-lives, but in no case <14 days prior to start of the study treatment on Cycle 1, Day 1, except if approved by the Sponsor.
15. Major surgery, chemotherapy, systemic therapy (excluding 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.
16. Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE Version 4.0] Grade 0 or Grade 1) from acute non-hematologic toxicity (except all grades of alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to Screening.
17. Isolated extramedullary relapse (i.e., testicular, CNS).
18. Congenital long QT syndrome or a QTc interval ≥ 450 ms at Screening (unless secondary to pacemaker or bundle branch block).
19. 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 the Investigator agree and document

should not be exclusionary.

- 20.** 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-301, used as monotherapy, in patients with relapsed or refractory CD25-positive AML or CD25-positive ALL. The study will determine the MTD, as well as evaluate the preliminary activity, PK, and pharmacodynamics (PD) of ADCT-301.

In Part 1, patients will be assigned to treatment according to a 3+3 dose-escalation design and oversight by a Dose-Escalation Steering Committee (DESC). In Part 2, all patients will be assigned to the dose level of ADCT-301 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 anti-cancer treatment. After documentation of disease progression or start of new anti-cancer 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 treatment at any time and for any reason, without prejudice to their future medical care. Patients may also be withdrawn by the Investigator or others at the study site.

A patient may be withdrawn from treatment 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).

- Non-compliance, including lost to follow-up.
- Other (e.g., pregnancy, development of contraindications).
- The Investigator determines 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.

Note: Patient enrollment will be halted, pending a safety analysis and review with the appropriate regulatory authority(ies):

- if any patient in Part 1 or Part 2 experiences a CTCAE Grade 5 AE, or 2 non-hematologic CTCAE Grade 4 AEs, which are not attributable to the underlying disease, and for which relationship to ADCT-301 cannot be ruled out, within 30 days of their last dose of ADCT-301.
- in the event of another single case of GBS. Patients currently on trial having clinical benefit or not yet having reached first bone marrow assessment can continue on study once informed and they consent to continue treatment.

Note: Patients who experience a dose-limiting toxicity (DLT) during Cycle 1 are to be permanently discontinued from the study.

Efficacy Assessments:

Assessment of response to treatment with ADCT-301 will be based on bone marrow samples (aspirate or biopsy, if aspirate unattainable). The activity of ADCT-301 will be evaluated based on the Investigator's evaluation of the patient's response to ADCT-301 as CR, CRi, PR, PD, or NR.^{8,11}

Complete response is defined as achieving each of the following:

- Bone marrow differential showing $\leq 5\%$ blast cells and absence of blast cells with Auer rods.
- Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$.
- Absence of extramedullary disease.
- Patient is independent of red blood cell (RBC) transfusions.

Complete response with incomplete blood count recovery is defined as achieving all CR criteria except that values for ANC may be $< 1.0 \times 10^9/L$ and/or values for platelets may be $< 100 \times 10^9/L$.

Partial response is defined as achieving each of the following:

- ANC $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$.
- Bone marrow differential showing a $\geq 50\%$ decrease from baseline in

the percentage of bone marrow blast cells to a level >5% and ≤25%,
or
bone marrow differential showing <5% blast cells and presence of Auer rods.

No response is defined as not achieving CR, CRi, or PR.

Progressive disease is defined as:

- For patients with CR or CRi, the first date of reappearance of blast cells in bone marrow and/or peripheral blood to a level ≥5%, or development of extramedullary disease.
- For patients with PR, the first date of an increase in blast cells in bone marrow and/or peripheral blood such that the patient does not continue to meet the criteria for PR.

DOR and ORR will be defined among responders (CR, CRi, or PR); OS and PFS will also be determined.

**Pharmacokinetic,
Pharmacodynamic,
and [REDACTED]
Assessments:**

The PK profile of ADCT-301 (total antibody; drug-to-antibody ratio [DAR] ≥0), PBD-conjugated antibody (DAR ≥1), and free warhead SG3199 will be assessed. Additional PK, ADA, cytokines, and serum CD25 (sCD25); blood samples will be collected at the discretion of the Investigator during any visit where toxicity is observed. A PK, ADA, cytokines, and sCD25 sample will also be collected concurrently with any other blood draw to assess safety (e.g., Unscheduled Visit), if possible.

The PK profile will include determination of standard PK parameters (e.g., maximum concentration [C_{max}], time to C_{max} [T_{max}], AUC_{0-last}, AUC_{0-τ}, AUC_{0-∞}, AI, V_{ss}, MRT, λ_z, t_{1/2}, C_L, and V_z).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Safety Assessments:

[REDACTED]

Safety will be assessed based on AEs, serious AEs (SAEs), treatment discontinuations due to AEs, DLTs, measurements of cytokines in serum, periodic 12-lead electrocardiogram (ECG) recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, biochemistry, coagulation panel, pregnancy testing (for women of child-bearing potential) and urinalysis test results. Adverse events will be graded according to CTCAE Version 4.0.

Definition of DLT:

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

- A hematologic DLT is defined as:
 - Grade 3 or higher event of neutropenia and/or thrombocytopenia or a Grade 4 anemia, with a hypocellular bone marrow lasting for 6 weeks or more after the start of a cycle, in the absence of residual leukemia (i.e., with <5% blasts). In case of a normocellular bone marrow with <5% blasts, 8 weeks with \geq Grade 3 pancytopenia will be considered a DLT.
- 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 AEs (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 3 or higher skin ulceration.
 - Peripheral sensory or motor neuropathy \geq Grade 2.

The DLT observation period for dose-escalation will be 1 cycle. Patients who experience a DLT during Cycle 1 are to be permanently discontinued from the study.

Investigational Product, Dosage, and Mode of Administration:

ADCT-301 is a sterile formulation containing PBD-conjugated HuMax[®]-TAC (DAR \geq 1), HuMax[®]-TAC (DAR = 0), and SG3249. It is provided pre-formulated in 10-mL glass vials containing approximately 30 mg of ADCT-301 per vial (deliverable volume 5.4 mL at 6 mg/mL). The appropriate quantity of ADCT-301 will be diluted in 50 mL of 5% dextrose in water (D5W).

Patients will receive a 1-hour intravenous (IV) infusion of ADCT-301 on

Day 1 of Cycle 1. If ADCT-301 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient, at the Investigator's discretion.

The investigational product administration schedule is as follows:

Every 3-Week Administration

Patients will be given ADCT-301 on Day 1 of each 3-week (21-day) treatment cycle.

Weekly Administration

Patients will be given ADCT-301 (weekly [QW]) on Days 1, 8, and 15 of each 3-week (21-day) treatment cycle.

A patient will maintain the same treatment schedule throughout the duration of the trial.

Once a patient achieves CR/CRi, frequency or dose may be adjusted by the DESC based on emerging safety, efficacy, and PK profile.

The trial will be continuously monitored for emerging safety, efficacy and/or PK profile, and the DESC will determine if it is appropriate to maintain a QW schedule, revert to an every 3-week (Q3W) schedule, or test other dosing regimens.

Dose-Escalation Design:

Dose-escalation (Part 1) will be conducted according to a 3+3 design. The initial dose of ADCT-301 will be 3 µg/kg (Dose Level 1), and the highest allowed dose will be 150 µg/kg every three weeks (50 µg/kg every week). The DLT observation period for dose-escalation will be 1 cycle. The first patient at each new dose level must be observed for 7 days for occurrence of AEs prior to treating the second patient at that dose level. 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 experience 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; therefore, is 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.

The number of dose levels will depend on the emergent toxicity profile of ADCT-301 and will be decided by the DESC; PK and PD evaluations may also inform decision making.

During Part 1 (dose-escalation), the DESC may expand enrollment at doses below the current dose level as part of the dose-escalation process.

No more than 9 additional patients (e.g., 3 cohorts of 3 patients) will be enrolled in the remaining dose escalation portion of this study (max. dose level 50 µg/kg/week) from the date of protocol amendment number 5, unless 2 additional patients attain a PR, CR or CRi, in which case additional patients will be treated at a dose patients have cleared the DLT period, to determine if there is sufficient evidence of clinical activity to continue the study.

Additional patients may only be added at a lower dose level provided there is at least 1 patient who has achieved a PR or better ([Section 7.1](#)). 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.

Every 3-Week Administration

Patients will be given ADCT-301 on Day 1 of each 3-week treatment cycle. When the dose is escalated, the dose may increase by 100% if no DLTs are observed at the current level (e.g., at 6 µg/kg, the dose increase is 6 µg/kg). Once a DLT is observed at a given dose level, the next dose may only increase by 50% (e.g., at 6 µg/kg, the dose increase is 3 µg/kg). The dose may never increase by more than 100%, or more than an absolute value of 20 µg/kg at dose levels below 100 µg/kg and 50 µg/kg for dose levels between 100 and 150 µg/kg, whichever is less. A patient will maintain the same treatment schedule throughout the duration of the trial.

Weekly Administration

Patients will be given ADCT-301 (QW) on Days 1, 8 and 15 of each 3-week treatment cycle.

The first dose level for the QW dosing will be based on the safety and tolerability of patients who have been treated on the Q3W schedule. The first 3 patients will be given a cumulative dose each cycle that is comparable to (but not higher than) the highest dose tested at the Q3W dose schedule at which 3 patients completed the DLT observation period without a DLT. For example, if the highest Q3W dose tested at which 3 patients did not experience a DLT was cohort 92 µg/kg, the first cohort to receive QW dosing will receive 30 µg/kg each week for 3 weeks.

When the dose is escalated, the dose may increase by 50% if no DLTs are observed at the current level. Once a DLT is observed at a given dose level, the next dose may only increase by 25%. The dose may never increase by more than 50%, or more than an absolute value of 20 µg/kg/week,

whichever is less. During Part 1, the DESC may expand enrollment at doses below the current dose level as part of the dose-escalation process. Additional patients may only be added at a lower dose level provided there is at least 1 patient who has achieved a partial response (PR or better). 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 Part 2 (dose expansion), 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.

Sample Size:

A maximum of 80 patients (up to 50 patients in Part 1 and up to 30 patients in Part 2) may be enrolled at approximately 10 study sites in Part 1 and 10 study 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
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC _{0-∞}	area under the concentration-time curve from time zero to infinity
AUC _{0-last}	area under the concentration-time curve from time zero to the last quantifiable concentration
AUC _{0-τ}	area under the concentration-time curve from time zero to the end of the dosing interval
β-HCG	Beta-human chorionic gonadotropin
BMA	bone marrow aspirate
BSA	body surface area
BSI	before-start of infusion
CBC	complete blood count
CD	cluster of differentiation
sCD	serum cluster of differentiation
CFR	Code of Federal Regulations
C _L	Clearance
C _{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRi	complete response with incomplete blood count recovery
CRO	contract research organization
CSF	cerebrospinal fluid
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
EBV	Epstein-Barr virus
ECG	electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	end of infusion
EOT	end of treatment
FDA	Food and Drug Administration
FLT3-ITD	FMS-like tyrosine kinase 3 internal tandem duplications
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HbsAg	hepatitis B surface antigen
HSV1 / 2	Herpes Simplex Virus Type 1 / Type 2
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSTD	highest non-severe toxic dose
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL-2R	interleukin-2 receptor
INR	International Normalized Ratio
IP	investigational product
IRB	institutional review board
IV	intravenous
IVF	intravenous fluid
kDa	kilodalton
LSC	leukemic stem cell
MNC	mononuclear cells
MRT	mean residence time
MTD	maximum tolerated dose
NR	no response
ORR	overall response rate
OS	overall survival
PABA	para-aminobenzoic acid
PBD	pyrrolbenzodiazepine
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics or progressive disease
PEG	polyethylene glycol
PFS	progression-free survival
Ph	Philadelphia chromosome
PK	pharmacokinetic
PLEX	plasma exchange
PR	partial response

Abbreviation	Definition
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell
Q3W	every 3 weeks
QTc	corrected QT interval
QW	every week
QWBA	quantitative whole-body autoradiography
SAE	serious adverse event
SAP	statistical analysis plan
SEER	US Surveillance Epidemiology and End Results
SUSAR	suspected unexpected serious adverse reaction
TAC	t-cell activation antigen
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
λ_z	terminal elimination phase rate constant
T_{max}	time to maximum concentration
$t_{1/2}$	terminal half-life
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at steady-state
Val	valine
V_z	volume of distribution
VZV	varicella zoster virus
WB	whole blood
WBC	white blood cell
WHO	World Health Organization

1 Introduction

ADCT-301 is an antibody-drug conjugate (ADC), composed of the human monoclonal antibody, HuMax[®]-TAC, directed against human cluster of differentiation 25 (CD25), and conjugated through a cleavable linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin. The PBD dimers are highly efficient anti-cancer drugs that bind in the minor groove of DNA and form highly cytotoxic DNA interstrand cross-links.¹⁶ The schematic representation of ADCT-301, and the different components that may be formed following the administration of this ADC to humans, are presented in Figure 1.

