

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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16.1.9 Documentation of Statistical Methods

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Statistical Analysis Plan

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

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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 Conference on Harmonisation harmonised tripartite guideline E6(R1), Good Clinical Practice.

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1 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under ADC Therapeutics (ADCT) Protocol ADCT-301-002.

This SAP should be read in conjunction with the study [protocol](#) and [case report form \(CRF\)](#).

2 Study Objectives

See the planned study objectives in the corresponding section in the protocol.

3 Study Design

Refer to the corresponding section in the protocol.

3.1 Sample Size Consideration

Refer to the corresponding section in the protocol.

3.2 Randomization

This study is not randomized.

3.3 Modifications to the statistical section of the protocol

The trial was terminated early, prior to the completion of dose escalation (part 1), therefore, only Part 1 data has been analyzed and a selected or modified analysis from the statistical section of the protocol will be performed. Please see details in each section.

4 Statistical methods

All analyses use SAS® version 9.4 or higher. Summary tables will be organized by each dose level; if some dose levels have only a few subjects, then dose levels can be combined into dose ranges. All available data will be used in the analyses, and important data will be included in data listings, sorted by dose level, subject, and by visit within subject. Missing data will not be imputed, except via censoring in survival analyses and as otherwise specified.

Unless otherwise noted, categorical data will be presented using counts and percentages, with the number of subjects in the analysis set by treatment group as the denominator for percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places, and percentages will not be displayed for zero counts. Continuous data, unless otherwise noted, will be summarized using the number of observations (n), mean, standard deviation (std), median, minimum, and maximum. Minima and maxima will be rounded to the precision of the original value, and means, medians, and confidence intervals (CIs) if presented will be rounded to 1 decimal place greater than the precision of the original value. The std will be rounded to 2 decimal places greater than the precision of the original value, up to a maximum of 3 decimal places.

No hypothesis testing will be performed in this study.

4.1 Analysis Sets

4.1.1 Safety Analysis Set

The safety analysis set consists of all subjects who receive study drug.

4.2 Subject Disposition

For the Safety analysis set, the number and percentage of subjects who discontinued study treatment and discontinued the study for each reason will be tabulated for each dose level.

Subject disposition data will be listed.

The number and percentage of patients with any important clinical study report (CSR) reportable protocol deviation will be summarized overall and by type of deviation. The pre-defined important CSR reportable protocol deviations are listed below; in addition, any other protocol deviations deemed by ADCT medical to be important CSR reportable deviations will be included in the summary.

1. Patient entered the study even though they did not satisfy the entry criteria
2. Patient received an excluded concomitant treatment
3. Patients who developed withdrawal criteria during the study but were not withdrawn.
The withdrawal criteria include:
 - Grade 3 or higher hypersensitivity reaction
 - a recurrent Grade 3 or 4 toxicity, excluding hematological toxicity
 - a protocol-defined dose-limiting toxicity (DLT) during Cycle 1

- a dosing delay >21 (except in case of potential patient benefit, which must be approved by the Sponsor) or
 - diagnosis of polyradiculopathy/GBS with the level 1 of diagnostic certainty
 - Grade ≥ 3 neurologic toxicities, defined as peripheral sensory and peripherally motor neuropathies
4. toxicity recurs at the 2nd reduced dose level and at a severity that would mandate a treatment withdrawal Patient who received the wrong treatment or incorrect dose. For example,
- actual dose of study drug was more than 15% greater than protocol defined planned dose level
 - patient started next cycle less than 18 days later after Day 1 of the most recent treatment cycle

4.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be tabulated for the Safety analysis set.

Variables include the following:

- Sex (female, male)
- Race (white, black or African-American, Asian, American Indian or Alaska native, native Hawaiian or other Pacific Islander, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Age (years)
- Age group (< 65, ≥ 65 - < 75, ≥ 75 years)
- Height (cm)
- Weight (kg)
- Body mass index (kg/m²)
- ECOG PS

Demographic and baseline characteristics data will be listed.

