



**STATISTICAL ANALYSIS PLAN
FOR PROTOCOL NIT-112**

Sponsor:	NeoImmuneTech, Inc. 2400 Research Blvd, Suite 250 Rockville, MD 20850 USA
Protocol Number:	NIT-112
Protocol Title:	A Phase 1b Study Evaluating the Safety, Tolerability and Preliminary Anti-tumor Activity of NT-I7 (efineptakin alfa) a Long-acting Human IL-7, post- Kymriah® (Tisagenlecleucel), post-Yescarta® (Axicabtagene ciloleucel), or post- Breyanzi® (Lisocabtagene Maraleucel) in Subjects with Relapsed/Refractory Large B-cell Lymphoma
Protocol Version:	Version 11.0
Protocol Date:	20 Nov 2023

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SAP Version:	Final Version 3.0	Facsimile:	1-301-528-2300
SAP Date:	22 July 2024		

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APPROVAL PAGE

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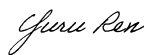
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ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

<u>Abbreviation/Acronym</u>	<u>Definition</u>
AE	Adverse Event
ASA	American Statistical Association
ASTCT	American Society for Transplantation and Cellular Therapies
AUC _{0-t}	Area under the time-concentration curve from time 0 to the last measurable concentration
BMI	Body Mass Index
BOR	Best Overall Response
BP	Blood Pressure
CAR	Chimeric Antigen Receptor
CL	Clearance
C _{last}	Last Measured Concentration
C _{max}	Maximum Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DL	Dose Level
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
FDG	Fluorodeoxyglucose
ICANS	Immune Effector Cell-Associated Neurotoxicity Syndrome
ICH	International Council on Harmonization
IM	Intramuscular
IWG	International Working Group
LBCL	Large B-cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIT	NeoImmuneTech, Inc.

ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term level of MedDRA
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS [®]	Statistical Analysis System
SoC	Standard of Care
SOC	System Organ Class
$t_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment-Emergent Adverse Event
T_{last}	Time of the Last Measured Concentration
t_{max}	Time to maximum concentration
US	United States
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan describes the planned analyses and reporting for the clinical trial protocol NIT-112, conducted by NeoImmuneTech, Inc. The reader of this Statistical Analysis Plan (SAP) is encouraged to review the complete protocol and amendments as this plan contains only a limited overview of protocol information. The main objectives of this plan are to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this SAP are structured to provide sufficient detail to meet the requirements specified by the International Council on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All work planned and presented in this Statistical Analysis Plan will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents were reviewed in preparation of this Statistical Analysis Plan:

- Protocol 11.0/ 20Nov2023
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)

2. PROTOCOL DESIGN

2.1 Design Overview

This is a multicenter Phase 1b study evaluating the safety, tolerability and preliminary anti-tumor activity of NT-I7 administration following standard of care (SoC) CAR (Chimeric Antigen Receptor) T-cell therapy for eligible subjects with relapsed/refractory (r/r) large B-cell lymphoma (LBCL). The study consists of a Dose Escalation phase followed by a Dose Expansion phase.

Up to 42 subjects in the Dose Escalation phase, and up to 15 subjects in the Dose Expansion phase will be enrolled at approximately 20 study centers.

The Treatment Schema is illustrated in [Figure 2-1](#) and [Figure 2-2](#).

Figure 2-1 Study Design Schema

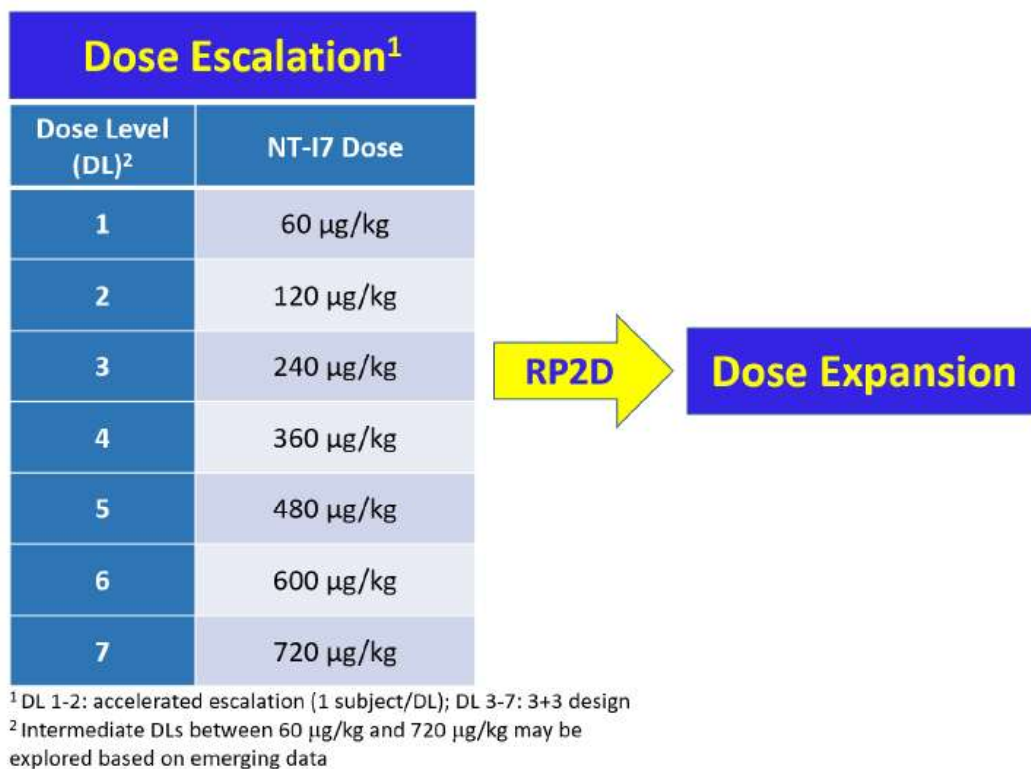
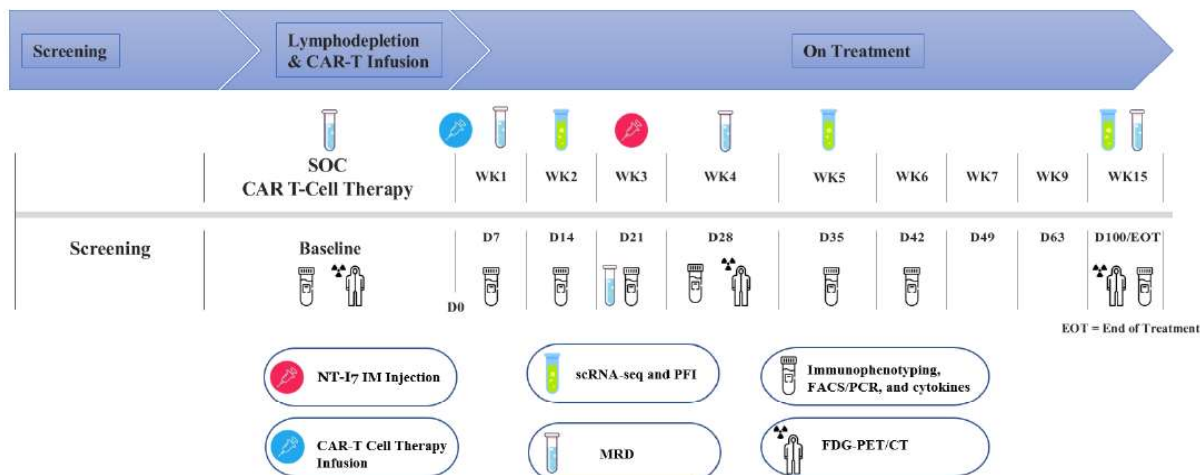