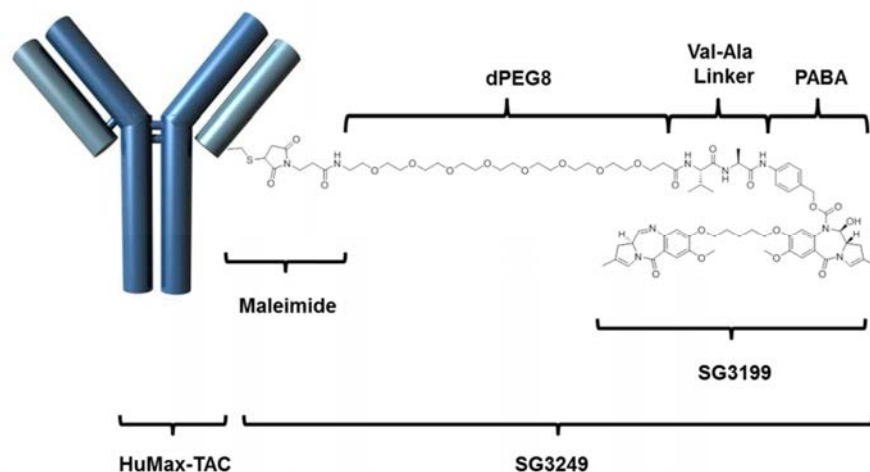


Figure 1. Schematic Representation and Chemical Structure of ADCT-301

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

The make-up of ADCT-301 includes:

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

The interleukin-2 receptor (IL-2R) is made up of 3 subunits: α (CD25), β (CD122) and γ (CD132). CD25, or T-cell activation antigen (TAC), is the alpha-chain of IL-2R.^{5,6} ADCT-301 binds with picomolar affinity to human CD25. After binding and internalization, ADCT-301 is transported to the lysosomes, where the protease-sensitive linker is cleaved and free PBD dimers are released inside the target cell. The released PBD dimers bind into the minor groove of DNA in a sequence-selective manner, and form highly cytotoxic DNA interstrand cross-links.¹⁶ 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.¹

2 Study Rationale and Justification for Dose Level Selection

2.1 Clinical Background

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common leukemia in adults and results in the largest number of deaths due to leukemia in the USA. The diagnosis will account for 38% of an estimated 54,270 new cases of leukemia and 42% of estimated deaths due to leukemia in 2015.² It is more common in older adults (median age at onset, 67 years), with 72% of cases diagnosed at ages 55 years and older.

The overall 5-year survival rate for AML is 26%, with younger patients (age <45 years) having a higher survival rate (>50%) compared with older patients (~10% for patients 65-74 years).²³ Cytotoxic induction therapy is associated with high rates of complete response/remission, especially for younger patients who are able to tolerate treatment. The discrepancy between the high response rates achieved with induction therapy and poor long-term survival is due to the inability to prevent or overcome disease relapse.^{4,14} The majority of patients with AML will eventually relapse or develop refractory disease. The prognosis for these patients is poor and most patients will die from progressive disease (PD).

Acute lymphoblastic leukemia is a hematologic malignancy characterized by the clonal expansion of lymphoid blast cells (B- or T-cell lineage) in the peripheral blood, bone marrow, and/or other tissues. As per the US Surveillance Epidemiology and End Results (SEER) statistical fact sheets, an estimated 6,250 new cases of ALL will be diagnosed in the US in 2015 (0.4% of all cancer cases). It is the most common leukemia diagnosed in children with more than half (58%) of all new cases occurring in patients younger than 20 years of age. The expected overall 5-year survival rate for ALL is approximately 68%.²⁴

Due to advances in therapy and supportive care, survival rates for ALL have been improving across all age groups. Children younger than 15 years have the best prognosis, with an expected 5-year survival rate of 88%. However, survival rates for older patients have not improved to the same extent. The expected 5-year survival for adolescents and young adults (ages 15 to <20 years) with ALL is approximately 61%, which decreases to approximately 40 to 45% for adults older than 40 years of age.²⁴

Compared with children, ALL in older patients is more often associated with poor prognostic factors, including a higher relapse rate, cell markers associated with poor outcomes, low incidence of favorable subtypes, higher incidence of minimal residual disease (MRD), and poorer tolerance to induction therapy.^{17,21,30}

There are specific subtypes of ALL associated with specific cytogenetic changes and expression of certain cell surface markers that confer a poor prognosis. While the addition of tyrosine kinase inhibitors to the treatment protocols of patients with Philadelphia chromosome (Ph)+ and Ph-like ALL have improved remission rates and disease-free survival, patients unable to undergo hematopoietic stem cell transplantation still have a poor prognosis with a 3-year overall survival (OS) of 14%.¹⁸

CD25, or TAC, is the 55-kilodalton (kDa) alpha-chain of IL-2R.⁶ In normal human tissue, expression of CD25 is mainly limited to activated T- and B-cells.^{5,6} It is not expressed on normal human hematopoietic stem cells,²⁹ but has been demonstrated in subpopulations of chemotherapy-resistant human leukemic stem cells (LSC).¹⁰ Survival of quiescent, chemotherapy-resistant LSCs may play a role in the development of relapsed or refractory disease in AML.^{10,19}

CD25 expression has been demonstrated in newly diagnosed and relapsed AML^{7,13,33} and in late-stage myelodysplastic syndrome related AML.²⁰ Expression of CD25 by AML blast cells is associated with adverse outcomes, including induction failure, relapse, and shortened OS.^{7,13,20,33}

Expression of cluster of differentiation 25 (CD25) independently confers a poor prognosis for patients with ALL and is commonly found in patients with Ph+ ALL.²²

It is not yet understood what biological role, if any, CD25 may play in the development of adverse outcomes. However, the availability of treatment specifically targeted to cells expressing CD25 may provide additional therapeutic options for these patients.

2.2 Non-clinical Efficacy and Safety of ADCT-301

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

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

Toxicities included body weight loss, nephrotoxicity, and cutaneous adverse events (AEs). The highest non-severe toxic dose (HNSTD) in the GLP-compliant study in cynomolgus monkeys was determined to be 0.15 mg/kg. As per guidance from the Food and Drug Administration (FDA), a starting dose of 10 μ g/kg (1/6 of the HNSTD, based on body surface area [BSA]) could be proposed for this first study in patients with AML. However, based on anomalous exposure data observed on some dosing days at the 0.15 mg/kg dose level (no explanation in the formulation or dosing records), a lower starting dose of 3 μ g/kg was chosen for this study to offset any uncertainty associated with the 0.15 mg/kg dose level and to increase the margin of safety.

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

2.3 Safety of Commercially Available Antibodies Directed against CD25

The safety profiles of monoclonal antibodies directed against CD25 (IL2-R α), such as Simulect[®] (basiliximab, Novartis Pharmaceuticals, NJ, USA) and Zenapax[®] (daclizumab, Roche Pharmaceuticals, NJ, USA), have been well characterized. Both products are indicated for prophylaxis of acute organ transplant rejection in patients receiving renal transplant. The most frequently reported AEs identified in the prescribing information for both products are gastrointestinal disorders, including abdominal pain, constipation, diarrhea, nausea, and vomiting.^{25,27}

3 Study Objectives

3.1 Primary Objectives

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

- Evaluate the safety and tolerability and determine the maximum tolerated dose (MTD) of ADCT-301 in patients with CD25-positive relapsed or refractory AML or CD25-positive ALL (Part 1).
- Determine the recommended dose of ADCT-301 for Part 2.
- Evaluate the safety and tolerability of ADCT-301 in Part 2 at the dose level recommended in Part 1.

3.2 Secondary Objectives

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

- Evaluate the clinical activity of ADCT-301, based on the patient’s response to treatment (complete response [CR], CR with incomplete blood count recovery [CRi], partial response [PR], PD, no response [NR]) and determination of the overall duration of response (DOR), overall response rate (ORR), OS, and progression-free survival (PFS).
- Characterize the pharmacokinetic (PK) profile of ADCT-301 (total antibody, drug-to-antibody ratio [DAR] ≥ 0), PBD-conjugated antibody (DAR ≥ 1), and free warhead SG3199.
- Evaluate anti-drug antibodies (ADAs) to ADCT-301 in blood before, during, and after treatment with ADCT-301.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



4 Investigational Plan and Patient Selection

4.1 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-301, used as monotherapy, in patients with relapsed or refractory CD25-positive AML or CD25-positive ALL. The study will determine the MTD, as well as evaluate the preliminary activity, PK, and pharmacodynamics (PD) of ADCT-301.

Patients will receive a 1-hour IV infusion of ADCT-301 on Day 1 of Cycle 1. If ADCT-301 is well tolerated after the first infusion, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient, at the Investigator's discretion. Weekly (QW) administration will be evaluated as described in [Section 4.1.1](#). Additional treatment schedules may be considered based on emerging data.

For each patient, the study will include a Screening period (up to 28 days), a treatment period (until withdrawal, [Section 5.2.1](#)), 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.

In Part 1, patients will be assigned to treatment according to a 3+3 dose-escalation design ([Section 4.1.1](#)) and oversight of a Dose-Escalation Steering Committee (DESC) ([Section 7.3.1.2](#)). In Part 2, (expansion), all patients will be assigned to the dose level of ADCT-301 identified in Part 1.

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 anti-cancer treatment. After documentation of disease progression or start of new anti-cancer 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.

4.1.1 Dose-escalation (Part 1) and Determination of Maximum Tolerated Dose

Dose-escalation will be conducted according to a 3+3 design (Figure 2). The initial dose of ADCT-301 will be 3 µg/kg (Dose Level 1), and the highest allowed dose will be 150 µg/kg every three weeks (50 µg/kg every week).

The DLT (see Section 7.3.1.1 for further details) observation period for dose-escalation will be 1 cycle. The first patient at each new dose level must be observed for 7 days for occurrence of AEs prior to treating the second patient at that dose level. 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, therefore, is 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.

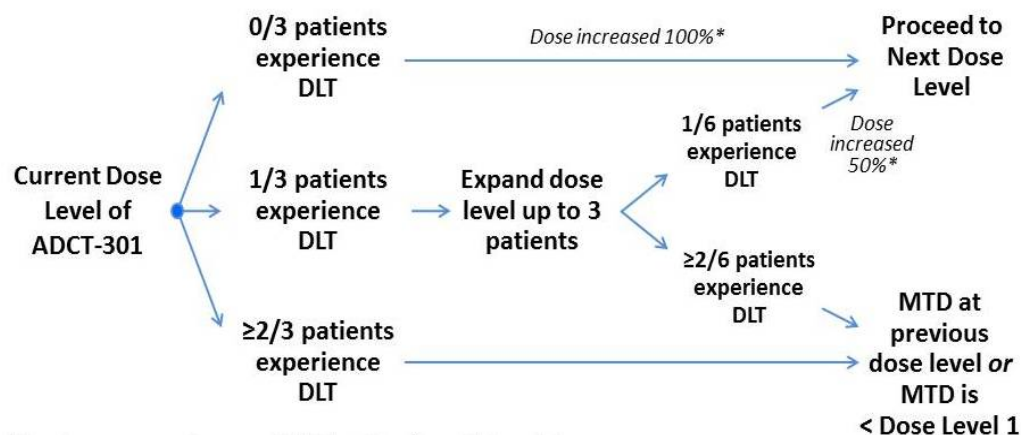


Figure 2. Schematic Representation for Dose-escalation (3+3) Design

* For every 3 weeks (Q3W) administration, the dose increase will never exceed 100% or 20 µg/kg at dose levels below 100 µg/kg and 50 µg/kg for dose levels between 100 and 150 µg/kg, whichever is less. Dose adjustment for other treatment schedules, such as QW dosing are included below. 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-301 and will be decided by the DESC ([Section 7.3.1.2](#)); PK and PD evaluations may also inform decision making.

During Part 1 (dose-escalation), the DESC may expand enrollment at doses below the current dose level as part of the dose-escalation process. Additional patients may only be added at a lower dose level provided there is at least 1 patient who has achieved a PR or better ([Section 7.1](#)).

No more than 9 additional patients (e.g., 3 cohorts of 3 patients) will be enrolled in the remaining dose escalation portion of this study (max. dose level 50 µg/kg/week) from the date of protocol amendment number 5, unless 2 additional patients attain a PR, CR, or CRi, in which case additional patients will be treated at a dose patients have cleared the DLT period, to determine if there is sufficient evidence of clinical activity to continue the study.

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.

Every 3-Week Administration

Patients will be given ADCT-301 on Day 1 of each 3-week treatment cycle.

When the dose is escalated, the dose may increase by 100% if no DLTs are observed at the current level (e.g., at 6 µg/kg, the dose increase is 6 µg/kg). Once a DLT is observed at a given dose level, the next dose may only increase by 50% (e.g., at 6 µg/kg, the dose increase is 3 µg/kg). The dose may never increase by more than 100%, or more than an absolute value of 20 µg/kg at dose levels below 100 µg/kg and 50 µg/kg for dose levels between 100 and 150 µg/kg, whichever is less.

Weekly Administration

Patients will be given ADCT-301 (QW) on Days 1, 8, and 15 of each 3-week treatment cycle.

The first dose level for the QW dosing will be based on the safety and tolerability of patients who have been treated on the Q3W schedule. The first 3 patients will be given a cumulative dose each cycle that is comparable to (but not higher than) the highest dose tested at the Q3W dose schedule at which 3 patients completed the DLT observation period without a DLT. For example, if the highest Q3W dose tested at which 3 patients did not experience a DLT was cohort 92 µg/kg, the first cohort to receive (QW) dosing will receive 30 µg/kg each week for 3 weeks.

When the dose is escalated, the dose may increase by 50% if no DLTs are observed at the current level. Once a DLT is observed at a given dose level, the next dose may only increase by 25%. The dose may never increase by more than 50%, or more than an absolute value of 20 µg/kg/week, whichever is less.

A patient will maintain the same treatment schedule throughout the duration of the trial.

Weekly dosing will be implemented at the discretion of the DESC (and in accordance with local ethics committee approvals). Once a patient achieves CR/CRi, frequency or dose may be adjusted by the DESC based on emerging safety, efficacy, and PK profile.

The trial will be continuously monitored for emerging safety, efficacy, and/or PK profile and the DESC will determine if it is appropriate to maintain a QW schedule, revert to a Q3W schedule, or test other dosing regimens.

4.1.2 Dose Expansion (Part 2)

During Part 2 (dose expansion), patients will be monitored for safety using the same DLT criteria employed during Part 1 (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.

