STATISTICAL ANALYSIS PLAN

Protocol Title	Phase 1/2a, Single Dose Study Investigating NTLA-5001 in Subjects with Acute Myeloid Leukemia
Protocol Number	ITL-5001-CL-001
Compound	NTLA-5001
Study Phase	Phase 1/2a
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SIGNATURE PAGE

Statistical Analysis Plan: ITL-5001-CL-001

Phase 1/2a, Single Dose Study Investigating NTLA-5001 in Subjects with Acute Myeloid Leukemia

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{see appended Signature Page}

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 VERSION HISTORY

This SAP for Protocol ITL-5001-CL-001 is based on the protocol version 2.0 dated 22 December 2021.

Table 1 Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 / 06 January 2023	2.0 / 22 December 2021	N/A	N/A

2 INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study ITL-5001-CL-001. This document may modify the plans outlined in the protocol. Details will be included in Section 7.

2.1 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• Dose escalation: To identify dose for use in the expansion cohorts	• safety and tolerability as determined by AEs • dose-limiting toxicities (DLTs) (dose escalation only)
• Dose expansion: To evaluate the safety and tolerability of NTLA-5001 in subjects with AML and blasts <5% of bone marrow (Arm 1) and in subjects with AML and blasts ≥5% of bone marrow (Arm 2)	
Secondary	
• To characterize the cell kinetics (CK) of NTLA-5001 in peripheral blood	• frequency and persistence of NTLA-5001 according to the TCR transgene copy number (via droplet digital polymerase chain reaction [ddPCR])
• To estimate the anti-tumor activity of NTLA-5001 in subjects with AML	• Disease response (including measurable residual disease [MRD] response), duration of response/ remission, event free survival and time to disease progression
Exploratory	
• To estimate other cancer-related outcomes in subjects with AML	• overall survival • Eastern Cooperative Oncology Group (ECOG) performance status • QOL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) instrument and length of hospital stay after NTLA-5001 infusion
• To characterize subject AAV exposure	• presence of adenovirus vector in blood and urine
• To characterize immunologic parameters and characteristics of NTLA-5001 cells after administration in subjects with AML	• plasma cytokine levels • WT1 expression on tumor • NTLA-5001 characteristics including flow cytometry, phenotype, editing, and gene expression • bone marrow immune parameters and NTLA-5001 cell kinetics

2.2 Study Design

This is Phase 1/2a, first-in-human, single-dose study to investigate NTLA-5001 in subjects with Acute Myeloid Leukemia (AML). The design is according to guidance for first-in-human trials and for the investigation of advanced therapy medicinal products, including the European Medicine Agency "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products"; and draft guidance "Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials"; and the FDA draft guidance "Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment". The design is to ensure the safety and well-being of trial subjects and to mitigate risk to the greatest extent possible.

This study consists of 2 phases: dose escalation and dose expansion. A subject that meets all inclusion and none of the exclusion criteria will be enrolled into the leukapheresis phase in Arm 1 for subjects with AML blasts <5% of bone marrow or in Arm 2 for subjects with AML blasts ≥5% of bone marrow. During screening, MRD will be measured in bone marrow by central laboratory assessment. After study entry, subjects may have repeat BM assessment prior to Arm assignment based on whether screening biopsy was prior to study consent, interval since screening study, change in condition, or bridging therapy. If an Arm 1 subject is found to have ≥5% bone marrow blasts at repeat BM assessment prior to the administration of lymphodepleting chemotherapy, the subject may be re-assigned to Arm 2 or, if Arm 2 is not yet enrolling subjects, the subject may receive NTLA-5001 at Dose Level -1.