Figure 2-2 Treatment Schema



Dose Escalation Phase

The Dose Escalation phase is designed to assess the safety and tolerability, including determination of the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D), of NT-I7 when administered after CAR T-cell therapy infusion for r/r LBCL. Seven dose levels (DL) are planned: the starting DL (DL1) will be 60 µg/kg, and the highest DL to be tested (DL7) will be 720 µg/kg, as outlined in [Section 2.2](#). Other intermediate

DLs between 60 µg/kg and 720 µg/kg may be explored based on emerging data.

The Dose Escalation phase will begin with an accelerated phase with 1 subject per cohort at the first 2 DLs (DL1 = 60 µg/kg and DL2 = 120 µg/kg), followed by a standard 3+3 design on the remaining 5 DLs (see [Section 2.2](#)), each with a cohort of 3 independent subjects each time and with a maximum total of 6 subjects per cohort. If at least 2 Grade ≥ 2 adverse events (AEs) or any 1 Dose Limiting Toxicity (DLT) are observed in the single subject enrolled in either DL1 or DL2, the accelerated phase will convert to a conventional 3+3 design at the DL where the AEs or DLT are observed and remain so for all the DLs above. In addition to converting to the 3+3 design, the next DL will not exceed 50% of the previous DL. Similarly, if a 2nd DLT occurs in a DL, the next DL in the escalation scheme will not exceed 33% of the previous DL.

The subjects must complete the full 3-week DLT window to be considered evaluable for DLTs. Subjects who discontinue from the study before completion of the full 3-week DLT window for reasons other than the occurrence of a DLT (e.g., withdrawal of consent, rapid tumor progression, death due to rapid tumor progression, AE that does not meet DLT criteria) will not be considered evaluable for DLTs and will be replaced.

In all DLs that followed the 3+3 design in DL3-5, subjects were dosed in a 3-week staggered fashion: the 1st subject in a DL was monitored for 3 weeks; after 3 weeks, if the safety was acceptable, the 2nd subject was enrolled and treated at that same DL; similarly, the 3rd subject was enrolled and treated only if the safety appeared to be acceptable for both the 1st and 2nd subjects after the 2nd subject has been monitored for 3 weeks. If additional subjects were required for a DL, they would be enrolled and treated in a similar 3-week staggered fashion.

No DLTs were observed in Dose Level 1-5. There was no subject at any dose level who experienced the first ADR between 14 days to 21 days after NT-I7 administration. Given these results, starting at Dose Level 6, if a DLT is not observed in the first subject after 2 weeks, then the second and third subjects can be dosed simultaneously. The DSMC will occur once the final subject in a cohort has completed the 3-week DLT period.

A dose schedule for an individual dose level will not be taken into expansion until the Dose Escalation phase has been completed or an MTD has been determined, whichever occurs first.

The RP2D will be based on an accumulation of all available data. All available data including clinical Pharmacokinetics (PK), Pharmacodynamics (PD), anti-tumor activity (including best ORR) and safety, and nonclinical pharmacology data will be pooled. Integrated dose-response and exposure response analyses will be conducted to determine the RP2D.

Dose Expansion Phase

Once RP2D has been determined from the Dose Escalation phase, up to 15 subjects will

be enrolled in the Dose Expansion phase and treated at the RP2D to further evaluate the safety and preliminary anti-tumor activity of NT-I7 administration following SoC CAR T-cell therapy for eligible subjects with r/r LBCL. Subjects in the Dose Expansion cohort can enroll simultaneously.

Treatment Plan:

- NT-I7 (aka rhIL-7-hyFc, efineptakin alfa):
NT-I7 will be administered as an intramuscular (IM) injection at the appropriate DL for each cohort. Each subject will receive only one NT-I7 injection administered on Day 21 +/-2 days (post- CAR T-cell therapy infusion). Subjects will be hospitalized for NT-I7 injection and monitored for at least 24 hours after NT-I7 injection. If subjects develop Grade 2 or higher AEs, subjects will remain hospitalized until resolution of AEs to grade 1 or better. Subjects can be kept in the hospital longer at the discretion of the treating physicians.
- Kymriah:
Kymriah will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SoC use.
- Yescarta:
Yescarta will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SoC use.
- Breyanzi:
Breyanzi will be administered per manufacturer's recommendations and in accordance with FDA prescribing guidelines and best institutional practices for SoC use.
- Duration of Treatment, Study and Follow-up:
The study treatment enrollment date is at the start of NT-I7 treatment. The duration of the study will be approximately 3 months following NT-I7. Subjects will then be followed up per standard of care and per the REMS program for the SoC CAR T-cell therapy the subject received.