4.2 Selection of Study Population

A maximum of 80 patients (up to 50 patients in Part 1 and up to 30 patients in Part 2) may be enrolled at approximately 10 study sites in Part 1 and 10 study 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.

4.2.1 Inclusion Criteria

1. Male or female age 18 years or older.
2. Patients with:
 - Relapsed or refractory CD25-positive* AML** who have failed, or are intolerant to, any established therapy known to provide clinical benefit at current state of disease.
 - Myelodysplastic syndrome who have received treatment with hypomethylating agents and subsequently present with CD25-positive* AML** and who failed, or are ineligible for standard induction therapy.
 - Relapsed or refractory CD25-positive *ALL** 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.

Note: *CD25-positive is defined as determination of CD25 expression by $\geq 5\%$ of blast cells within bone marrow (aspirate or biopsy), assessed at an approved clinical laboratory.
**Diagnosis and classification as per World Health Organization (WHO) classification of acute leukemias.³⁴

3. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

4. Serum/plasma creatinine ≤ 1.5 mg/dL, or if the patient has a serum/plasma creatinine > 1.5 mg/dL, creatinine clearance must be > 60 mL/min/ 1.73m^2 , as calculated by the Cockcroft and Gault equation.⁹
5. Serum/plasma 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.
6. Total serum/plasma bilirubin ≤ 1.5 times the ULN. Patients with known Gilbert's syndrome may have a total bilirubin up to ≤ 3 times ULN.
7. Women of child-bearing potential must have a negative urine or serum beta-human chorionic gonadotropin (β -HCG) pregnancy test within 7 days prior to the Day 1 visit.
8. Women of child-bearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-301. Men with female partners who are of child-bearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-301.

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

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

9. White blood cell count value of $< 15,000$ cells/ μL prior to C1D1.

4.2.2 Exclusion Criteria

1. Patients who have an option for any treatment with proven clinical benefit for CD25-positive AML or CD25-positive ALL at current state of disease.
2. Known active central nervous system (CNS) leukemia, defined as morphologic evidence of leukemic blasts in the cerebrospinal fluid (CSF), use of CNS-directed intrathecal treatment for active disease within 28 days prior to Screening, or symptomatic CNS leukemia (i.e., cranial nerve palsies or other significant neurologic dysfunction) within 28 days prior to Screening.

Note: Patients may have a history of CNS leukemic involvement if they have received prior treatment for CNS involvement and no evidence of active disease (defined as ≥ 2 consecutive spinal fluid assessments with no evidence of disease) is present at Screening. Prophylactic intrathecal chemotherapy is not a criterion for exclusion.

3. Active graft-versus-host disease.
4. Autologous or allogenic transplant within the 60 days prior to Screening.
5. Known history of immunogenicity or hypersensitivity to a CD25 antibody.
6. Known history of positive serum human ADA, or known allergy to any component of ADCT-301.
7. History of symptomatic autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma], systemic lupus erythematosus, Sjögren's syndrome, autoimmune vasculitis [e.g., Wegener's granulomatosis]).
8. History of neuropathy considered of autoimmune origin (e.g., polyradiculopathy including Guillain-Barré syndrome and myasthenia gravis); other CNS autoimmune disease (e.g., poliomyelitis, multiple sclerosis).
9. History of recent infection (within 4 weeks of C1D1) considered to be caused by one of the pathogens listed in [section 7.3.4.5](#): HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, Campylobacter jejuni, or enterovirus D68.
10. 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).

11. History of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome.
12. Pregnant or breastfeeding women.
13. Significant medical comorbidities, including uncontrolled hypertension (diastolic blood pressure >115 mm Hg), unstable angina, congestive heart failure (greater than New York Heart Association class II), severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, poorly controlled diabetes, severe chronic pulmonary disease, coronary angioplasty, myocardial infarction within 6 months prior to Screening, or uncontrolled atrial or ventricular cardiac arrhythmias.
14. Use of any other experimental medication(s) within 14 days or 5 half-lives, but in no case <14 days prior to the start of study treatment on Cycle 1, Day 1, except if approved by the Sponsor.

15. Major surgery, chemotherapy, systemic therapy (excluding 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.
16. Failure to recover (to Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0 Grade 0 or Grade 1) from acute non-hematologic toxicity (except all grades of alopecia or Grade 2 or lower neuropathy), due to previous therapy, prior to Screening.
17. Isolated extramedullary relapse (i.e., testicular, CNS).
18. Congenital long QT syndrome or a QTc interval ≥ 450 ms at Screening (unless secondary to pacemaker or bundle branch block).
19. 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 the Investigator agree and document should not be exclusionary.
20. Any other significant medical illness, abnormality, or condition that would, in the Investigator's judgment, make the patient inappropriate for study participation or put the patient at risk.

5 Study Procedures

5.1 Procedures by Study Day – Every 3-Week Dosing Schedule (Q3W)

The following procedures will be performed during the study. Regardless of dosing schedule, all patients will complete the same Screening procedures described in [Section 5.1.1](#), as well as the same procedures described for the End of Treatment (EOT; [Section 5.1.8](#)), 12-Week Follow-up Visit ([Section 5.1.9](#)) and Long-term Follow-up ([Section 5.1.10](#)).

Visit procedures described in [Section 5.1.2](#) – [Section 5.1.7](#) are for patients on the Q3W Schedule.

The Schedule of Procedures for the Q3W and QW dosing schedules are shown in [Table 1](#) and [Table 3](#), respectively, in [Appendix 13.1](#). Timings for sample collections for assessment of PK, ██████████ and other parameters for the Q3W dosing schedule are shown in [Table 2](#), and Cycle 1 and Cycle 2+ of the QW dosing schedule in [Table 4](#) and [Table 5](#), respectively, in [Appendix 13.1](#).

For QW dosing, most of the assessments will remain uniform with the Q3W dosing assessments, with the following exceptions:

- Study drug administration will occur at Days 1, 8, and 15
- The Q3W Day 19 assessments will be performed on Day 15 (concurrently with the 3rd QW dose) for the QW patients
 - Note: Bone marrow aspirate (BMA) or biopsy for QW patients is still performed at Day 19 ± 3 days but must be performed prior to the first dose of the next cycle.
- Pharmacokinetic and Pharmacodynamics, ADA, serum CD25 (sCD25), WBC population, cytokines, and additional renal function studies sampling schedule is adjusted according to the prescribed dosing schedule.

5.1.1 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) is to be obtained prior to performing any study evaluations. Results (clinical laboratory, 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, significant diagnoses, all cancer treatment [including surgery, radiation therapy, chemotherapy, etc.], and FLT3-ITD status, if available).
- Serum or urine β -HCG pregnancy testing (women of child-bearing potential only).
- Physical examination, including neurological examination and including whole-body skin assessment. Whole-body skin assessment does not have to be performed by a dermatologist. However, any unexplained lesion is to be referred to a dermatologist for further evaluation and skin biopsy, if clinically warranted. The examination must include a determination if the patient has had any infection. At the discretion of the investigator, evaluation of any reported infection must be conducted to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s) as specified in the exclusion criteria.
 - Neurological assessment (as part of the physical examination) including strength, sensation, and deep-tendon reflexes throughout; examination does not need to be conducted by neurologist unless there are abnormal findings not explained by previous medical history (e.g., a patient with left sided weakness known to be a result of a previous CVA would not need to see a neurologist as part of this study) and that could be linked to or may be an early indicator of polyradiculopathy/GBS, such as ascending (bilateral) sensory loss or motor weakness.
- Vital signs (arterial blood pressure, heart rate, respiratory rate, body temperature), height and weight measurements.
- ECOG performance status.
- Collection of information on disease related mutations, including FLT-3, if available.
- Bone marrow aspirate (or biopsy if aspirate unattainable):
 - Evaluation of CD25 expression on blast cells, assessed at an approved local clinical laboratory (see Inclusion Criterion 2, [Section 4.2.1](#)).
 - Confirmation of disease, as per the WHO classification of acute leukemias,³⁴ at an approved local clinical laboratory.
- [REDACTED]
- [REDACTED]

- Hematology, coagulation panel, biochemistry, and urinalysis parameters.
 - Patients with a WBC value >15,000 cells/ μ L may receive treatment with hydroxyurea and/or leukopheresis, to lower the WBC value to <15,000 cells/ μ L prior to Day 1, Cycle 1 dosing. Hydroxyurea may be used during the first cycle to control WBC count at Investigator discretion.
 - Collection of mononuclear cells (MNC) sample.
- 12-lead electrocardiogram (ECG).
- Collection of 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.

5.1.2 Day 1 (\pm 3 days) of Each Cycle

Day 1 of each cycle occurs on infusion day. The following procedures will be performed prior to ADCT-301 infusion at each cycle, unless otherwise specified. Timing for sample collections and procedures is provided in [Appendix 13.1](#).

- Serum or urine pregnancy test (women of child-bearing potential, Cycle 1 only) required if the screening pregnancy test was obtained >7 days prior to Day 1.
- Physical examination, including neurological examination and including whole-body skin assessment, unless a physical examination was performed within 3 days prior to Day 1. The examination must include a determination if the patient has had any infection. At the discretion of the investigator, evaluation of any reported infection must be conducted to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s) as specified in the exclusion criteria.
- On Day 1 of Cycle 1, vital signs are to be measured before the start of the infusion, every 30 minutes during the infusion, and at the end of infusion. If no clinically significant changes occur during this first infusion, vital sign measurements are to be obtained prior to infusion start and end of infusion for all subsequent infusions. For Cycles 1 and 2, patients will also have vital signs measured 1 hour after the end of infusion and at discharge.
Note: Timing of measurements is \pm approximately 5 minutes.
- Weight, unless an assessment was performed within 3 days prior to Day 1.
- ECOG performance status, unless an assessment was performed within 3 days prior to Day 1.
- Hematology, coagulation panel, and biochemistry parameters will be measured prior to dosing unless the last sample was collected:
 - <24 hours before the start of ADCT-301 infusion on Day 1 of Cycle 1, or
 - <72 hours before the start of ADCT-301 infusion on Day 1 of Cycle 2 and subsequent cycles.

- Sample collection for:
 - Additional renal function studies
 - UrinalysisPrior to dosing unless the last sample was collected.
 - <24 hours before the start of ADCT-301 infusion on Day 1 of Cycle 1, or
 - <72 hours before the start of ADCT-301 infusion on Day 1 of Cycle 2 and subsequent cycles.
- 12-lead ECG (Cycles 1 and 2), before the start of infusion, at end of infusion, and at 3 hours after the end of infusion ([Section 7.3.5](#)).
- Sample collection for central laboratory analysis of soluble CD25 and ADA (all cycles).
- Sample collection for central laboratory analysis of PK parameters for Q3W is before the start of the ADCT-301 infusion, at the end of the infusion, and at 1, 3, and 6 hours after the end of the ADCT-301 infusion (Cycles 1 and 2). In all subsequent cycles, samples will be collected before the start of the ADCT-301 infusion and at the end of the infusion.
- Sample collection and shipment for central laboratory analysis of peripheral WBC populations (Part 2).
- Sample collection for cytokine analysis before the start of the ADCT-301 infusion and at 6 hours after the end of the infusion in Cycles 1 and 2.
- Collection of AE information.
- Collection of concomitant medication information.
- Premedication administration, if applicable ([Section 6.2](#)).
- ADCT-301 administration.

5.1.3 Day 2 (Cycles 1 and 2)

The following procedures will be performed 24 hours after the end of infusion:

- 12-lead ECG.
- Sample collection for central laboratory analysis of PK parameters.
- Sample collection for cytokine analysis.

5.1.4 Day 3 (Cycles 1 and 2)

The following procedures will be performed 48 hours after the end of infusion:

- Sample collection for central laboratory analysis of PK parameters.
- Sample collection and shipment for central laboratory analysis of peripheral WBC populations (Part 2).

5.1.5 Day 5 (Cycles 1 and 2)

The following procedures will be performed 96 hours after the end of infusion:

- Sample collection for central laboratory analysis of PK parameters.
- Sample collection and shipment for central laboratory analysis of peripheral WBC populations (Part 2).

5.1.6 Day 8 (± 1 day) of Each Cycle

- Physical examination, including neurological examination and including whole-body skin assessment (Cycles 1 and 2). The examination must include a determination if the patient has had any infection. At the discretion of the investigator, evaluation of any reported infection must be conducted to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s) as specified in the exclusion criteria.
- Weight (Cycles 1 and 2).
- Vital signs.
- Hematology and biochemistry parameters.
- Urinalysis and sample collection for additional renal function studies.
- Sample collection for central laboratory analysis of PK (Cycles 1 and 2).
- Sample collection for central laboratory analysis of peripheral WBC populations (Part 2).
- Collection of AE information.
- Collection of concomitant medication information.

5.1.7 Day 19 (± 3 days) of Each Cycle

NOTE: If the timing of the assessments required at the Day 1 visit for the next cycle coincides with the Day 19 visit, assessments that are included at both Day 19 and Day 1 are to be performed only once.

- Physical examination, including neurological examination and including whole-body skin assessment for Cycles 1 and 2. The examination must include a determination if the patient has had any infection. At the discretion of the investigator, evaluation of any reported infection must be conducted to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s) as specified in the exclusion criteria.
- Weight and vital signs measurements (Cycles 1 and 2).
- Hematology and biochemistry parameters.
- Urinalysis and sample collection for additional renal function studies.
- Sample collection for central laboratory analysis of PK (Cycles 1 and 2).
- Sample collection for central laboratory analysis of peripheral WBC populations (Part 2).
- Collection of AE information.

- Collection of concomitant medication information.

5.1.7.1 Bone Marrow Aspirate or Biopsy

A BMA (or biopsy if aspirate unattainable) will be obtained at the Day 19 visit (± 3 days) of each cycle, beginning with Cycle 2, and repeated at each subsequent cycle, until disease progression, CR (Section 7.1), or CRi is achieved. Once CR/CRi is achieved, sampling will be repeated at least every 3 cycles, or, as clinically indicated.