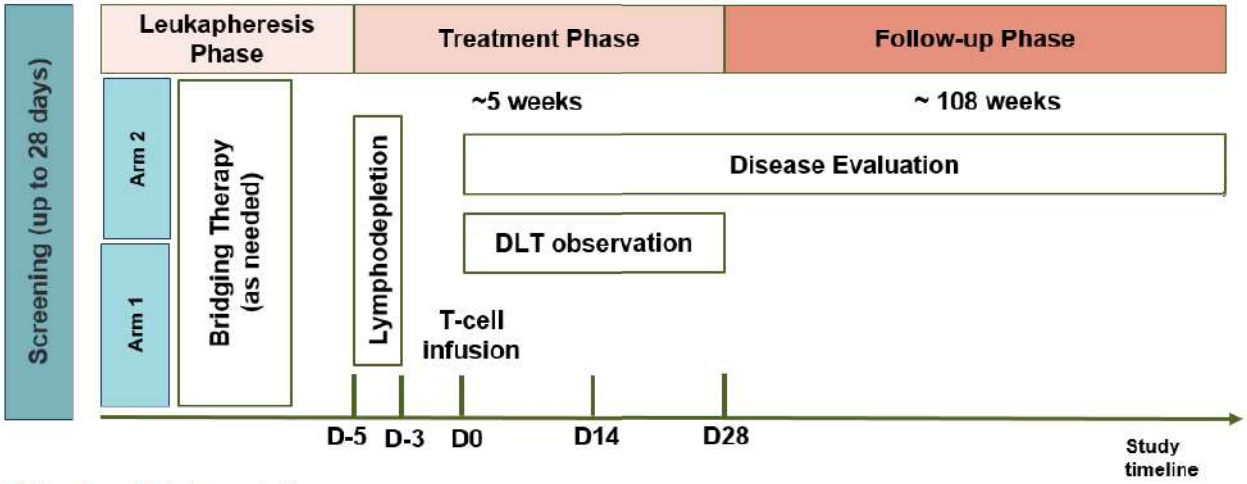
The dose escalation phase of the study will consist of up to 3 cohorts of subjects in Arm 1 and 3 cohorts of subjects in Arm 2. Each Arm 1 cohort will include up to 6 subjects, as detailed in dose escalation below. Each Arm 2 cohort will include 3 to 6 subjects. Once a dose is identified for detailed assessment of safety in Arm 1 subjects and 6 subjects have been enrolled at that dose, an expansion cohort will be opened for an additional 9 subjects in Arm 1. Once a dose is identified for detailed assessment of safety in Arm 2 subjects, a safety expansion cohort will be opened for an additional 9 subjects in Arm 2.

Each subject will undergo leukapheresis for collection of peripheral blood mononuclear cells (PBMC). [redacted] After leukapheresis, subjects who meet criteria for treatment and who have manufactured NTLA-5001 that meet release requirements will enter the treatment phase for the administration of lymphodepleting chemotherapy and study medication.

Each subject in the treatment group will receive lymphodepleting chemotherapy on Day -5, -4, and -3. A subject will be administered a single dose of NTLA-5001 on Day 0. Subjects will be observed in hospital for a minimum of 7 days following dosing, and subjects must remain within 2 hours of the location of the trial site to receive any needed follow up assessments or care until Day 14. UK subjects will be observed in hospital for a minimum of 14 days following dosing. Additional visits will take place at Week 2, 4, 8, and 16, then at 12-week intervals through Week 112 or until the subject is no longer receiving clinical benefit. Subjects who are no longer receiving clinical benefit will continue to be followed with clinic visits to assess subject survival and AEs every 12 weeks until 112 weeks after administration of NTLA-5001. After participating

in this study, all subjects will be followed as part of a long-term monitoring program per local and national regulations. All subjects will be followed for a minimum of 5 years in the UK and for a minimum of 15 years in the US.

Figure 1 Study Schema



DLT = dose limiting toxicities

3 STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

3.1 Statistical Hypotheses

There is no statistical hypothesis for the study.

3.2 Sample Size Determination

No formal sample size calculation was performed for this study.

Dose escalation will consist of up to 3 dose escalation cohorts in each of 2 Arms. Each Arm 1 cohort will include up to 6 subjects. Each Arm 2 cohort will include 3 to 6 subjects. Therefore, up to 36 evaluable subjects are anticipated to be enrolled in this portion of the study.

Once a dose is identified for detailed safety assessment in an Arm, a safety expansion cohort will be opened for up to 9 additional subjects to be dosed at that dose level. Thus, up to a total of 18 subjects will be dosed in safety expansion cohorts across the 2 Arms.

4 ANALYSIS SETS

For purposes of analysis, the following analysis sets are defined in Table 2.