2.2 Treatment Groups

Treatment will be administered in the hospital as [Table 2-1](#) below:

Table 2-1: Study Treatment Details

Study Treatment	Dosage Formulation	Unit Dose Strength	Dosage Level(s)	Route	Regimen or Treatment Day	Sourcing
Kymriah	Suspension for intravenous infusion	0.6 to 6.0 x 10 ⁸ CAR-positive viable T cells/ bag (ranges from 10-50mL)	N/A	Intravenous infusion	Day 0	Provided by SoC
Yescarta	Suspension for intravenous	2 x 10 ⁶ CAR-positive viable T	N/A	Intravenous infusion	Day 0	Provided by SoC

Study Treatment	Dosage Formulation	Unit Dose Strength	Dosage Level(s)	Route	Regimen or Treatment Day	Sourcing
	infusion	cells per kg of body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL				
Breyanzi	Suspension for intravenous infusion	A single dose contains 50 to 110×10^6 CAR-positive viable T cells with each component supplied separately in one to four single-dose vials	N/A	Intravenous infusion	Day 0	Provided by SoC
NT-I7	Solution for injection	25 mg/1.0 mL	Dose in $\mu\text{g/kg}^a$	Intramuscular injection	Day 21 (+/- 2 days)	Provided by Sponsor (NIT)

^a Refer to [Table 2-2](#) for assigned dose level.

Table 2-2: NT-I7 Dose Level for Dose Escalation Phase¹

Dose Level (DL) ²	NT-I7 Dose
1	60 $\mu\text{g/kg}$
2	120 $\mu\text{g/kg}$
3	240 $\mu\text{g/kg}$
4	360 $\mu\text{g/kg}$
5	480 $\mu\text{g/kg}$
6	600 $\mu\text{g/kg}$
7	720 $\mu\text{g/kg}$

¹ DL1-2: accelerated escalation (1 subject/DL); DL 3-7:3+3 design

² Intermediate DLs between 60 $\mu\text{g/kg}$ and 720 $\mu\text{g/kg}$ may be explored based on emerging data.

2.3 Randomization and Stratification

Not applicable.

2.4 Blinding

Not applicable.

2.5 Protocol Objective(s)

2.5.1 Primary Objectives

For Dose Escalation Phase:

- To evaluate the safety and tolerability of NT-I7 when administered after SoC CAR T-cell Therapy infusion for r/r LBCL

- To determine the MTD and/or the Recommended Phase 2 Dose (RP2D) of NT-I7 when administered after SoC CAR T-cell Therapy infusion for r/r LBCL

2.5.2 Secondary Objectives

For Dose Escalation Phase:

- To explore the preliminary anti-tumor activity of NT-I7 when administered after CAR T-cell Therapy infusion for r/r LBCL based on:
 - Duration of Response (DOR)
 - Progression-Free Survival (PFS)
 - Overall Survival (OS)

For Dose Escalation and Dose Expansion Phase:

- To continue evaluating the effect of NT-I7 when administered after CAR T-cell Therapy infusion on the safety profile with regards to:
 - Rates of grade 3 and higher Cytokine Release Syndrome (CRS)
 - Rates of grade 3 and higher Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
- The effect of NT-I7 on CAR T-cells expansion

2.5.3 Exploratory Objectives

For Dose Escalation and Expansion Phases:

- To make a preliminary assessment of PK parameters of CAR T-cell Therapy when NT-I7 is administered post-SoC CAR T-cell therapy
 - Parameters of expansion, including maximum concentration (C_{max}) and time to maximum concentration (T_{max})
 - Parameters of persistence, including the terminal half-life ($T_{1/2}$), last measured concentration (C_{last}), and time of last measured concentration (T_{last})
 - Area under the curve for CAR T-cell expansion for days 0-21 (prior to NT-I7 administration), and days 22-100 (after NT-I7 administration and 3 months post CAR T-cell Therapy infusion)
- To evaluate the immunogenicity of NT-I7
 - Incidence of anti-drug antibody (ADA) to NT-I7 during the study relative to Day 21 (pre-dose NT-I7)
- To evaluate the Pharmacokinetic profile of NT-I7
 - Serum concentration of NT-I7 administered on Day 21 pre-dose and at specified timepoints for the following parameters: Area under the concentration time-curve (AUC), maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), and clearance (CL).

For Dose Expansion Phase:

- To explore the Overall Response Rate (ORR) of NT-I7 when administered after

CAR T-cell Therapy infusion for r/r LBCL

2.5.4 Exploratory Objective for Correlative Analysis

For Dose Escalation and Expansion Phases:

- To evaluate the effect of NT-I7 when administered after SoC CAR T-cell Therapy on the expansion of lymphocytes, CAR T-cells, and serum cytokines in vivo.

For Dose Expansion Phase:

To correlate baseline and post-treatment responses

- Plasma minimum residual disease (MRD) and compared to SoC Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)-CT imaging

2.6 Study Outcome Measures

2.6.1 Primary Outcome Measures

- Incidence, nature, and severity of adverse events (AEs) graded according to national cancer institute (NCI) common terminology criteria for adverse events (CTCAE) v5.0, except grading of CRS and ICANS which will be based on American Society for Transplantation and Cellular Therapies (ASTCT) guidelines.
- Incidence and nature of DLTs.
- Potential correlation of dose levels with safety and efficacy parameters.