A bone marrow sample (aspirate or biopsy if aspirate unattainable) will also be collected at the EOT Visit (Section 5.1.8) for those patients who have not demonstrated disease progression and if their most recent sample was obtained more than 12 (± 1) weeks prior to the EOT Visit.

Response to treatment with ADCT-301 (Section 7.1) is to be performed by an approved clinical laboratory.

5.1.8 End of Treatment Visit

The following procedures will be performed within 30 days (+ 7 days) after treatment discontinuation:

- Serum or urine pregnancy test.
- Physical examination, including neurological examination and including whole-body skin assessment. The examination must include a determination if the patient has had any infection. At the discretion of the investigator, evaluation of any reported infection must be conducted to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s) as specified in the exclusion criteria.
- Weight and vital signs measurements.
- ECOG performance status.
- Hematology, coagulation panel, and biochemistry parameters.
- Urinalysis and sample collection for assessment of additional renal function studies.
- 12-lead ECG.
- Sample collection for central laboratory assessment of PK, soluble CD25, ADA, and cytokines.
- Sample collection for central laboratory analysis of peripheral WBC populations (Part 2).
- Collection of AE information.
- Collection of concomitant medication information.
- Bone marrow sample (see Section 5.1.7.1).

5.1.9 12-Week Follow-up Visit

Each patient will have a sample taken for assessment of PK and ADA at 12 weeks (± 1 week) after their last dose of ADCT-301.

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

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

For all patients, collection of AEs and SAEs will continue for 84 days (12 weeks) after the last dose of study drug or initiation of new anti-cancer treatment (see [Section 7.3.2.2](#)).

5.1.10 Long-term Follow-up

Patients who discontinue treatment for any reason other than disease progression will continue to be followed by telephone contact approximately every 12 weeks from the last disease assessment until disease progression or initiation of new anti-cancer treatment. After documentation of disease progression or start of new anti-cancer 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.

5.2 Withdrawal of Patients from the Study

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

5.2.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from treatment at any time and for any reason, without prejudice to their future medical care. Patients may also be withdrawn by the Investigator or others at the study site.

A patient may be withdrawn from treatment 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).
- Non-compliance, including lost to follow-up.
- Pregnancy.
- Other (e.g., development of contraindications).

- The Investigator determines 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.

Note: Patient enrollment will be halted, pending a safety analysis and review with the appropriate regulatory authority(ies), if any patient in Part 1 or Part 2 experiences a CTCAE Grade 5 AE, or 2 non-hematologic CTCAE Grade 4 AEs, which are not attributable to the underlying disease, and for which relationship to ADCT-301 cannot be ruled out, within 30 days of their last dose of ADCT-301.

Note: Patients who experience a DLT during Cycle 1 are to be permanently discontinued from the study.

5.2.2 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 7.3.2.6](#)).

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 5.1.8](#)). Patients who fail to return for final assessments are to be contacted by the investigative site. Following a minimum of two 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.

5.2.3 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.

6 Study Treatments

6.1 Method of Assigning Patients to Treatment

In Part 1 (dose-escalation), patients will receive an IV infusion of ADCT-301 according to their assigned schedule.

The first patient at each new dose level must be observed for 7 days for occurrence of AEs prior to treating the second patient at that dose level. Patients will be entered sequentially to each dose level. The dose-escalation procedure is described in [Section 4.1.1](#).

In Part 2, (expansion), all patients will be assigned to the dose level of ADCT-301 identified in Part 1 by the DESC. Once the recommended Part 2 dose is determined, patients receiving lower dose levels of ADCT-301 may be offered continued treatment at the recommended dose.

6.2 Prophylactic Treatments for Hypersensitivity

If 1 patient experiences a CTCAE Grade 2 or higher infusion-related hypersensitivity reaction ([Appendix 13.2](#)) 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-301 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-301 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-301 infusion.
- For 2 days following administration of ADCT-301 on Day 1, all patients are to take dexamethasone 4 mg orally, twice per day.

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

If a patient experiences a CTCAE Grade 1 or 2 hypersensitivity reaction, the following medications (or equivalent) should be administered for 48 hours after ADCT-301 infusion:

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

Any patient who experiences a CTCAE Grade 3 or higher hypersensitivity reaction ([Appendix 13.2](#)) 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.

6.3 Treatments Administered

In Part 1 (dose-escalation), each patient will be assigned a dose level as described in [Section 4.1.1](#). In Part 2 (expansion), all patients will be assigned to the dose level identified in Part 1 by the DESC.

Patients will receive a 1-hour IV infusion of ADCT-301 on Day 1 of Cycle 1. If ADCT-301 is well tolerated after the first infusion, the infusion duration may be shortened to a 30-minute IV infusion 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 6.2](#).

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

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

However, skin rash has been reported in the ADCT-301 program, as well as with another investigational agent containing the same pyrrollobenzodiazepine warhead.²⁸ The rash has been limited to areas at risk for sun exposure; it is therefore recommended that precautions are taken to avoid prolonged exposure of skin to direct sunlight.

6.4 Dose Delays and Modifications

Patients will receive the first 2 cycles, irrespective of blood count recovery. For patients achieving a CR/CRi, the subsequent cycle would be delayed until peripheral blood count recovery (absolute neutrophil count [ANC] $>0.5 \times 10^9/L$ and/or platelets $>50 \times 10^9/L$).

The Investigator should suspend ADCT-301 dosing for up to 21 days for any patient who experiences a protocol-defined DLT during any treatment cycle. At the discretion of the Investigator, the dose may also be delayed for up to 21 days for any toxicity that does not meet DLT criteria. Resumption of dosing with ADCT-301 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-301. Following recovery to CTCAE Grade 1 or to baseline grade, treatment with ADCT-301 may resume at the Investigator's discretion.

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

Dosing frequency may be adjusted according to individual patient response as described in [Section 4.1.1](#).

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

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

Patients who experience a DLT ([Section 7.3.1.1](#)) during Cycle 1 are to be permanently withdrawn from the study. Patients who experience the following significant toxicities will be immediately and permanently withdrawn from treatment with ADCT-301:

- Any patient who experiences a CTCAE Grade 3 or higher hypersensitivity reaction, regardless of premedication, during any cycle of treatment ([Appendix 13.2](#)).
- Any patient who experiences a recurrent CTCAE Grade 3 or 4 toxicity, excluding hematological toxicity.
- Any patient who requires a dosing delay >21 consecutive days from the planned Day 1 dosing at any time during treatment (except in case of potential patient benefit, which must be approved by the Sponsor).

Neurological toxicities: dose delay/permanent discontinuation

Patients experiencing any new neurological toxicities \geq Grade 1, not explained by previous medical history, that could be linked to or may be an early indicator of polyradiculopathy/GBS, such as ascending (bilateral) sensory loss or motor weakness, need to be immediately evaluated by a neurologist and dosing of ADCT-301 needs to be delayed until polyradiculopathy/GBS is ruled out. Should further clinical, radiologic, or laboratory evidence support the diagnosis of polyradiculopathy/GBS with the level 1 of diagnostic certainty ([Appendix 13.3](#)), treatment with ADCT-301 must be stopped and patient must be permanently discontinued.

Patients with Grade \geq 3 neurologic toxicities, defined as peripheral sensory and peripherally motor neuropathies, must be permanently discontinued.

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

6.5 Study Stopping Rules

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

- Two additional patients (from date of December 14, 2017) develop polyradiculopathy/GBS (Level 1 of diagnostic certainty; [Appendix 13.3](#)). Continuation of patients who have shown clinical benefit will be discussed with the relevant regulatory authority(ies) if this stopping rule is applied.
- \geq 30% of patients experience a specific Grade 4 or higher non-hematologic treatment-emergent AE.

Furthermore, patient enrollment will be halted, pending a safety analysis and review with the relevant regulatory authority(ies):

- if any patient in Part 1 or Part 2 experiences a CTCAE Grade 5 AE, or 2 non-hematologic CTCAE Grade 4 AEs, which is not attributable to the underlying disease, and for which relationship to ADCT-301 cannot be ruled out, within 30 days of their last dose of ADCT-301.
- in the event of another single case of GBS. Patients currently on trial having clinical benefit or not yet having reached first bone marrow assessment can continue on study once informed and they consent to continue treatment.

6.6 Identity of Investigational Product

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

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

6.6.1 ADCT-301 Drug Product

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

6.7 Management of Clinical Supplies

6.7.1 Study Drug Packaging and Storage

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

All study drugs must be stored in a secure area (e.g., a locked cabinet). ADCT-301 should be protected from light and stored frozen (-65°C or below). ADCT-301 should be thawed under ambient conditions.

6.7.2 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-301 will be removed from the vial with a syringe and diluted into a 50 mL IV bag containing 5% dextrose in water (D5W). The amount of the product to be diluted will depend on the dose level and the body mass of the patient. Once the ADCT-301 has been transferred, the bag should be mixed to ensure homogeneity of the dosing solution. The contents of the IV bag will then be administered to the patient with a dosing pump per institutional guidelines for intravenous fluid (IVF) administration.

Additional instructions regarding study drug handling, storage, and preparation are included in the Pharmacy Manual.

6.7.3 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.

6.8 Overdose Management

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

6.9 Treatment Compliance

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

6.10 Concomitant Treatment

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

6.10.1 Prohibited During Study

- Other anti-cancer therapy, with the exception of hormonal therapy for maintenance treatment of breast and prostate cancer.
- Hydroxyurea is not permitted after Cycle 1 unless approved by the Sponsor.
- Other investigational agents.
- Chronic treatment with corticosteroids (prednisone ≥ 12.5 mg/day or dexamethasone ≥ 2 mg/day, excluding inhaled steroids).
- Live vaccines.

6.10.2 Permitted During Study

After confirmation and documentation of eligibility, supportive care treatments (transfusions, etc.) can be prescribed as medically appropriate. Hematopoietic growth factors are permitted as per the American Society of Clinical Oncology guidelines;³¹ however, prophylactic use of growth factors is not allowed during the first treatment cycle.

Patients with a WBC value $>15,000$ cells/ μL at the Screening Visit may receive hydroxyurea prior to and during the first cycle of treatment and/or leukopheresis to lower the WBC value to $<15,000$ cells/ μL prior to study drug administration on Day 1, Cycle 1 ([Section 5.1.1](#)).

If CTCAE 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 ([Section 6.2](#)).

Concomitant steroid use is permitted as follows:

- Replacement doses of steroids for patients with adrenal insufficiency.
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)
- Intrathecal medication for CNS prophylaxis (not for active disease) per institutional standard of care practices.
- Prophylactic treatment with dexamethasone as follows may be instituted by the DESC based on emerging safety and PK profile:
 - Dexamethasone 4 mg oral BID the day before investigational product (IP) administration, the day of IP administration, and the day after IP administration (Week 1/Day 1 of each cycle only, regardless of treatment schedule).
 - A 2-day course of dexamethasone 4 mg PO BID will be given (Week 1/Days 1 and 2 of each cycle). If possible, the first dose should be given at least 2 hours prior to IP administration.

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

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

It is recommended starting management of polyradiculopathy/GBS with either IVIg 0.4 g/kg/day for 5 days or plasma exchange (PLEX) once diagnosis of polyradiculopathy/GBS has been considered by a neurologist; this would be at CTCAE Grade 2 symptoms for neuropathy or Score 1 as per GBS disability scale ([Appendix 13.4](#)).

Diagnostic workup should include:

- Neurology consultation
- MRI spine with and without contrast to rule out compressive lesion and evaluate for nerve root enhancement or thickening
- Electrodiagnostic studies (nerve conduction studies)
- Pulmonary function tests
- Lumbar puncture: CSF typically has albuminocytologic dissociation with protein elevation disproportionate to WBC—although note that CSF WBC are often elevated in GBS associated with immune checkpoint inhibitors
- Serum antibody testing for GBS (ganglioside antibodies) when possible

Management includes:

- IVIg or PLEX as above
- If IVIg and/or PLEX do not result in improvement, consider using steroids (Gu 2017)¹⁵
- Admission to inpatient unit with capability for rapid transfer to ICU-level monitoring
- Frequent focused neurological examination (at least twice daily)
- Frequent pulmonary function monitoring
- Monitoring for autonomic dysfunction
- Non-opioid management of neuropathic pain
- Treatment of constipation/ileus
- Anticoagulation
- Physical therapy

7 Study Assessments and Procedures

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

7.1 Efficacy Assessments

Assessment of response to treatment with ADCT-301 will be based on bone marrow samples (aspirate or biopsy if aspirate unattainable). Bone marrow samples will be obtained as described in [Section 5.1.7.1](#) and [Table 1](#) and [Table 3](#) for the Q3W and QW dosing schedules, respectively.

The activity of ADCT-301 will be evaluated based on the Investigator's evaluation of the patient's response to ADCT-301 as CR, CRi, PR, PD or NR. ^{8,11}

- Complete response is defined as achieving each of the following:
 - Bone marrow differential showing $\leq 5\%$ blast cells and absence of blast cells with Auer rods.
 - Absolute neutrophil count $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$.
 - Absence of extramedullary disease.
 - Patient is independent of red blood cell (RBC) transfusions.
- Complete response with incomplete blood count recovery is defined as achieving all CR criteria except that values for ANC may be $< 1.0 \times 10^9/L$ and/or values for platelets may be $< 100 \times 10^9/L$.
- Partial response is defined as achieving each of the following:
 - Absolute neutrophil count $\geq 1.0 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$.
 - Bone marrow differential showing a $\geq 50\%$ decrease from baseline in the percentage of bone marrow blast cells to a level $> 5\%$ and $\leq 25\%$,
or
bone marrow differential showing $< 5\%$ blast cells and presence of Auer rods.
- No response is defined as not achieving CR, CRi, or PR.
- Progressive disease is defined as:
 - For patients with CR or CRi, the first date of reappearance of blast cells in bone marrow and/or peripheral blood to a level $\geq 5\%$, or development of extramedullary disease.
 - For patients with PR, the first date of an increase in blast cells in bone marrow and/or peripheral blood such that the patient does not continue to meet the criteria for PR.