4.4 Pre-treatment disease characteristics and Medications History

Cancer history will be presented for the Safety analysis set. Cancer history will include the following variables:

- Disease diagnosis subtype (Acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL))
- extramedullary involvement

Cytogenetic analysis will include the following variables:

For ALL:

- ALL with t(9;22)(q34;q11.2); BCR-ABL (Philadelphia chromosome)
- ALL with t(v;11q23) (MLL rearranged)
- ALL with t(1;19)(q23;p13.3); TCF3-PBX1 (E2A-PBX1)
- ALL with t(12;21)(p13;q22); ETV6-RUNX1 (TEL-AML1)
- Hyperdiploid > 50

- Hypodiploid
- t(5;14)(q31;q32); IL3-IGH
- Other

For AML:

- AML with t(8;21)(q22;q22); RUNX1/RUNX1T1
- AML with inv(16)(p13,q22) or t(16;16)(p13.1;q22);]CBFB/MYH11
- AML with t(15;17)(q22;q12)PML-RARA
- AML with t(9;11)(p22;q23): MLLT3-MLL
- AML with t(6;9)(p23;q34) DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26);RPN1-EVI1
- AML (megakaryoblastic) with t(1;22)(p13;q13): RBM15-MKL1
- AML with mutated NPM1
- AML with mutated CEBPA
- Other

All cytogenetic analysis data will be listed.

Multilineage dysplasia syndrome data will be listed.

Bone marrow evaluation (bone marrow aspirate and/or bone marrow biopsy) at screening will be listed.

Medical history will be summarized by SOC and preferred term. All medical history data will be listed.

4.5 Prior anticancer therapy

The number and percent of patients who had prior stem cell transplant and radiotherapy will be summarized.

The number of lines of prior systemic therapies will be summarized. Number of lines is derived from the unique number of regimen number reported on the prior systemic treatment CRF page and the mobilization treatment and/or conditioning treatment from the prior stem cell transplant, if appropriate.

Prior stem cell transplant, radiotherapy and systemic therapy data will be listed.

4.6 Prior or Concomitant Medications (other than anticancer therapies)

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

Patient listing of all prior and concomitant medications will be provided. Pre-medication for dosing (for example, prophylaxis for hypersensitivity) will listed separately.

4.7 Exposure to Treatment

4.7.1 Extent of ADCT-301 Exposure

ADCT-301 exposure will be summarized for the Safety analysis set by dose level. The following items will be tabulated.

- Duration of treatment (in weeks) = (date of last dose – date of first dose +1)/7
- Number of infusions
- Cumulative dose (in ug/kg) = sum of (dose administered at each infusion [ug] /last available weight before each infusion[kg]),
where dose administered at each infusion[ug]=concentrated IP volume [in mL]* 6 mg/mL *1000 or serially diluted IP volume[in mL]/50* 6 mg/mL *1000; for partial infusion, multiply by (1- volume of dosing solution not administered [in mL]/ 50 mL)
- Relative dose intensity (%) = (Cumulative dose / (Duration of treatment + 6/7 for QW or + 20/7 for Q3W))/ planned weekly dose intensity *100%,
where planned weekly dose intensity = planned dose level at cycle 1 day 1 for QW, or planned dose level at cycle 1 day 1 ÷ 3 for Q3W, for example, =10 ug/kg for 30ug/kg Q3W planned dose level.
For patients who switched from Q3W to QW or vice versa, the relative dose intensity is not calculated.

Relative dose intensity will be additionally presented categorized (<60%, >=60 - <80%, >=80 - <90%, >=90 - <110%, >=110%) Exposure data and infusion details will be listed together.

Exposure data will be listed.

4.7.2 Subsequent Anticancer Therapy or Procedure

Subjects' subsequent anticancer therapy or procedure including systemic therapy, radiation, transplant, or other, along with the start date of subsequent anticancer therapy or procedure will be listed.