2.6.2 Secondary Outcome Measures

The following secondary efficacy outcome measures will be evaluated:

For Dose Escalation phase:

- Duration of Response (DOR) defined as the time from the first occurrence of a documented objective response (Partial Response [PR] or Complete Response [CR]) to the time of the first documented disease progression or death from any cause, whichever occurs first per the Lugano classification as determined by the investigator.
- Progression-Free Survival (PFS) defined as the time from the SoC CAR-T administration (Day 0) to the first occurrence of progression or death from any cause, whichever occurs first, per the Lugano classification as determined by the investigator.
- Overall Survival (OS) defined as the time from first SoC CAR-T treatment(Day 0) to death from any cause.

For Dose Escalation and Dose Expansion phases:

- Rates of grade 3 and higher CRS

- Rates of grade 3 and higher ICANS
- Quantitative DNA PCR and/or FACS for CAR-T PK analysis

2.6.3 Exploratory Outcome Measures

For Dose Escalation and Dose Expansion phases:

- PK parameters of expansion, including maximum concentration ($C_{\max}$) and time to maximum concentration ($T_{\max}$)
- PK parameters of persistence, including the terminal half-life ($t_{1/2}$), last measured concentration (C_{last}), and time of last measured concentration (T_{last})
- Area under the curve for CAR T-cell expansion for days 0-21 (prior to NT-I7 administration), and days 22-100 (after NT-I7 administration and 3 months post CAR T-cell Therapy infusion)
- Incidence of anti-drug antibody (ADA) to NT-I7 during the study relative to Day 21 (pre-dose NT-I7)
- Serum concentration of NT-I7 administered on Day 21 pre-dose and at specified timepoints for the following parameters: Area under the concentration time-curve (AUC), maximum serum concentration ($C_{\max}$), minimum serum concentration ($C_{\min}$), and clearance (CL).

For Dose Expansion phases

- Overall Response Rate (ORR) at 3 months

2.6.4 Exploratory Outcome Measures for Correlative Analysis

- Flow cytometry-based comprehensive immunophenotyping of T cells, T-cell subtypes and myeloid subsets in peripheral blood. Additional markers may include, but are not limited to, Ki-67
- Quantitative DNA PCR and/or FACS for measuring CAR T-cell expansion
- Serum cytokine profiling
- Single cell RNA sequencing (scRNA-seq) of peripheral blood before NT-I7 administration, on D35 +/- 2 days (i.e., approximately 2 weeks after NT-I7 administration), and at the time of relapse
- LBCL immunophenotyping pre-treatment (before CAR T-cell Therapy infusion) and at the time of relapse
- Polyfunctional analyses to assess the number and percentage of CAR T-cell and non-transduced T cells that are able to express and secrete various cytokines and chemokines before NT-I7 administration and on D35 +/- 2 days
- Plasma Minimal Residual Disease (MRD), and compared to SoC FDG PET-CT imaging (dose expansion only)

2.6.5 Safety Measures

- Incidence of Treatment-Emergent Adverse Events (TEAE)

- Incidence of withdrawals from the study due to TEAEs
- Changes and shifts in laboratory measurements over time
- Changes in vital signs over time
- Changes and shifts in Electrocardiogram (ECGs) over time
- Physical examination over time
- Changes in eastern cooperative oncology group (ECOG) performance status over time

3. SAMPLE SIZE DETERMINATION, STATISTICAL POWER, AND SIGNIFICANCE LEVEL

Dose Escalation Phase

This is a 3+3 dose escalation design that will recruit approximately 17-42 subjects. This sample size is selected based on clinical judgment and not based on statistical power calculation; it is deemed adequate to provide clinically meaningful descriptive results consistent with study objectives.

Dose Expansion Phase

15 subjects are planned for enrollment to ensure 13 evaluable subjects. Since the primary goal of the Dose Expansion phase is focused on evaluating toxicity in a larger sample size, the sample size calculation should be based on safety. Any grade CRS has been reported in, approximately, 50% of patients treated with CD19 CAR-T SoC (Kymriah 58%, Yescarta, 92%, Breyanzi 42%) and ~10% of patients will have Grade 3 or higher CRS (Kymriah 22%, Yescarta, 6%, Breyanzi 2%). ICANS are observed on average in 37% of patients treated with CD19 CAR-T SoC (Kymriah 21%, Yescarta, 60%, Breyanzi 30%) and ~14% of patients will have Grade 3 or higher ICANS (Kymriah 12%, Yescarta, 21%, Breyanzi 10%). The sample size was calculated and demonstrated by NIT that addition of NT-I7 does not change the safety profile of these therapies. A sample size of 15 patients will prove that NT-I7-treated patients develop any grade CRS in less than 20% of cases ($n = 3$) and any grade ICANS in less than 13% of cases ($n = 2$).

4. INTERIM ANALYSIS

An Interim Analysis will be performed at the completion of the Dose Escalation phase. A Data Safety Monitoring Committee (DSMC) will make decisions for dose escalation or dose-de-escalation in the Dose Escalation phase and determine the RP2D; in the Dose Expansion phase, the DSMC will monitor for subject safety and scientific integrity during the study.

In addition, the safety of the enrolled subjects will be continuously monitored by the site investigators/staff/Sponsor or Sponsor designee and the Study Stopping Rules will be followed. All immediate safety concerns must be discussed with the Sponsor and/or Sponsor's designee upon occurrence and/or awareness of the event to determine appropriate care for the subject, including whether the subject should continue or discontinue study treatment.

4.1 Goals

The objective of this IA is to review the current data for safety, efficacy, and determine the MTD and RP2D for the second phase of the study.

4.2 Analysis Population

The IA population will be the subjects who have completed the dose escalation phase.

4.3 Procedures for Data Preparation

The procedures of the IA include the following:

1. Cutoff dates for collection of Electronic Case Report Forms (eCRFs), data querying, database lock and analysis will be established based on an estimated target date at the completion of the Dose Escalation.
2. All data received by the cutoff date will be entered, validated, queries generated and resolved, or pending queries documented.
3. The data snapshot for the IA will be taken.
4. The statistician will generate planned data and information for the DSMC.