As defined in [Section 8.6.2](#), DOR and ORR will be defined among responders (CR, CRi, PR); OS and PFS will also be determined.

[REDACTED]

7.2.1 Pharmacokinetic Profile Assessments

The PK profile of ADCT-301 (total antibody; $DAR \geq 0$), PBD-conjugated antibody ($DAR \geq 1$), and free warhead SG3199 will be assessed.

Additional PK, ADA, cytokines, and sCD25 blood samples will be collected, at the discretion of the Investigator, during any visit where toxicity is observed. A PK, ADA, cytokines, and sCD25 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 the actual collection times are recorded.

The PK profile will include determination of standard PK parameters: C_{max} , T_{max} , area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_{0-last}), area under the concentration-time curve from time zero to the end of the dosing interval ($AUC_{0-\tau}$), area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), accumulation index (AI), volume of distribution at steady-state (V_{ss}), mean residence time (MRT), and terminal elimination phase rate constant (λ_z), $t_{1/2}$, C_L , and V_z .

[REDACTED]

7.3 Safety and Tolerability Assessments

Safety will be assessed based on AEs, SAEs, treatment discontinuations due to AEs, DLTs, measurements of cytokines in serum, periodic 12-lead ECG recordings, physical examinations, vital signs measurements, ECOG performance status, and hematology, biochemistry, coagulation panel, pregnancy testing (for women of child-bearing potential) and urinalysis test results. Adverse events will be graded according to CTCAE Version 4.0. A schedule of the safety assessments is provided in [Appendix 13.2 \(Table 6\)](#).

7.3.1 Dose-Limiting Toxicities and Dose-Escalation Scheme

7.3.1.1 Definition of Dose-Limiting Toxicities

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

- A hematologic DLT is defined as:
 - Grade 3 or higher event of neutropenia and/or thrombocytopenia or a Grade 4 anemia, with a hypocellular bone marrow lasting for 6 weeks or more after the start of a cycle, in the absence of residual leukemia (i.e., with <5% blasts). In case of a normocellular bone marrow with <5% blasts, 8 weeks with \geq Grade 3 pancytopenia will be considered a DLT.
- 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 AEs (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 3 or higher skin ulceration.
 - Peripheral sensory or motor neuropathy \geq Grade 2.

Note: The DLT observation period for dose-escalation will be 1 cycle. Patients who experience a DLT during Cycle 1 are to be permanently discontinued from the study.

7.3.1.2 Safety Oversight by the Dose-Escalation Steering Committee

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

Membership of the DESC will include:

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

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

- Monitor the safety of the study and review its progress at monthly intervals or more frequent intervals as required.
- 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.
- Determine if it is appropriate to maintain a QW schedule, revert to a Q3W schedule, or test other dosing regimens.

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.

7.3.2 Adverse Events

7.3.2.1 Definitions of Adverse Events

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

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

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

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

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

7.3.2.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the patient signs the ICF up to 84 days (12 weeks) after the last dose of study drug, or initiation of new anti-cancer treatment.

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

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

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

7.3.2.3 Reporting Adverse Events

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

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

Pharmacovigilance Department



7.3.2.4 Assessment of Severity

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

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

a Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

7.3.2.5 Assessment of Causality

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

All AEs, regardless of assessment of causality, are reported in the eCRF.

All SAEs considered at least possibly related to the study drug will be considered unexpected; and therefore, reported as suspected unexpected serious adverse reactions (SUSARs).

7.3.2.6 Follow-Up of Patients Reporting Adverse Events

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

7.3.3 Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical study Pregnancy Report Form. To ensure patient safety, each pregnancy must be reported as described for reported AEs in [Section 7.3.2.3](#), upon learning of its occurrence. The pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. The outcome of the pregnancy will be reported on the Pregnancy Outcome Form. Spontaneous miscarriages must be reported as an SAE.

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

7.3.4 Clinical Laboratory Analyses

Samples will be collected at the time points specified in [Appendix 13.1](#).

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

7.3.4.1 Hematology

The complete blood count (CBC) includes WBC with 5-part differential, platelet count, hemoglobin, hematocrit, and ANC. Peripheral blasts will be included in the hematology analysis for Part 2 only. If the WBC value is $<400 \times 10^6/L$, a differential is not required. The coagulation panel includes prothrombin time (PT), International Normalized Ratio (INR), and partial thromboplastin time (PTT). Patients taking coumarin-derivative anticoagulants should be monitored closely and their anticoagulant dose adjusted as needed.

7.3.4.2 Biochemistry

Tests for clinical biochemistry include ALT, AST, 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 include creatinine clearance⁹..

7.3.4.3 Urinalysis

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

7.3.4.4 Additional Renal Function Studies

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

7.3.4.5 Additional Microbiological Serological studies

Patients will be regularly examined and asked whether they have been suffering from an infection during their participation in the trial. If there is a reasonable suspicion that such infection could have been caused by one of the pathogens listed below, appropriate microbiological workup must be conducted. Should such workup indicate that infection was indeed caused by one of those microorganisms, re-dosing must be delayed so that there is at least a four-week window between symptom resolution and the next dose of ADCT-301.

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

7.3.5 Electrocardiograms

On Day 1 of Cycles 1 and 2, a 12-lead ECG is to be performed before the start of the ADCT-301 infusion, within 30 minutes of the end of infusion, and 3 (± 30 minutes) and 24 (± 2.4) hours after the end of infusion. On Day 1 of Cycle 3 and subsequent cycles, a 12-lead ECG is to be performed before the start of ADCT-301 infusion.

Any abnormalities, including those that worsen from baseline, believed to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs or SAEs.

Measurement of the QTc interval may be obtained according to the formula used by the institution; however, the Fridericia formula is preferred.¹² The same formula used to confirm eligibility must be applied within a patient for the duration of the study.

7.3.6 Physical Examination

Physical examinations will include a complete review of body systems, including whole-body skin assessment. Whole-body skin assessment does not have to be performed by a dermatologist. However, any unexplained lesion is to be referred to a dermatologist for further evaluation and biopsy if clinically warranted. Physical examination will also include a neurological examination of strength, sensation, and deep tendon reflexes; unexpected findings will be referred to a neurologist for further evaluation. Height will be measured at the Screening Visit (Day -28 to -1) and weight will be assessed before treatment as follows:

Every 3-Week Schedule: Day 1 of each cycle, Days 8 and 19 of Cycles 1 and 2, and at the EOT Visit.

Weekly Schedule: Days 1, 8, 15 of each cycle and at the EOT Visit.

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

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

7.3.7 Vital Sign Measurements

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

7.3.8 Eastern Cooperative Oncology Group Performance Status

The patient's performance status will be assessed according to the time points in the schedule of events ([Appendix 13.1](#)) using the ECOG performance status grades below:²⁶

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

7.4 Sample Handling, Storage and Shipment

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

During the study, whole blood samples will be collected for PK, ADA, cytokines, CD25 expression, PD (soluble CD25 [sCD25], analysis of peripheral WBC populations), CD34 expression (and other CD markers), and safety analyses (clinical chemistry, cytokine and hematology). MNCs isolated from BMA and MNCs isolated from whole blood samples will be collected for screening and disease assessment.

For PK, ADA, cytokines, sCD25 and cytokine, whole blood samples are to be collected and processed on site. The resulting serum samples should be aliquoted and stored until shipment. Each sample must be clearly labeled with the following information: study number, study center number, patient number, tube identification, and the sample collection time point (by day and hour), when necessary.

The central laboratory samples are to be packed in sufficient dry ice and shipped from the study center to the central laboratory. Where possible, samples should be stored at -70°C or below. Samples should be shipped according to the sample shipment schedule provided in Laboratory Manual. [REDACTED]

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

For the analysis of peripheral WBC populations, whole blood is to be collected and shipped, as per the Central Laboratory Manual, directly to the testing central laboratory for immediate processing.

Bone marrow samples and whole blood samples for Screening and disease assessment are to be taken and processed on site according to local clinical procedures. At Screening, any remaining sample material is then to be processed and frozen according to the Laboratory Manual. The resulting MNC cell preparation should be transferred as frozen samples (-70°C or below) to the testing central laboratory.

8 Statistical and Analytical Plan

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

8.1 Safety Endpoints

Safety will be assessed based on AEs, SAEs, treatment discontinuations due to AEs, DLTs, measurements of cytokines in serum, 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.

8.2 Endpoints

8.2.1 Primary Endpoints

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

- Assessment of DLTs (Section 7.3.1.1) and determination of the MTD (Section 4.1.1) for ADCT-301 during Part 1.
- Determination of the recommended dose of ADCT-301 for Part 2 by the DESC.
- Assessment of safety parameters in Parts 1 and Part 2 (Section 8.6.1), schedule of safety assessments in the Schedule of Procedures for the Q3W and QW dosing schedules in Table 1 and Table 3, respectively (Appendix 13.1).

8.2.2 Secondary Endpoints

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

- Determination of DOR, ORR, OS, and PFS (Section 8.6.2).
- Determination of PK parameters (Section 7.2) for ADCT-301 (total antibody; $DAR \geq 0$), PBD-conjugated antibody ($DAR \geq 1$), and free warhead SG3199.
- Measurement of ADAs to ADCT-301 before, during, and after treatment with ADCT-301 (Section 8.6.3).

[REDACTED]

[REDACTED]

8.3 Sample Size Calculations

This is a Phase 1 study with a maximum total sample size of 80 patients. It is expected that Part 1 will enroll up to 50 patients, and Part 2 will enroll up to 30 patients.

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

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

8.4 Analysis Sets

Six 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 from the study during the first 21-day cycle without experiencing a DLT.
- The Efficacy analysis set will consist of all patients with valid baseline data who receive at least 2 doses of study drug, or who have documented progression of disease at any time after the first dose of study drug.
- The PK analysis set will consist of all patients who receive study drug and have sufficient concentration data for PK analysis.
- The PD analysis set will consist of all patients who receive study drug and have sufficient data available for analysis.

8.5 Description of Subgroups to be Analyzed

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

8.6 Statistical Analysis Methodology

8.6.1 Safety Analyses

8.6.1.1 Analyses of Adverse Events

An AE will be considered to be a TEAE if it begins or worsens on or after the patient's first study medication dose date and before the last dose date up to 84 days (12 weeks).

Planned summaries of TEAEs will be detailed in the SAP and will include:

- All TEAEs.
- All serious TEAEs.
- All treatment-related TEAEs.
- All treatment-related serious TEAEs.
- All TEAEs resulting in study drug discontinuation.
- All DLTs.

Other AE analyses of interest will be specified in the SAP.

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

8.6.1.2 Clinical Laboratory Results

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

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

8.6.1.3 Additional Safety Assessments

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

8.6.2 Efficacy Analysis

Determination of DOR and ORR will be based on the Investigator's evaluation of the patient's response to ADCT-301 (Section 7.1). Overall survival and PFS will also be determined.

8.6.2.1 Duration of Response

Duration of response will be defined among responders (CR, CRi, 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 is defined for patients with CR or CRi as the first date of reappearance of blast cells in bone marrow and/or peripheral blood to a level $\geq 5\%$, or development of extramedullary disease. In patients with PR, it is defined as the first date of an increase in blast cells in bone marrow and/or peripheral blood such that the patient does not continue to meet the criteria for PR (Section 7.1). 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 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. Further details on censoring rules will be outlined in the SAP.

8.6.2.2 Overall Response Rate

The ORR is defined as the proportion of patients with a best overall response of CR, CRi, or PR at the time each patient discontinues treatment with ADCT-301.

8.6.2.3 Overall Survival

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

8.6.2.4 Progression-Free Survival

Progression-free survival is defined as the time from first dose of study drug until the first date of either disease progression or death due to any cause. The date of disease progression is defined for patients with CR or CRi as the first date of reappearance of blast cells in bone marrow and/or peripheral blood to a level $\geq 5\%$, or development of extramedullary disease. In patients with PR, PFS is defined as the first date of an increase in blast cells in bone marrow and/or peripheral blood such that the patient does not continue to meet the criteria for PR (Section 7.1).

Patients without disease progression or patients who died after an extended loss to follow-up will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up. Further details on censoring rules will be outlined in the SAP.

[REDACTED]

8.6.4 Study Drug Exposure

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

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

8.7 Data Quality Assurance

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

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

The clinical research associate will review eCRFs for accuracy and completeness by remote monitoring, during on-site monitoring visits, and after transmission to the Sponsor;

any discrepancies will be resolved with the Investigator or designee, as appropriate. After entry of the data into the clinical study database they will be verified for accuracy.

8.7.1 Data Management

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

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

Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse events will be coded using the Medical Dictionary for Regulatory Activities Version 18.0. Concomitant medications will be coded using WHO Drug Dictionary 01 June 2015.

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

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Conference on Harmonisation (ICH) guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study 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 ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted. The Investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

9.3 Patient Information and Consent

A written ICF, in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50, 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 study 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 active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study and [REDACTED]

10 Investigator's Obligations

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

10.1 Confidentiality

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

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

10.2 Financial Disclosure and Obligations

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

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

10.3 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR 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 or equivalent, where applicable.

- Curriculum vitae for the Investigator and each sub-Investigator listed on Form FDA 1572 or equivalent, where applicable.
- 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.