Table 2 Analysis Sets

Population	Description
Enrolled Set	All subjects who meet all inclusion/exclusion criteria
DLT Evaluable Set	All subjects who receive NTLA-5001 and either experience DLT(s) regardless of whether a full dose was administered or receive the full assigned dose without DLTs and complete Day 29 assessments. Subjects without DLTs who do not receive the full dose of NTLA-5001 as per their assigned dose cohort or did not complete Day 29 assessments are not evaluable for DLTs.
Full Analysis Set (FAS)	All subjects who undergo leukapheresis
Safety Analysis Set	All subjects who receive NTLA-5001
Cell Kinetics (CK) Analysis Set	All subjects who receive NTLA-5001 and have at least one evaluable CK sample

5 GENERAL METHODOLOGY AND CONVENTIONS

Qualitative/categorical data will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category.

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation, minimum, maximum and first and third quartile (Q1 and Q3).

5.1 Data Handling

5.1.1 Data Cutoff Date

Data after the cutoff date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.1.2 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., "< 1.0") will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on subject listings to include the sign.

5.2 Definition of Study Day

The study day for assessments occurring on or after the start of NTLA-5001 infusion will be calculated as:

Study day = Date of the assessment/event - start date of NTLA-5001 infusion + 1.

The study day for assessments occurring prior to the start of NTLA-5001 infusion (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start date of NTLA-5001 infusion.

The study day will be displayed in all relevant data listings.

5.3 Definition of Baseline

Baseline is defined as the last measurement prior to the initiation of lymphodepleting chemotherapy.

If an assessment is planned to be performed prior to beginning lymphodepletion in the protocol and the assessment is performed on the same day as the first administration of lymphodepleting chemotherapy, it will be assumed that it was performed prior to the beginning of lymphodepletion.

Unscheduled assessments will be used in the determination of baseline. However, an unscheduled assessment performed on the day of the first administration of lymphodepleting chemotherapy will be considered to have been obtained after lymphodepletion started and therefore will not be used for baseline determination.

5.4 Safety Reporting Period

The safety reporting period is defined as the time from the date of NTLA-5001 infusion through the end of the study or (start date of new anticancer therapy – 1 day).

Note that the safety reporting period will be used for all safety analyses.

5.5 Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years:
1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

For reporting conventions, minimum and maximum values will be presented with the same decimal precision as collected in the raw data; mean, median, and quartiles should generally be presented to 1 more decimal place than the raw data; standard deviation should be displayed to 2 more decimal places than the raw data. P Non-zero percentages will be rounded to whole numbers for all populations smaller than 100 subjects, to 1 decimal place if a population includes $\geq$ 100 subjects. The rounding will be performed to closest integer/first decimal using the common mid-point between the two consecutive values. For example, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

Missing statistics, eg, when they cannot be calculated, should be presented as 'ND' for not done and 'NA' for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as 'NA'.

5.6 Methods to Manage Incomplete or Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

5.6.1 Handling of Incomplete or Missing Dates

Any imputations on incomplete or missing dates will occur at the analysis dataset level. Imputed dates will be presented in all data listings.

5.6.2 AE Dates

AE Onset Date:

- If the onset date is completely missing:
  - If the date of study drug infusion is earlier than AE stop date, then the onset date will be assigned as the date of study drug infusion.

- If the date of study drug infusion is after the AE stop date then the AE onset date will be imputed as the earliest of complete AE stop date or informed consent date.

- If year is present and month and day are missing or year and day are present and month is missing:
  - If year = year of first dose, then set month and day to month and day of study drug infusion.
  - If year < year of first dose, then set month and day to December 31.
  - If year > year of first dose, then set month and day to January 1.
- If month and year are present and day is missing:
  - If year = year of study drug infusion and month = month of study drug infusion, then set day to day of study drug infusion.
  - If year = year of study drug infusion and month < month of study drug infusion, then set day to last day of month.
  - If year < year of study drug infusion, then set day to last day of month.
  - If year > year of study drug infusion, then set day to first day of month.

AE Stop Date:

- If the AE stop date is completely missing (not an ongoing AE) and AE onset date is complete, then the stop date will be imputed as the latest of the subject withdrawal/ completion date, death date, or AE onset date.
- If year is present and month and day are missing or year and day are present and month is missing, set end month and day to December 31.
- If month and year are present and day is missing, set the day to last day of the month.

5.6.3 Exposure

No imputation will be done for the dosing date.

5.6.4 Date of Death

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing, it will be imputed as the day after the date of last contact.
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death.
  - Missing day and month: January 1st of the year of death.