4.4 Metrics to be Calculated for the Interim Analysis

Using this data, the statistician will prepare safety summaries and calculate the following metrics for the primary and secondary endpoints:

- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Rates of grade 3 and higher CRS
- Rates of grade 3 and higher ICANS
- Incidence of anti-drug antibody (ADA) to NT-I7 during the study relative to Day 21 (pre-dose NT-I7)

- Serum concentration of NT-I7 administered on Day 21 pre-dose and at specified timepoints for the following parameters: Area under the concentration time-curve (AUC), maximum serum concentration (Cmax), minimum serum concentration (Cmin), and clearance (CL).
- Rate of AEs related to NT-I7
- Rate of grade 3 or higher AEs related to NT-I7
- Rate of serious adverse events (SAEs) related to NT-I7

4.5 Data Provided to DSMC

The DSMC will receive a statistical report. The details of the content of the report are described in the DSMC charter.

4.6 Determination of RP2D

The Data Safety Monitoring Committee (DSMC) and the sponsor will make decisions on the MTD and RP2D per reviewing the current data for safety and efficacy.

4.7 Stopping Rule

There is no intent to stop the study due to this interim analysis. The study may be stopped due to DLTs on the cohort-by-cohort dose-escalation safety reviews.

Study Stopping Rules are applicable to all subjects that are considered enrolled and have received NT-I7 as below:

- Any Grade 5 AE (except for events related to disease progression or clearly unrelated deaths); OR
- Any Grade 4 or life-threatening toxicity attributable to NT-I7 that is unmanageable and unexpected; OR
- Subject incidence of > 33% for any of the following events regardless of duration (including

all subjects from Dose Escalation and Dose Expansion):

- o Grade 4 CRS
- o Grade 4 vital organ toxicity
- o Grade 3 or higher ICANS
- o Other nonhematologic SAE
- o New malignancy (distinct from recurrence/progression of previously treated malignancy)

5. PRIMARY HYPOTHESIS TO BE TESTED

There is no formal hypothesis testing for this study as the study is a Phase 1b evaluation and is not intended to be hypothesis generating. The study is not powered to reliably yield statistically significant conclusions.

6. ANALYSIS POPULATIONS

6.1 Safety Population

The safety population is defined as all subjects who received NT-I7. This population will be used for analysis of all safety evaluations.

6.2 Efficacy Evaluable Population

The Efficacy Evaluable Population is defined as all subjects who received NT-I7 and have at least one post baseline efficacy data. This population will be used for the analysis of efficacy parameters.

6.3 PK Evaluable Population

The PK evaluable population includes all patients in the safety population who provide adequate blood samples for PK evaluation and calculation of the PK parameters. This population will be used for the analysis of PK outcome measures.

6.4 DLT Population

The DLT population includes all patients in the safety population who completed the full 3-week DLT window or who did not complete the full 3-week DLT window due to the occurrence of a DLT.

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all safety parameters, baseline will be defined as the last available value before NT-I7 administration.

For PFS, OS, and tumor response, baseline will be defined on the date of CAR-T administration.

For DOR, baseline will be defined on the date of first response.

For NT-I7 PK and ADA, baseline will be defined as the last available value before NT-I7 administration.

For CAR-T expansion, baseline will be defined as the last available value before CAR-T administration.

For assessments where both pre-dose and post-dose measurements are collected on the date of the first treatment, the pre-dose assessment will be used as the baseline value.

7.2 Duplicate Data

For unplanned duplicate data within a protocol-specified visit, all collected data will be listed and the last measured value will be used for the analysis. If it is not possible to identify the “last measured value,” the average of the duplicate values will be used. In cases where additional ECGs are performed at the same visit, the Duplicate ECGs ¹ measurements will be used for the analysis.

7.3 Handling of Missing Data

7.3.1 Handling of Missing Data for Efficacy Evaluations

All efforts will be made to avoid missing data; however, there will be no imputation of missing data for this early phase study and all summaries will be based on observed data only.

7.3.2 Handling of Missing Data for Safety Evaluations

The below imputation rules will be followed for imputation of missing dates:

Partial/Missing Start Date	Missing day - Impute the 1st of the month unless month is same as month and year of first dose of study drug then impute first dose date
	Missing month – Impute January unless year is the same as first dose date then impute first dose month
	Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute Jan 1st of the same year as the end date.

¹ Duplicate ECGs refers to the additional ECG collection section with the leading question “Was a duplicate ECG performed” from the eCRF.

	When imputing a start date, ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or med.
--	--

7.4 Multicenter Clinical Trials

This is a multi-center clinical trial. There are approximately 20 centers.

7.5 Multiple Comparisons and Multiplicity

There will be no adjustment for multiple testing or multiplicity for this phase 1b trial. For all effectiveness outcome measures, inference will be based on a type I error rate of 0.05.

7.6 Covariates and Prognostic Factors

Not applicable.

7.7 Subgroups

The following subgroup analyses will be performed to all primary and secondary outcome measures.

- Type of CAR T-Cell Therapy: Kymriah, Yescarta, or Breyanzi
- End of Study Visit: < Day 100 or > Day 100

7.8 Standard Calculations and Definitions

7.8.1 Age

Age will be calculated as the number of completed years between the date of informed consent and the subject's birth date.

$$\text{Age (years)} = \text{integer of } [(\text{date of informed consent} - \text{date of birth}) / 365.25]$$

7.8.2 Change from Baseline

Change from baseline will be calculated for each post baseline visit as follows:

$$\text{Change From Baseline} = \text{Post baseline result at time} - \text{Baseline result}$$

7.8.3 Percent Change from Baseline

Percent change from baseline will be calculated for each post baseline visit as follows:

$$\text{Percent change from Baseline} = (\text{Post baseline result at time} - \text{Baseline result}) / \text{Baseline result} * 100$$

7.8.4 Time to PFS/OS

Time to event will be calculated according to the formula noted below:

$$\text{Time to event} = (\text{Date of Event} - \text{Date of CAR-T administration}) + 1$$

7.8.5 Duration of Response

Duration of Response will be calculated according to the formula noted below:

$\text{Duration of Response} = (\text{Date of first documented disease progression or death} - \text{Date of first occurrence of a documented objective response (PR or CR)} + 1$

8. STATISTICAL METHODS

All statistical analyses will be performed using SAS® for Windows, version 9.4 or later. All data collected during this study will be presented in subject data listings.