10.4 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

10.5 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs 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 SUSARs) is reported to the FDA and competent authorities of EU Member States, and to the IEC, in accordance with current legislation (US 21CFR.316 and EU Directive 2001/20/EC).

10.7 Investigator's Final Report

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

10.8 Records Retention

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

10.9 Publications

Following completion of the study, the results from the study may be reported at scientific meetings and/or published in scientific journals. The Sponsor will coordinate these activities and will work with the Investigator(s) to determine how the meeting abstracts, presentations and/or manuscripts are written and edited, the number and order of authors, the meeting and/or journal to which it will be submitted, and other related activities. The Sponsor acknowledges the right of the Investigator(s) to publish the results of this study after the entire study has completed, but also reserves the right to a 30-day window to review the publication for regulatory compliance as well as for protection of its intellectual property.

11 Study Management

11.1 Monitoring

11.1.1 Monitoring of the Study

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

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

11.1.2 Inspection of Records

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

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

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

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

11.2.2 Protocol Deviations

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

11.3 Study Termination

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

The end of the study is defined as the date on which the last patient completes the last EOT Visit to the study site.

11.4 Final Report

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

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

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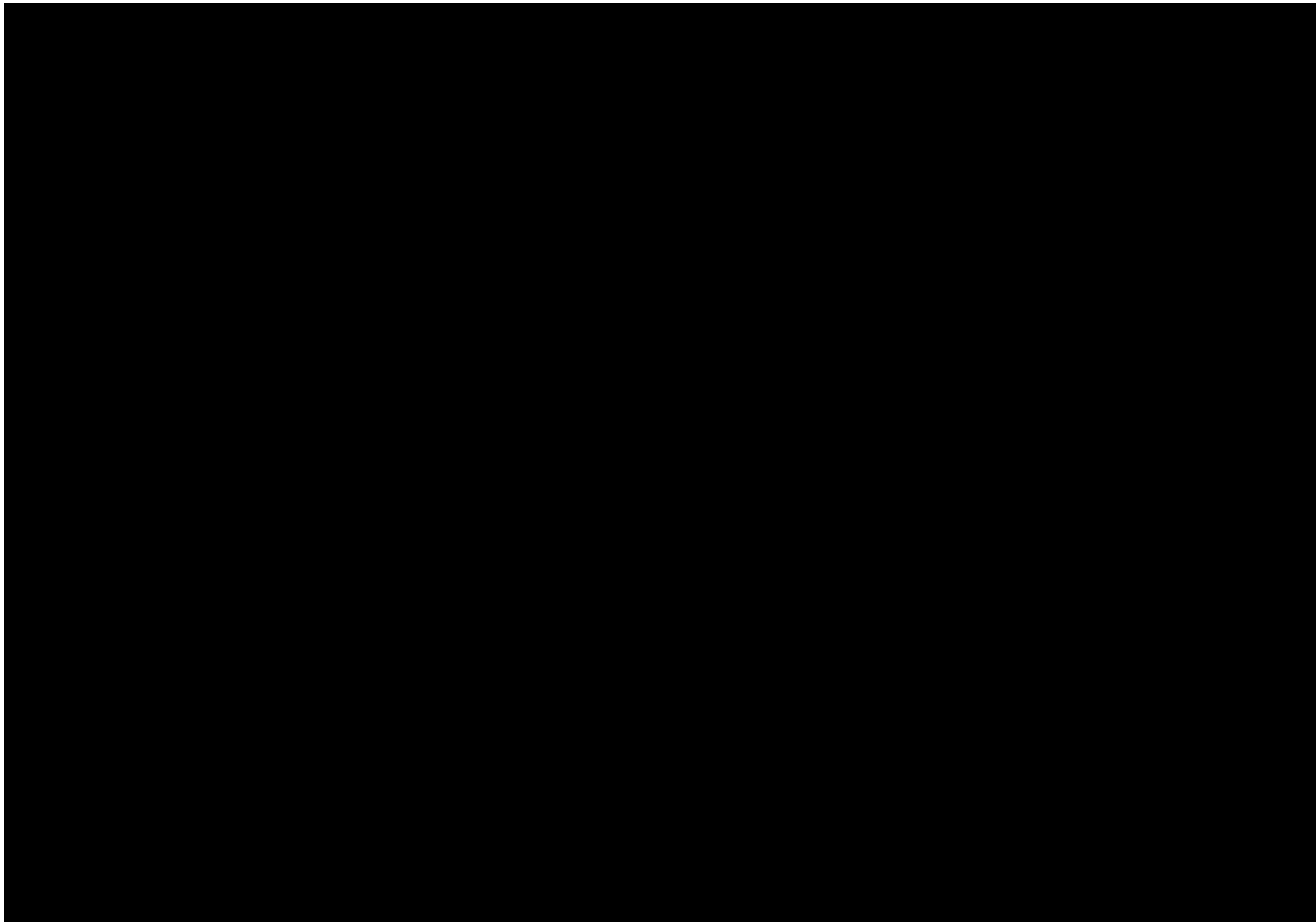
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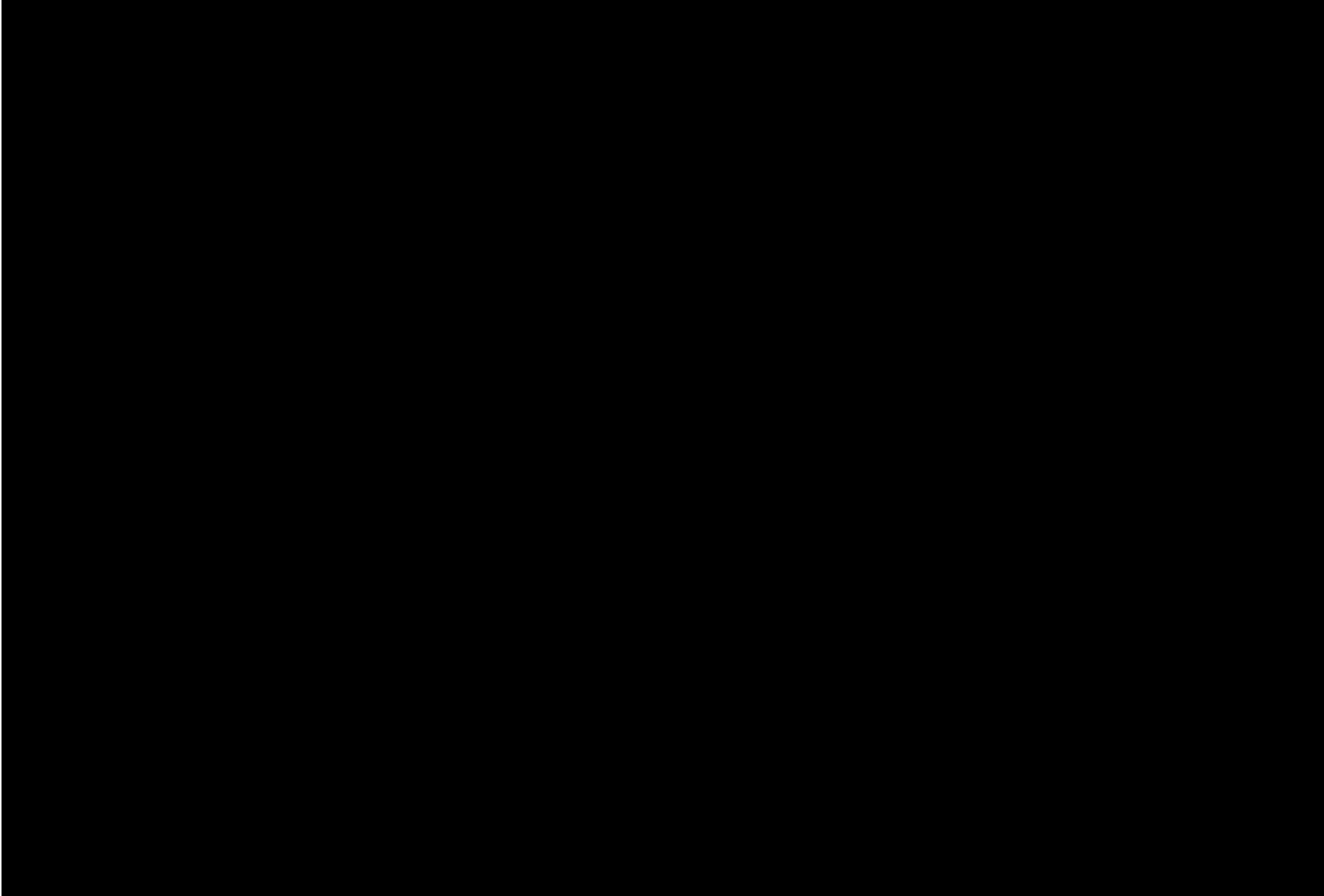
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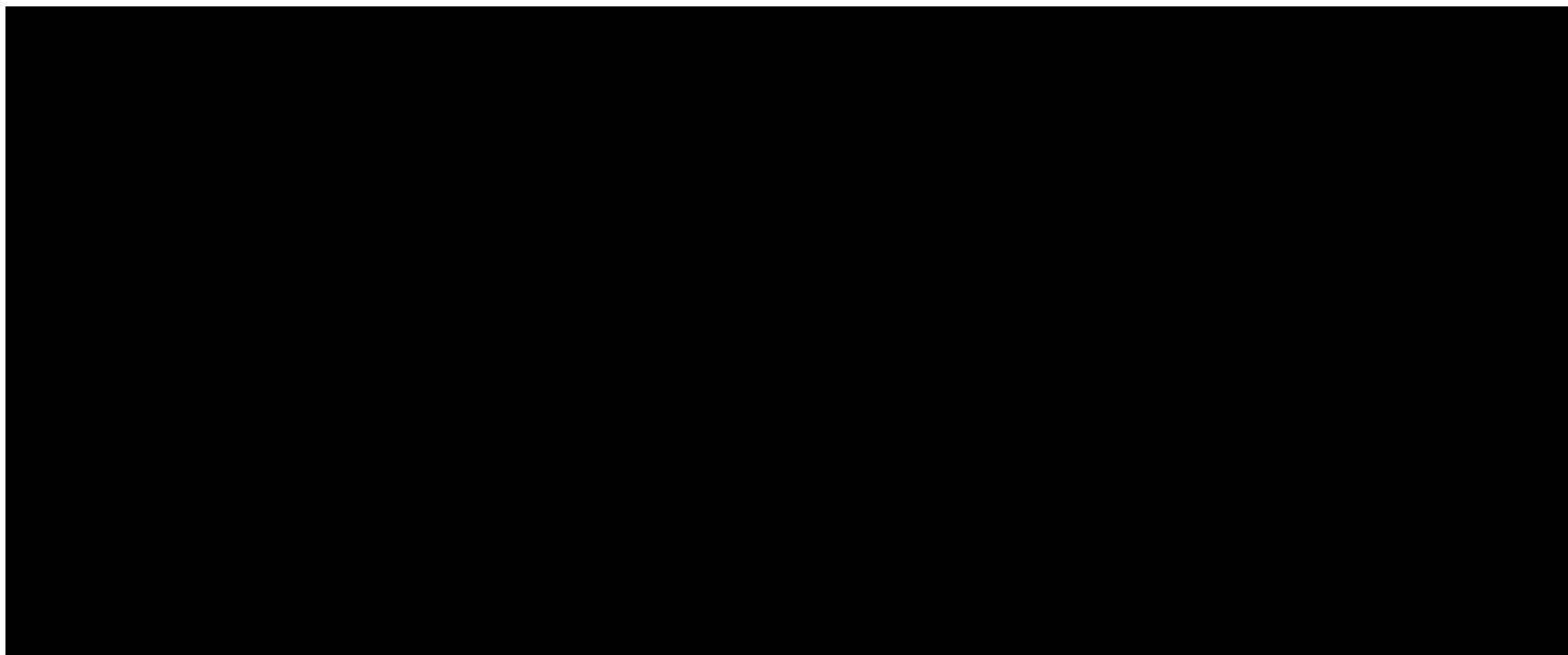
13 Appendices