4.8 Safety Analyses

General common rules

All safety analyses will be performed on the safety analysis set, unless otherwise specified, using the following common rules:

- The baseline value will be defined as the last non-missing value or measurement taken up to the first dose of the study drug
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

- If relevant, selected safety analyses may be summarized by age, sex, racial subgroups, and any pertinent subgroups.
- The toxicity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be taken into account in the summary. For subjects with multiple occurrences of the same event, the maximum grade will be used. If a subject has both missing and non-missing severity grades for treatment-emergent adverse events (TEAEs) within the same preferred term (PT), the missing severity of the TEAE will be treated as a lower severity grade (ie, the subject will be counted under the non-missing severity grade).

4.8.1 Dose-limiting Toxicities

DLT data will be listed.

4.8.2 Adverse Events, Serious Adverse Events, and Deaths

4.8.2.1 Analyses of adverse events

The primary focus of adverse event reporting will be on the TEAEs. A TEAE is defined as an adverse event that occurs or worsens in the period extending from the first dose of study drug to 84 days after the last dose of study drug, or start of new anti-cancer therapy, whichever is earlier.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, TEAE, or post-treatment. For example, if only the day of the AE onset is missing, the year and month will be compared with the first dose and 84 days after the last dose of study drug, or start of new anti-cancer therapy, whichever is earlier. And if the month and day of the AE onset are missing, the year will be compared with the first dose and 84 days after the last dose of study drug, or start of new anti-cancer therapy, whichever is earlier. The algorithm for imputing TEAE will be conservative and will classify an AE as a treatment emergent unless there is definitive information to determine it is non-TEAEs.

Analysis of all TEAE(s):

The following TEAE summaries will be generated for the safety analysis set.

- Overview of TEAEs, summarizing number of TEAEs and number (%) of subjects with any
 - TEAE
 - Related TEAE (including possibly related, probably related, or related)
 - Any \geq grade 3 TEAE
 - Serious TEAE
 - TEAE leading to death

- TEAE leading to permanent treatment discontinuation
- TEAE leading to ADCT-301 delay or reduction or interruption
- TEAE with at least one infusion related reaction
- All TEAEs by PT, showing number (%) of subjects with at least one TEAE, sorted by decreasing incidence of PTs
- All TEAEs by System Organ Class (SOC) and PT, showing number (%) of subjects with at least one TEAE, sorted by SOC in alphabetic order and decreasing incidence of PTs within SOC. This sorting order will be applied to all other AE tables, unless otherwise specified
- All TEAEs by SOC, PT and Maximum CTCAE grade
- All \geq grade 3 TEAEs by SOC, PT and Maximum CTCAE grade
- All related TEAEs by SOC, PT and Maximum CTCAE grade (including possibly related, probably related, or related)
- All Serious TEAEs by SOC and PT by SOC, PT and Maximum CTCAE grade

All AEs (including non-TEAEs), all SAEs (including non-TEAEs), all TEAEs leading to treatment withdrawal, all TEAEs leading to dose reduction, all TEAEs leading to dose delay, infusion related reaction and all TEAEs with fatal outcome will be listed.

In addition, neurologic AE (including the following Standardized MedDRA Queries (SMQ): Peripheral neuropathy (SMQ) [20000034], Guillain-Barre syndrome (SMQ) [20000131], and Demyelination (SMQ) [20000154]) will be listed.

4.8.2.2 Autoimmune AE, based on an ADCT specific query (includes Preferred Terms (PTs) selected based on autoimmune mediated events) will be listed. Deaths

Reasons for deaths will be summarized separately for 1) all deaths, 2) death on therapy or within 30 days after last dose of study drug.

4.8.1 Laboratory Data

Descriptive statistics (mean, standard deviation, median, and range) will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

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.

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.

Laboratory data, including urinalysis, will be listed. Pregnancy test results will not be listed, but will be included in datasets.

4.8.1 Electrocardiogram

ECG parameters (e.g. corrected QT interval [QTcF (Fridericia) or QTcB(Bazett)]) will not be converted or derived, but will be reported as provided by investigational sites.

Descriptive statistics (mean, standard deviation, median and range) for heart rate will be calculated and for their changes from baseline at each scheduled assessment.