The Safety population will be the primary analysis population for the analysis of the primary outcome measure. All the efficacy analyses presented here will be conducted using the Efficacy Evaluable population. All safety analyses will be conducted using the Safety population.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented by dose levels (DLs). For categorical variables both frequencies and percentages will be presented by DLs.

8.1 Summarizing Disposition and Baseline Data

8.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects who sign an informed consent to participate in this trial. The following will be summarized by DLs:

- The number of subjects who signed informed consent
- The number of subjects who are screen failures
- The number of subjects who received study treatment
- The number of subjects who completed the DLT Review Period
- The number of subjects who complete the study
- The number of subjects who discontinue prior to completion
 - Reasons for discontinuation will also be summarized descriptively by DLs.

In addition, there will also be a listing of all discontinued subjects, which will provide the specific reason for discontinuation.

8.1.2 Protocol Deviations

Protocol deviations for all subjects will be listed as by-subject listing and summarized descriptively according to the following categories:

- Informed consent not properly attained
- Did not meet Inclusion/Exclusion criteria but entered into study
- Developed withdrawal criteria during the study but not withdrawn
- Procedure performed out of window
- Received excluded concomitant medication
- Missed procedure or visit
- Other

Additionally, a by-subject listing of all deviations will also be prepared.

8.1.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, race, gender, ethnicity, height,

weight, Body Mass Index (BMI), etc.) will be presented as by-subject listing and summarized by dose levels (DLs) for all enrolled subjects. See [Section 7.1](#) for baseline definition.

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term (PT). Medical history. Prior anti-cancer treatment and disease history including relapsed/refractory status, Bone marrow biopsy and aspirate, Fresh and archival biopsy (Fresh -optional) will be provided as by-subject listings.

8.1.4 Prior and Concomitant Medications

Prior medication is defined as any medication with an end date prior to CAR-T treatment date. Concomitant medication is defined as any medication taken on or after the date of CAR-T infusion.

All prior and concomitant medications recorded in the case report form will be listed and coded to the drug substance level (i.e., generic term) using the most recent WHO Drug dictionary version and summarized by Anatomical Therapeutic Classification (ATC) class (2nd level, chemical subgroup) and PT. Subject will only be counted once within each ATC-2 code and within each preferred name.

8.1.5 Extent of Exposure

All treatment administration data will be listed and summarized by DLs for the Safety population.

8.2 Analysis of Outcome Measures

All data collected will be summarized according to the variable type. No inferential statistics are planned.

8.2.1 Analysis of Primary Outcome Measure

The primary outcome measure for the Phase 1b will be the safety and tolerability, including determination of the MTD and/or the RP2D, of NT-I7 when administered after SoC CAR T-cell Therapy in subjects with r/r LBCL, as assessed by the NCI CTCAE v5.0, except grading for CRS and ICANS will be based on ASTCT guidelines.

8.2.1.1 Maximum Tolerated Dose (MTD)

The MTD will be defined as the dose of NT-I7 that yields a DLT rate $\leq 33\%$. If an MTD is not reached, the highest administered dose evaluated for safety will be 720 $\mu\text{g/kg}$.

The proportion of subjects at the different dose levels (DLs) and the MTD will be summarized descriptively. Please refer to [Section 8.1.5](#) for exposure summary.

8.2.1.2 Dose Limiting Toxicity (DLT)

All toxicities will be graded using NCI-CTCAE Version 5.0, with the exception of CRS and ICANS which will be graded using ASTCT guideline. Dose-limiting toxicity is defined

as any AE occurring within the first 21 days after NT-I7 administration that is considered to be at least possibly, probably, or definitely related to the study treatment (NT-I7) per the investigator, and that meets at least one of the non-hematologic or hematologic criteria listed below.

Hematologic criteria

- Any Grade 5 toxicity
- Grade 4 neutropenia lasting more than 5 days
- Febrile neutropenia of more than 5 days ($ANC < 1.0 \times 10^9/L$, fever $\geq 38.5^\circ C$)
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding or
- Any requirement for platelet transfusion not recovering to baseline at the end of DLT period
- Grade 4 anemia, unexplained by underlying disease
- Grade 4 hematological toxicities lasting more than 21 days

Non-hematologic criteria

- Any Grade 5 toxicity
- Grade 3 or higher non-hematologic toxicity.
- Hy's law criteria
- Any Grade ≥ 4 CRS or Grade 3 CRS that does not improve to Grade ≤ 1 within 72 hours
- Any Grade ≥ 3 ICANS. Note: Grading of CRS and ICANS is based on ASTCT guidelines
- The following exceptions are acceptable (i.e., not considered DLTs)
 - Grade 3 or 4 electrolyte abnormalities that lasts < 24 hours to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
 - Grade 3 nausea, vomiting or diarrhea that resolves to Grade 2 or less within 72 hours with symptomatic treatment
 - Grade 3 liver enzyme abnormalities improving to grade 2 or better within 72 hours

DLT will be included as the subset of adverse event analysis. AEs with DLT will be presented as by-subject listings, and/or summarized descriptively by each cohort.

8.2.1.3 Recommended Phase 2 Dose (RP2D)

The RP2D will be based on an accumulation of all available data. All available data including clinical PK, PD, safety, and anti-tumor activity will be analyzed. Integrated dose-response and exposure-response analyses will be conducted to determine the RP2D.

8.2.2 Analysis of Secondary Outcome Measures

In this Phase I study efficacy is a secondary objective. The efficacy analysis will be conducted on the Efficacy Evaluable population. Comparative assessments are not planned.