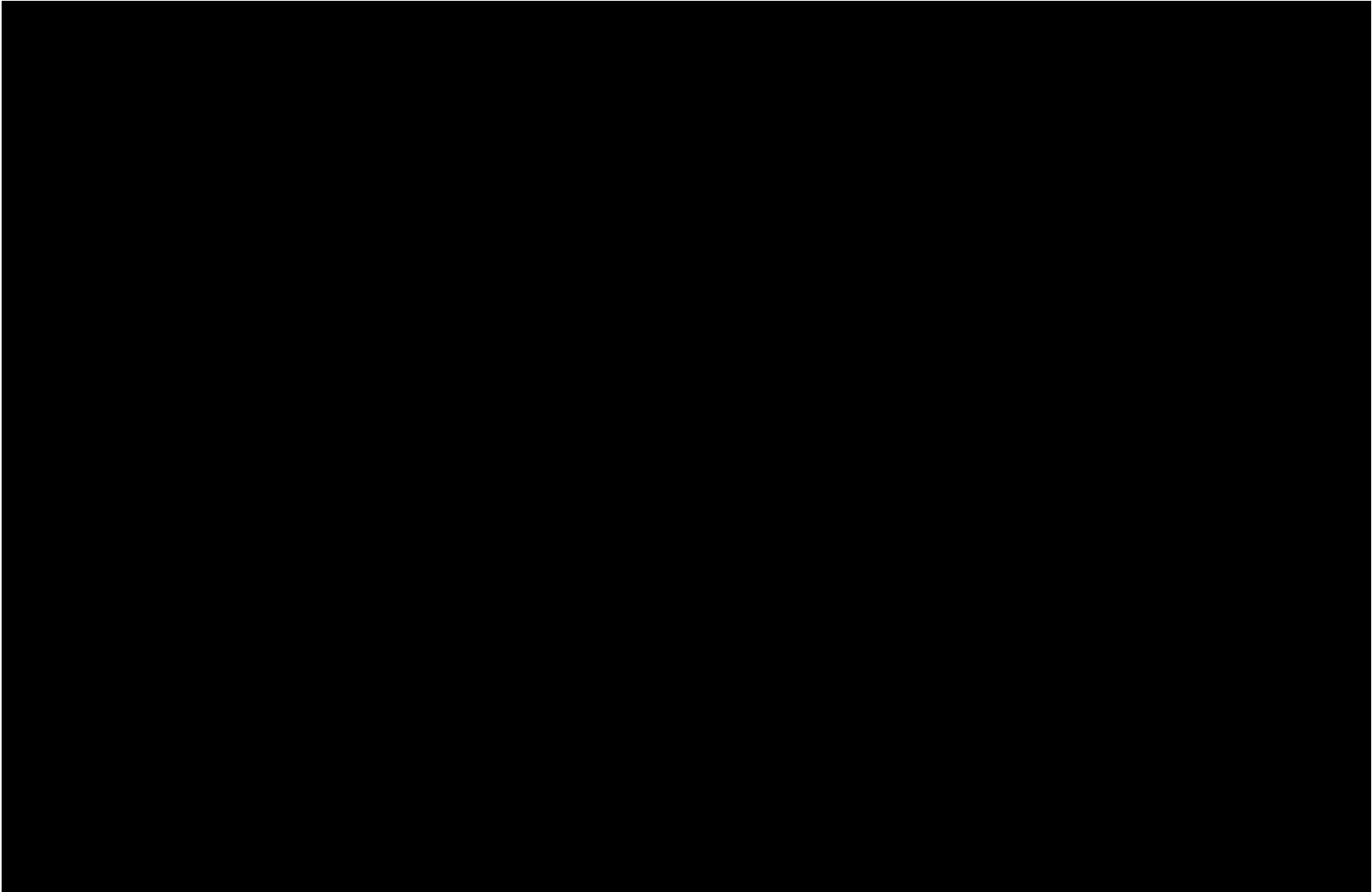
13.1 Appendix: Schedule of Events

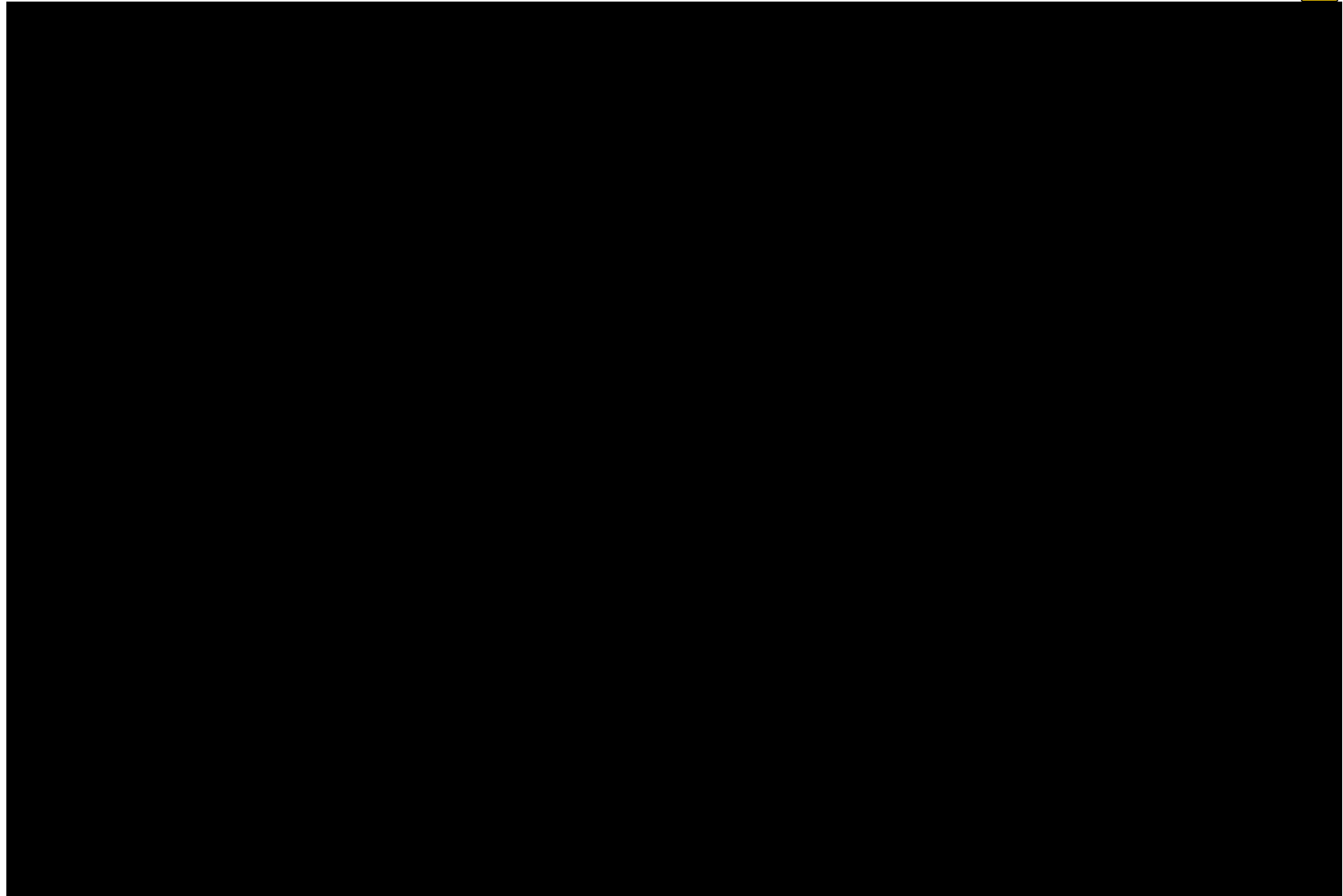
The Schedule of Procedures for the Q3W and QW dosing schedules are shown in [Table 1](#) and [Table 3](#), respectively. Timings for sample collections for assessment of PK, PD, [REDACTED], and other parameters for the Q3W dosing schedule are shown in [Table 2](#), and Cycle 1 and Cycle 2+ of the QW dosing schedule in [Table 4](#) and [Table 5](#), respectively.