The following abnormal QTc (including QTcF, QTcB and QTc with unspecified method) will be reported by a frequency table:

At any post-baseline with absolute value

450 - 480 ms

481 - 500 ms

>= 501 ms

Change from Baseline

31 – 60 ms

>60 ms

For patients with unspecified QTc method at either baseline or post-baseline, consistent correction method is assumed within a patient, when calculating the change from baseline.

All ECG data will be listed, both for quantitative data and for overall interpretation (normal, abnormal –clinically significant, abnormal –not clinically significant) reported by investigational sites.

4.8.1 Vital Signs

Descriptive statistics (mean, standard deviation, median, and range) for vital signs data, including systolic and diastolic blood pressure, heart rate, respiration rate, and body temperature, will be calculated for the raw data and for their changes from baseline at each scheduled assessment.

All vital signs data will be listed together with body weight.

4.8.2 ECOG Performance Status

All ECOG data will be listed.

4.9 Efficacy Analyses

Due to the early termination of the trial, efficacy data will be listed only. Disease assessment (CR, CRi, PR, PD, NR or NE) data will be listed.

4.10 Pharmacokinetic Analyses and Pharmacodynamic Measures

The actual blood sampling time and actual amount of dose administered will be recorded and used in calculation of pharmacokinetic (PK) parameters. All PK samples will be evaluable as

long as the actual collection times are recorded. Analysis of the ADCT-301 total antibody [drug-to-antibody ratio ($\text{DAR} \geq 0$)], PBD-conjugated antibody ($\text{DAR} \geq 1$), and SG3199 (unconjugated warhead) concentrations in serum will be analyzed using a noncompartmental analysis method. The PK parameters from analysis will include maximum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time zero to the last quantifiable concentration ($\text{AUC}_{0\text{-last}}$), area under the concentration-time curve from time zero to the end of the dosing interval ($\text{AUC}_{0\text{-}\tau}$), area under the concentration-time curve from time zero to infinity (AUC), accumulation index (AI), apparent terminal half-life ($T_{1/2}$), apparent systemic clearance (CL), and volume of distribution at steady state (V_{ss}).

Data presentation by tables will include individual patient concentrations by nominal time, individual patient PK parameters, statistical summaries (mean, standard deviation, median, range, geometric mean, geometric standard deviation, and n) of concentrations by dose cohort and nominal time, and statistical summary of PK parameters.¹ Data presentation through figures will include individual patient concentrations by actual time, and mean (standard error) of concentrations by nominal time.

At selected times as indicated in the Schedule of Events tables, samples for ADCT-301 antidrug antibodies (ADA) were also collected concurrently with selected PK samples. Results from ADA testing will include tabular summarization for number/proportion of patients with positive pre-dose ADA response, number of patients with post-dose ADA response only, and number of patients with positive ADA response at any time. The denominator will be the total number of patients tested for ADAs in the study. For instances in which a positive ADA titer is observed, results from testing for neutralizing antibody potential will be reported.



¹ N.b. statistical summarization for T_{max} and $T_{1/2}$ will include median, minimum and maximum values.

5 Interim Analyses

NA

6 Data handling conventions

6.1 General conventions

6.1.1 Missing data

Handling of missing relationship to investigational product of AEs

If the assessment of the relationship to investigational product is missing, then the relationship to investigational product has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation should be done at the data level.

Handling of missing severity/grades of AEs

If the severity/grade is missing for one of the treatment emergent occurrences of an AE, the maximal severity of the remaining occurrences will be considered. If the severity is missing for all the occurrences a “missing” category will be added in summary table.

No other imputation of values for missing data will be performed.

6.1.2 Unscheduled visits

Unscheduled visit measurements of laboratory data will be used for computation of baseline and worst values and/or grades. Re-windowing for unscheduled visits will not be performed.

6.1.3 Duplicated visit

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value per visit. Unless otherwise noted throughout the rest of this document, when a single value is needed, the following rule(s) will be used:

- If more than 1 assessment occurs during the same nominal visit, select the record closest to the nominal day for that visit.
- If there are 2 assessments that are equidistant from the nominal day, the data of the assessment after the scheduled study day will be used.
- The last measurement will be used if multiple measurements are taken on the same day.