5.6.5 Other Missing or Partial Dates

Imputation methods for other partial dates are as follows:

- If the day of the month is missing for a start date used in a calculation, the 1st of the month will be used to replace the missing date.
- If both the day and month are missing, the first day of the year is used
- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively

These rules are used unless the calculations result in negative time durations (e.g., date of resolution cannot be prior to date of onset). In such case, the resolution and onset dates will be the same and the duration will be set to 1 day.

6 STATISTICAL ANALYSES

6.1 Primary Endpoints

The primary endpoint for the dose escalation phase is the incidence of dose-limiting toxicities (DLTs).

AEs that meet the criteria for a DLT will be denoted in the overall AE listing.

6.2 Secondary Endpoints

Cell kinetics data profiles will be presented in a data listing based on the CK Analysis Set.

Response is assessed by the investigators per the response criteria defined in Appendix 4 in the protocol, with status and date at each assessment recorded on the "Disease Response Assessment" CRF. Disease response data will be presented in a data listing based on the Safety Analysis Set.

6.3 Exploratory Endpoints

6.3.1 Adeno-associated Virus

Presence of adenovirus vector in blood and urine data will be assessed. Results will be presented in a data listing based on the Safety Analysis Set.

6.3.2 Biomarkers

Biomarker data will be summarized based on the Safety Analysis Set.

Individual levels of circulating cytokines at baseline and post drug administration will be presented in a data listing. Graphical representation of individual cytokine-time profile will be provided.

6.4 Baseline and Other Summaries and Analyses

6.4.1 Baseline Summaries

6.4.1.1 Demographic Characteristics

The following demographic and baseline characteristics will be summarized by number and percentage based on the Safety Analysis Set:

- Sex (Female, Male, Undifferentiated, Unknown)
- Race (White or Caucasian, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not Reported, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown)

Age at Screening (years), height (cm), weight (kg), body mass index (BMI) (kg/m^2) will be summarized with descriptive statistics.

In addition, a data listing will be created based on the FAS.

6.4.1.2 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized by number and percentage based on the data collected on the "AML History" and "ECOG Assessment" eCRF. The summary will be based on the Safety Analysis Set.

- Original WHO diagnosis
- AML Risk category (Favorable/Intermediate/Adverse)
- Presence of extramedullary disease (Yes/No/Unknown)
- History of GvHD (Yes/No)
- Type of GvHD (Acute/Chronic/Overlap)
- Last maximum grade of GvHD (Grade 1/2/3/4)
- ECOG performance status at baseline

In addition, a data listing will be created based on the FAS.

6.4.2 Study Conduct and Subject Disposition

6.4.2.1 Disposition

The percentages below will be calculated based on the number of subjects treated and summarized as follows:

- Number of subjects enrolled, those who received leukapheresis, and those who were treated
- Number (%) of subjects who completed the study (ie, followed for 112 weeks)
- Number (%) of subjects who discontinued the study prior to Week 112 visit, overall and by the main reason for discontinuation of the study

Duration of follow-up will be presented in a data listing based on the Safety Analysis Set. It is calculated as follows:

> Duration of follow up (months) = (Last date the subject is known to be alive – Date of study drug infusion +1) / 30.4375

6.4.2.2 Protocol Deviations

Potentially important protocol deviations will be identified prior to database lock and will be presented in a data listing based on the Safety Analysis Set.

6.4.3 Extent of Exposure

Exposure will be presented based on the Safety Analysis Set.

6.4.3.1 NTLA-5001 Product

Data recorded on the "NTLA-5001 Dosing" eCRF including assigned dose level, infusion start date/time, stop date/time and reason for infusion alteration will be provided in a data listing for subjects who received NTLA-5001 infusion.

6.4.3.2 Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy may be administered in the inpatient or outpatient setting for up to 3 consecutive days (Day -5, Day -4, and Day -3) at 24-hour (± 3 hours) intervals. Data recorded on the "Lymphodepleting Chemotherapy" eCRF will be provided in a data listing including the following information:

- Type of lymphodepleting chemotherapy
- Start and end date
- Dose administered (unit)
- Body surface area (m^2)

6.5 Safety Summaries and Analyses

All safety analyses will be based on the Safety Analysis Set. All safety data that occurred during the safety reporting period as defined in Section 5.4 will be listed.

6.5.1 Adverse Events

An AE is considered a treatment emergent adverse event (TEAE) if the event started or worsened during the safety reporting period as defined in Section 5.4.