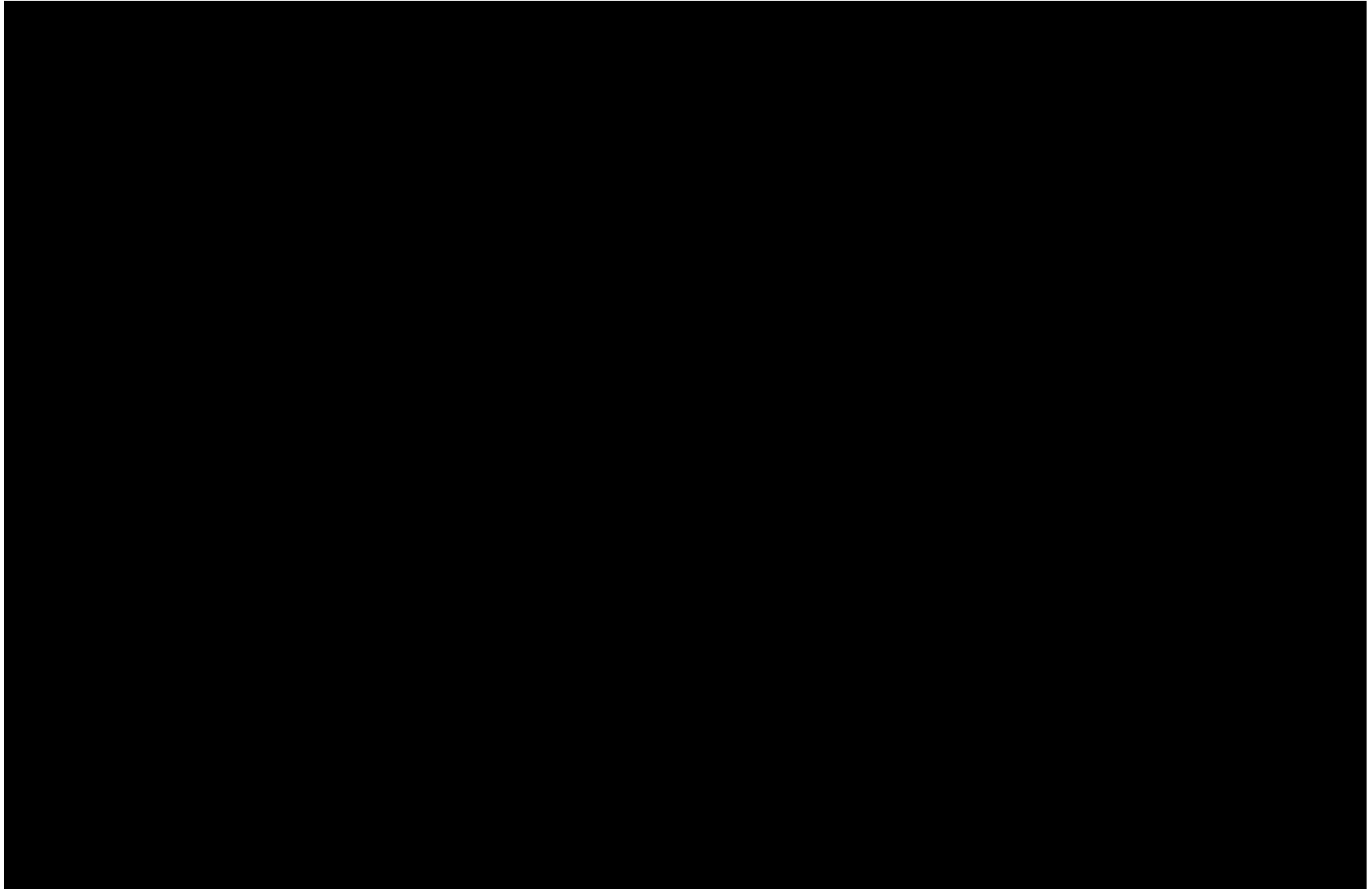


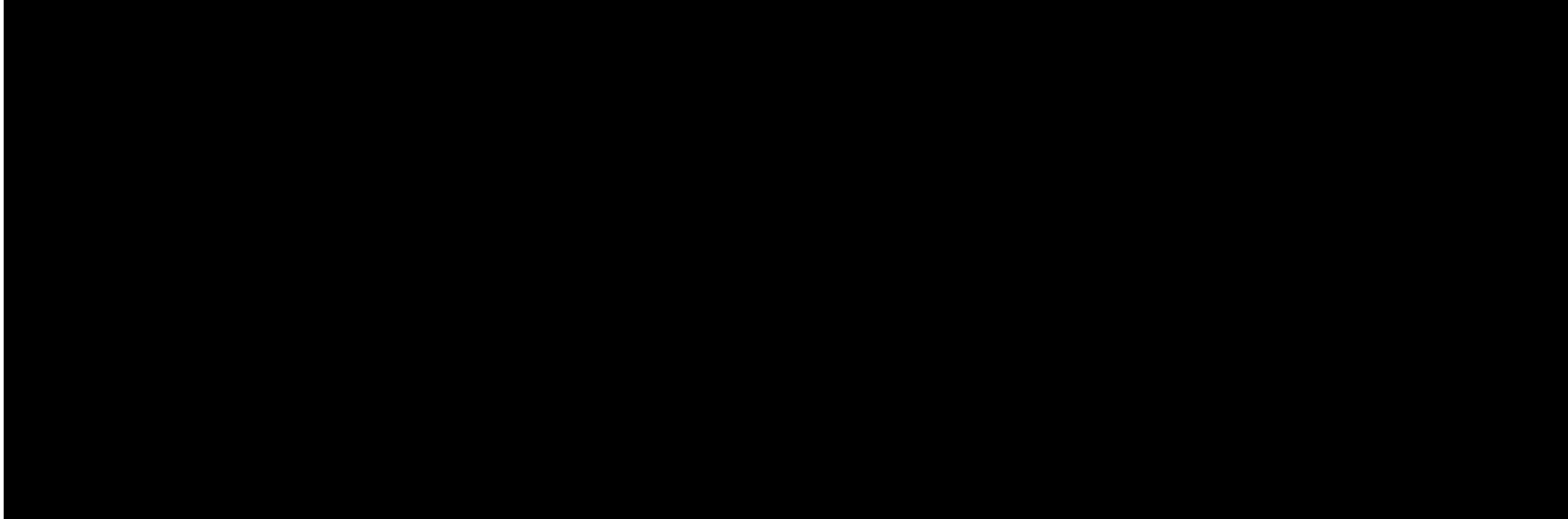


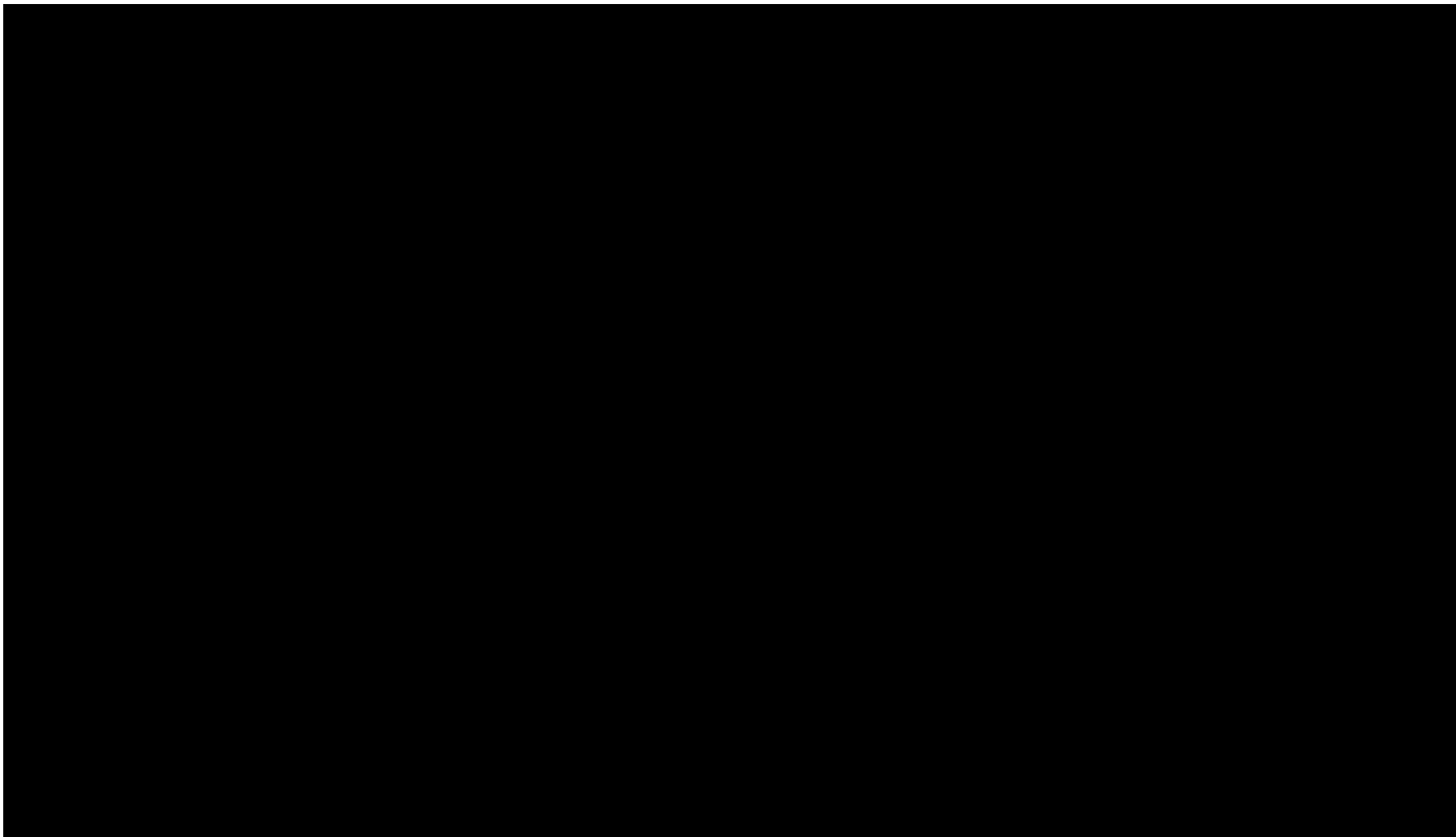


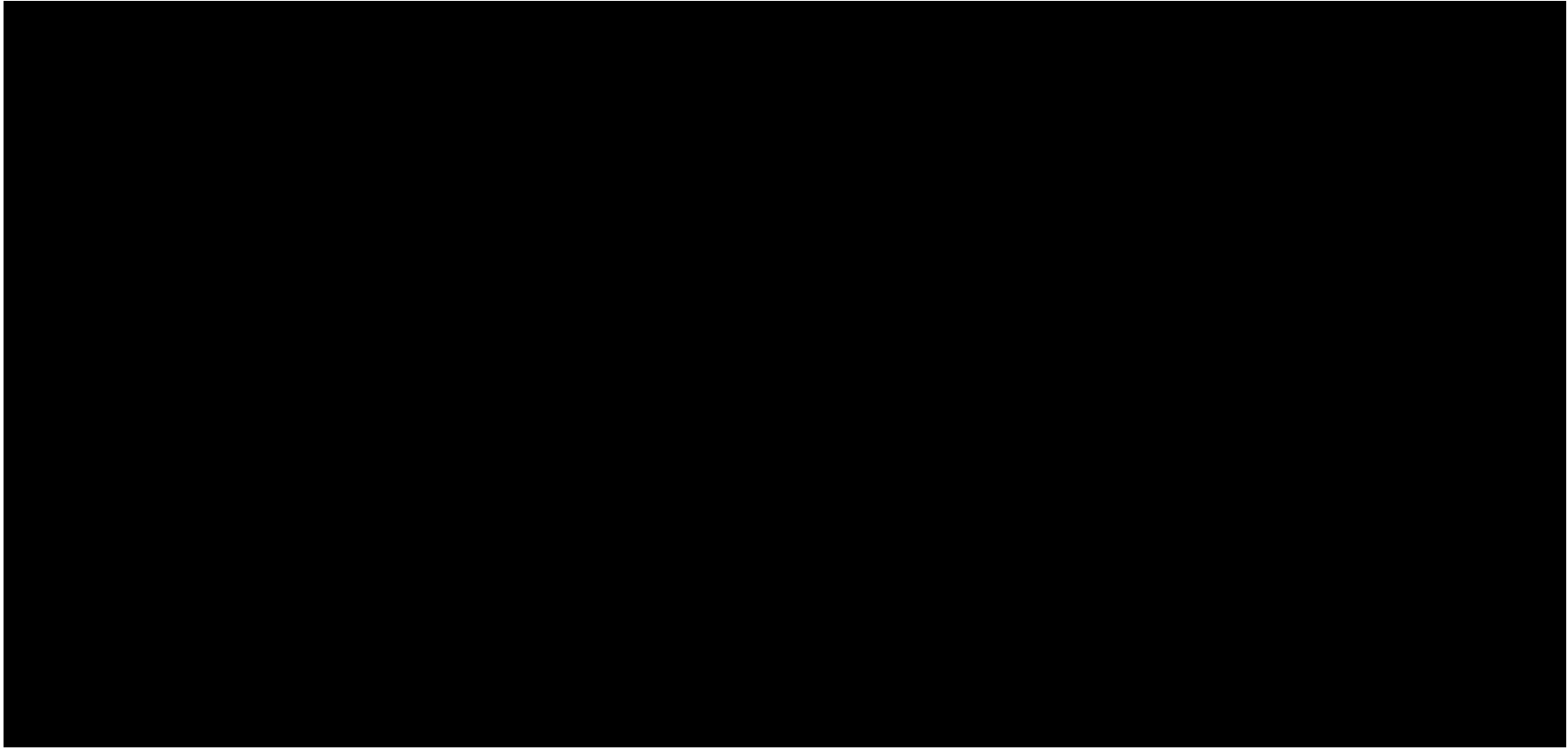












13.2 Appendix: CTCAE Immune System Hypersensitivity Grades

Table 6: 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 medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or intravenous fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately 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	Asymptomatic or mild symptoms;	Moderate; minimal, local	Severe or medically	Life-threatening	Death

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
disorders - Other, specify	clinical or diagnostic observations only; intervention not indicated	or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	consequences; urgent intervention indicated	

Abbreviations: **ADL**, Activities of daily living; **NSAIDs**, non-steroidal anti-inflammatory drugs.

* Adapted from CTCAE V4.0 – June 14, 2010, Immune system disorders.

13.3 Appendix: Clinical case definitions: Level 1 of diagnostic certainty for Guillain-Barré syndrome

- Bilateral AND flaccid weakness of the limbs^{1, 2, 3}
AND
- Decreased or absent deep tendon reflexes in weak limbs⁴
AND
- Monophasic illness pattern⁵ AND interval between onset and nadir of weakness between 12 h and 28 days AND subsequent clinical plateau⁶
AND
- Electrophysiologic findings consistent with GBS⁷
AND
- Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/ μ L)⁸
AND
- Absence of an identified alternative diagnosis for weakness⁹.

Reference: [Sejvar 2011](#)

¹ Weakness is usually, but not always, symmetric in nature, and usually has a pattern of progression from legs to arms (ascending). However, other patterns of progression may occur (e.g., beginning in the arms). The degree of weakness can range from mild to moderate to severe, i.e., complete paralysis.

² Respiratory or cranial nerve-innervated muscles may also be involved.

³ It is important that strength be assessed in a manner that takes into account subject age, sex, and level of functioning.

⁴ Decreased or absent tendon reflexes may also be seen in limbs without weakness. However, to meet case definition criteria, decreased or absent tendon reflexes must be observed in weak limbs.

⁵ Fluctuations in level of weakness, before reaching nadir, or during the plateau or improvement phases, occur in some cases, usually associated with the use of disease-modifying therapies. Such fluctuations usually occur within the first 9 weeks after onset and are followed by eventual improvement.

⁶ The eventual outcome is either stabilization at nadir OR subsequent improvement OR death.

⁷ Electrophysiologic patterns consistent with polyneuropathy of the types described for GBS. Electrophysiologic studies performed sooner than 7 days after weakness onset may be normal and should thus be repeated at a later time if possible, and “normal” studies may occur in otherwise typical cases of GBS. However, cases with persistently “normal” studies will not meet Level 1 criteria.

⁸ CSF (cerebrospinal fluid) protein concentrations should be elevated above what is considered normal reference values for the testing laboratory. CSF may be “normal” in otherwise typical cases of GBS; this is particularly true within the first week of illness. However, cases with persistently “normal” CSF, or CSF with ≥ 50 WBC, will not meet Level 1 criteria.

⁹ If an alternative diagnosis explaining flaccid weakness/paralysis is present a diagnosis of Guillain-Barré syndrome is excluded. However, in many, if not most cases, a comprehensive documentation of testing for various other etiologies will either be incomplete or unavailable. These case definitions are provided to give guidance in the absence of detailed information on investigations for alternative etiologies of flaccid paralysis.

13.4 Appendix: Guillain–Barré Syndrome Disability Scale

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

Reference: [Sejvar 2011](#)

Clinical Protocol Amendment Summary of Changes

A Phase 1, Open-label, Dose-escalation, Multicenter Study to Evaluate the Tolerability, Safety, Pharmacokinetics, and Activity of ADCT-301 in Patients with Relapsed or Refractory CD25-positive Acute Myeloid Leukemia or CD25-positive Acute Lymphoblastic Leukemia

The basis for Protocol Amendment 5 (19 January 2018) is the reported cases of Guillain-Barré syndrome (GBS) and polyradiculopathy from patients treated with ADCT-301.

Inclusion and exclusion criteria have been modified taking into account possible predisposing or potential mitigating factors that may contribute to the risk of developing GBS. Detailed safety monitoring specific for neurological and immune-related events have been added, as well as requiring a neurological examination as part of the physical examination. Treatment discontinuation and study stopping rules have also been modified.

Summary of Substantial Changes:

- Specific study stopping rules for fertility have been implemented for the remaining dose escalation portion of the study in Section 4.1.1, reducing the highest allowed dose for the study to 150 µg/kg every three weeks (50 µg/kg every week).
- Exclusion criteria have been expanded to exclude polyradiculopathy (inclusive of Guillain-Barré syndrome (GBS), which was already an exclusion for the study) and to provide more explicit restriction for entry of patients with a history of recent infection caused by a pathogen that may be associated with neurologic and immune-related disease(s): HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, Campylobacter jejuni, or enterovirus D68; Section 4.2.2.
- A neurological examination has been added as part of each complete physical examination, to include strength, sensation and deep-tendon reflexes throughout; Sections 5 and 7.3.6.
- Requirements for physical examination have been expanded to mandate assessment for any infection and evaluation of such to rule out infection with a microorganism that may be associated with autoimmune or neurological disease(s) as specified in the exclusion criteria; Sections 5 and 7.3.6.

As part of evaluation for any infection, additional microbiological serological studies have been specified if there is suspicion that such infection could have been caused by HSV1, HSV2, VZV, EBV, CMV, measles, Influenza A, Zika virus, Chikungunya virus, mycoplasma pneumonia, Campylobacter jejuni, or enterovirus D68.

Should such workup indicate that infection was indeed caused by one of these microorganisms, re-dosing must be delayed so that there is at least a four-week window between symptom resolution and the next dose of ADCT-301; Section 7.3.4.5.

- Requirement added for patients experiencing any autoimmune toxicities (e.g., endocrinopathies) \geq grade 1 to be followed at least weekly to quickly detect deterioration and modify dosing as per the dose limiting toxicity criteria; Section 6.4.

- Requirement added for patients experiencing certain types of infection associated with neurologic and immune-related disease(s) during the course of participation in this clinical study also must delay further dosing; Section 6.4.
- Recommendations pertaining to dose delay and modifications have been revised to include appropriate management of neurological toxicities, including polyradiculopathy/GBS; Section 6.4.
- Specific study stopping criteria for excessive toxicity, including neurologic or autoimmune toxicity, were implemented in Section 6.5.
- Specific treatment plans for the occurrence of Guillain-Barre and other neurologic toxicities have been added in Section 6.10.3.
- The definition for non-hematologic DLTs has been expanded to include peripheral sensory or motor neuropathy \geq Grade 2; Section 7.3.1.1.
- In order to better evaluate the change in white blood cell populations (such as activated T cells), additional PBMC samples will be collected:
 - on Day 3 and Day 5 of Cycles 1 and 2 for the every 3 week dosing regimen.
 - on Day 3 and Day 5 of Cycle 1 and Day 8 of Cycle 2 for the weekly dosing regimen.Section 5.1 and Tables 2, 4, and 5 of Appendix 13.1.
- Because data collected so far were inconclusive, sample collection and evaluation of the DNA cross-linking (comet assay/ γ H2AX) will be discontinued; Sections 3.3, 5.1, 7.2.2, 7.4, 8.2.3, 8.6.3, and Tables 2, 4, and 5 of Appendix 13.1.
- Clinical definition of GBS and the GBS disability scale have been included in Appendices 13.3 and 13.4.

In addition, administrative and editorial changes have been included, and revisions to the protocol text have also been applied to the synopsis section.