8.2.2.1 Duration of Overall Response (DOR)

Duration of response (DOR) for the responders is defined as the time from the first occurrence of a documented objective response (PR or CR) to the time of the first documented disease progression or death from any cause, whichever occurs first, per the Lugano classification as determined by the investigator.

DoR will be assessed statistically via Kaplan-Meier methods and presented descriptively for the responders.

All data will be presented as a by-subject listing.

8.2.2.2 Progression Free Survival (PFS)

Progression Free Survival (PFS) will be calculated using the formula in [Section 7.8.4](#). The censoring rule for PFS is described in [Table 8-1](#). These conventions are based on the April 2015 FDA Guidance for Industry, “Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics”. Kaplan-Meier analysis will be used to depict the median PFS (months).

Table 8-1 Date of Progression or Censoring for Progression-free Survival Situation

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	First treatment administration date	Censored
Progression documented between scheduled visits	Earliest of: • Date of progression assessment showing new lesion (if progression is based on new lesion); or • Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression assessment with no documented progression	Censored
New anticancer treatment started	Date of last progression assessment with documented non progression before start of new treatment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

Situation	Date of Progression or Censoring	Outcome
Death or progression after more than one missed visit	Date of last progression assessment with documented non progression	Censored

8.2.2.3 Overall Survival (OS)

Overall survival (OS) will be calculated using the formula in [Section 7.8.4](#). All subjects will be followed for survival according to the schedule of procedures through the end of the study (defined as 3 months after the final subject is enrolled or the sponsor stops the study, whichever occurs first). The censoring rule for PFS is described in [Table 8-2](#). Kaplan-Meier analysis will be used to depict the median OS (months).

Table 8-2 Date of Censoring for Overall Survival Situation

Situation	Date of Progression or Censoring	Outcome
Subject died	Date of Death	Dead
Subject known to be alive in the survival follow-up	Date of last day known to be alive	Censored
Subject completed the study	Date of study completion	Censored
Subject withdrew from the study or was lost to follow-up	Date of withdraw from the study or lost to follow-up	Censored
Subject did not withdraw nor lost to follow-up and is still in the study	Date of last visit	Censored

8.2.2.4 Cytokine Release Syndrome (CRS)

CRS based on clinical presentation will be identified. Subjects will be closely monitored for the development of fever, hypotension and hypoxia. Treatments including the use of tocilizumab and corticosteroids will be implemented, as appropriate, following the modified version of ASTCT grading guideline.

The subjects with identified CRS will be listed. The percentage of subjects with grade 3 and higher CRS will be summarized.

8.2.2.5 Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Subjects will be closely monitored with frequent neurologic examinations. ICANS will be graded using ASTCT guideline. The subjects with identified ICANS will be listed. The percentage of subjects with grade 3 and higher ICANS will be summarized.

8.2.2.6 Quantitative DNA PCR and/or FACS for CAR-T PK analysis

Quantitative DNA PCR and/or FACS for CAR-T PK analysis will be presented as by-subject listings. Summary statistics of raw data for each parameter will be presented by DLs and time point.

8.3 Analysis of Safety Data

All safety analyses will be conducted using the Safety population. All data collected will be summarized according to the variable type. No inferential statistics are planned.

8.3.1 Adverse Events

AEs will be classified by SOC and PT according to the CTCAE version v5.0 and coded using the most recent MedDRA dictionary version, except grading of CRS and ICANS which will be based on ASTCT guidelines.

TEAEs are defined as AEs with onset date on or after the NT-I7 treatment and within 100 days of NT-I7 administration. TEAEs will be summarized by DLs, System Organ Class, and PT. Similar summary will be applied to AEs with onset date after initiation of CAR T-cell therapy and before NT-I7 administration. The following summaries will be provided separately for TEAEs and AEs with onset date after initiation of CAR T-cell therapy and before NT-I7 administration:

- a) AEs Overall (*i.e.*, regardless of severity or relationship to treatment)
- b) AEs with Grade 3 or Higher
- c) Treatment related AEs
- d) Treatment related AEs with Grade 3 or Higher
- e) AEs leading to study discontinuation
- f) AEs leading to death
- g) Serious AEs
- h) Treatment related serious AEs

Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

All AEs recorded in the eCRF will be presented as by-subject listings.

8.3.2 Clinical Laboratory Evaluations

Clinical laboratory evaluations (biochemistry, hematology, coagulation, thyroid function test, lymphocyte subsets, urine analysis, and cardiac enzyme) will be listed and/or summarized, as follows.

8.3.2.1 Laboratory Values over Time

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented by DLs and time point. Data will be summarized as appropriate for the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.2.2 Individual Subject Changes (Shift Tables)

Laboratory data will be classified into grades according to CTCAE toxicity grading. A severity grade of 0 will be assigned when the value is within normal limits.

The following summaries will be produced for the hematology, biochemistry, coagulation, and urinalysis laboratory data (by laboratory parameter):

- Shift tables using the PI's lab interpretation (i.e., normal, abnormal (not clinically significant) and abnormal (clinically significant)) to compare baseline to the worst post-baseline value) will be produced for parameters without CTCAE grades.

8.3.2.3 Individual Clinically Significant Abnormalities

Clinically significant laboratory abnormalities will be listed.

8.3.3 **Vital Signs**

Vital sign assessments are performed in order to characterize basic body function. The parameters collected in this study are systolic BP (mmHg), diastolic BP (mmHg), temperature ($^{\circ}\text{C}$), heart rate (bpm), respiratory rate (rpm). All vital signs results will be listed as a by-subject listing.

8.3.3.1 Vital Sign Values Over Time

Summary statistics of raw data and change from baseline values for each vital sign parameter will be presented by DLs and time point. Data will be summarized as appropriate for the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.3.2 Individual Patient Changes on Notable Vital Sign Values

Clinically notable elevated values

- Systolic BP: ≥ 160 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 100 mmHg and an increase ≥ 15 mmHg from baseline.
- Body temperature: $\geq 39.1^{\circ}\text{C}$
- Heart rate: ≥ 120 bpm with increase from baseline of ≥ 15 bpm
- Respiration rate: ≥ 24 breaths per minute with increase of ≥ 6 breaths per minute from baseline

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Body temperature: $\leq 35^{\circ}\text{C}$
- Heart rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm
- Respiration rate: < 8 breaths per minute with decrease of ≥ 6 breaths per minute from baseline

Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e., both elevated and below normal values) will be summarized by dose levels (DLs).