All analyses will be based on TEAE unless otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not).

AEs will be coded using the current version (as of study start) of MedDRA. Severity of AEs will be assessed by the Investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 toxicity grading criteria except CRS and ICANS, which will be graded by the Investigator according to the ASTCT criteria (1).

An event will be considered treatment related if the investigator considered the event related to the study drug, ie, relationship to NTLA-5001 = "Possible" or "Probable", or if relationship is missing.

For summaries by System Organ Class (SOC) and preferred term (PT), each subject will be counted once per SOC and once per PT. In the summary of TEAEs by toxicity grade, subjects will be counted once at the highest severity reported at each level of summarization.

A high-level summary of AEs will include the number and percent of subjects with:

- Any TEAEs
- DLTs
- Treatment-related TEAEs
- Serious TEAEs
- Treatment-related serious TEAEs
- Grade ≥ 3 TEAEs
- Grade 3
- Grade 4
- Grade 5
- Treatment-related Grade ≥ 3 TEAEs
- Grade 3
- Grade 4
- Grade 5
- TEAEs leading to study drug infusion interruption
- Treatment-related TEAEs leading to study drug infusion interruption
- TEAEs leading to study drug infusion discontinuation
- Treatment-related TEAEs leading to study drug infusion discontinuation
- Treatment emergent AEs of special interest (AESIs)
- Treatment-related treatment emergent AESIs
- TEAEs leading to death
- Treatment-related TEAEs leading to death

The AESIs are defined in Section 8.5 in the protocol and will be summarized based on the data collected on the "Adverse Events" eCRF.

Adverse Events by Preferred Term

The following summaries will be provided by preferred term only by decreasing frequency.

- TEAEs by PT (all causality)
- Serious TEAEs by PT (all causality)
- Non-serious TEAEs by PT (all causality)

All AE data will be presented in a data listing.

6.5.2 Deaths

Data collected on the "Death" eCRF including date of death and primary cause of death will be presented in a data listing.

6.5.3 Laboratory Data

All laboratory test results will be presented in a data listing sorted by dose level, subject identifier, laboratory test, and date/time of collection. Values outside laboratory normal ranges will be flagged where appropriate. The central laboratory data and local laboratory data will be flagged accordingly.

6.5.4 Vital Signs

All vital sign data will be presented in a data listing.

6.5.5 Electrocardiograms

No electrocardiogram assessment is performed on this study.

6.6 Subgroup Analyses

No subgroup analysis is planned for this study.

6.7 Interim Analysis

No formal interim analysis is planned for this study.

A Data Monitoring Committee (DMC) will be established to perform periodic review of all safety data. Detailed are provided in a DMC Charter.

7 CHANGES TO PROTOCOL PLANNED ANALYSES

Analyses of the following data were planned in the protocol but will not performed as there were only 2 subjects who received NTLA-5001 when the study was terminated by the Sponsor.

- Overall survival
- Objective response rate
- Composite complete remission rate
- Duration of response
- Event free survival
- Time to progression
- Minimal residual disease
- Analysis of immune parameters and NTLA-5001 cells
- Frequency and persistence of TRAC and TRBC edits
- Gene expression patterns in NTLA-5001 cells
- Translocation rates in NTLA-5001 cells
- Measurement of WT1 expression on AML as assessed by reverse transcription-PCR
- ECOG performance status
- Quality of life as measured by the EORTC QLQ-C30 instrument

The Efficacy Evaluable Set was defined in the protocol and was specified to be used for all disease assessment related efficacy analysis. Disease response assessments will instead be presented in a data listing based on the Safety Analysis Set.

In addition, no summary tables or figures will be created for cell kinetics data. Only a data listing will be created.

8 SUPPORTING DOCUMENTATION

8.1 Appendix 1: List of Abbreviations

Abbreviation	Description
AE(s)	adverse event(s)
AESIs	adverse events of special interest
AML	acute myeloid leukemia
ASTCT	American Society for Transplantation and Cellular Therapy
CRS	cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DLT(s)	dose-limiting toxicity(ies)
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
GvHD	graft vs host disease
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PK	pharmacokinetic(s)
PT	preferred term
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SOC	system organ class
TEAE(s)	treatment-emergent adverse event(s)
WHO	World Health Organization

9 REFERENCES

1 Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.