8.3.3.3 Individual Clinically Significant Abnormalities

Clinically significant vital sign abnormalities (i.e., those vital sign abnormalities recorded as AEs) will be listed.

8.3.4 **Electrocardiogram (ECGs)**

The ECG parameters include ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), QT interval (msec), and QTc interval (msec). All ECG results will be listed as a by-subject listing.

8.3.4.1 ECG Values over Time

Summary statistics of raw data and change from baseline values for each ECG parameter will be presented by time point. Data will be summarized as appropriate for the variable type.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.4.2 Individual Patient Changes on Notable ECG Values

The number and percentage of patients having notable ECG interval values and newly occurring qualitative ECG abnormalities will be summarized by DLs.

Number and percentage of subjects with at least one occurrence of the below notable ECG changes will be summarized.

QT and QTc:

- (1) New >450 msec
- (2) New >480 msec
- (3) New >500 msec
- (4) Increase from baseline >30 msec
- (5) Increase from baseline >60 msec

Shift tables will also be presented for the categories of QT results (≤ 450 , 450-480, 480-500, >500) with counts and percentages of subjects, for shift (change) from baseline.

PR:

- (1) An increase >25% from baseline and PR >200 msec at any post-baseline assessment

QRS:

- (1) An increase >25% from baseline and QRS >110 msec at any post-baseline assessment

Ventricular rate:

- (1) A decrease >25% from baseline and HR <50 bpm at any post-baseline assessment
- (2) An increase >25% from baseline and HR >100 bpm at any post-baseline assessment

In addition, individual subject changes will be identified through shift tables. Shift tables will be presented for the investigator ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects, for shift (change) from baseline.

8.3.5 Physical Examination

Physical Examination findings will be presented as by-subject listing.

8.3.6 ECOG Performance Status

All data for ECOG performance status will be presented as by-subject listing and summarized descriptively by DLs by visit

A shift table will be presented based on ECOG Grade with counts and percentages of subjects to compare baseline to the worst post-baseline value.

8.3.7 Echocardiogram

All data from echocardiogram will be presented as a by-subject listing.

8.4 Analysis of Exploratory Outcome Measures

8.4.1 Overall Response Rate (ORR)

ORR at 3 months will be assessed by Investigators using FDG PET-CT and the Lugano classification. The ORR for each DLs will comprise of the proportion of subjects with a BOR of a CR or PR. All data will be presented as a by-subject listing and summarized descriptively based on efficacy evaluable population. Tables will be presented with counts and percentages of subjects for ORR at 3 months.

8.4.2 Immunogenicity Assessment

Analysis of Immunogenicity assessment will be performed by NIT. Data will be transferred from BioAgilytix to NIT and Amarex. Incidence of ADA to NT- I7 during the study relative to baseline and the presence of neutralizing ADA (NADA) will be summarized. All data will be listed as by-subject listing.

8.4.3 Preliminary assessment of PK parameters of CAR T-cell Therapy when administered NT-I7 post- CAR-T cell therapy.

Preliminary assessment of PK parameters of CAR T-cell Therapy when administered NT-I7 post- CAR-T cell therapy will be presented as by-subject listings and summarized descriptively. Data will be transferred from Navigate to NIT and Amarex.

8.4.4 Pharmacokinetic profile of NT-I7

PK samples will be collected from all subjects. Serial samples will be assessed following the PK timepoints in the [Table 8-3](#). Data will be transferred from BioAgilytix to NIT and Amarex.

Table 8-3 Pharmacokinetic timepoints (All subjects)

Treatment Cycle/Visit	Week 3				Week 4	Week 5
Scheduling Window	Day 21			Day 22	Day 28± 2 days	Day 35 ± 2 days
Hours	0 h	2 h (±15mins)	6 h (±30mins)	24 h (±1h)		
Pharmacokinetics*	X ^a	X ^b	X ^b	X ^b	X	X

^a To be collected prior to study agent(s) administration on a dosing day.

^b Blood draws are timed after NT-I7 administration is complete.

*Details on blood collection, handling, and shipping are provided in the Laboratory Manual.

PK concentration will be provided and transferred from BioAgilytix to NIT and Amarex.

All data will be presented as by-subject listings using PK Evaluable Population.

Descriptive statistics for the PK concentrations will be presented using scheduled sampling time by dose levels (DLs). Actual sampling time will be included in data listings. No inferential statistics will be performed on concentration data.

The PK parameters will be calculated from concentration-time profiles of plasma concentration. If time or concentration is missing, then the observation will be considered missing. Unless otherwise specified, computations involving sampling times will use actual times rather than scheduled times, except for pre-dose. Descriptive statistics including arithmetic means; standard deviation; median, minimum, and maximum values; and number of observations will be presented for all PK parameters. Geometric mean and geometric coefficient of variation (CV) will be provided for area under the plasma concentration vs time curve (AUC_{0-t}).

The following PK parameters will be calculated:

- Maximum observed plasma drug concentration (C_{max})
- Time to maximum observed plasma drug concentration (T_{max})
- Area under the plasma drug concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (T_{last}) (AUC_{0-t})
- Minimum observed concentration (C_{min}),
- Apparent plasma clearance (CL)
- Apparent terminal elimination half-life (t_{1/2})

- Time of the last measured concentration (T_{last})
- Last measured concentration (C_{last})

8.5 Exploratory Outcome Measures for Correlative Analysis

8.5.1 Effect of NT-I7 when administered after CAR T-cell Therapy on the expansion of lymphocytes, CAR T-cells, and serum cytokines in vivo

To evaluate the effect of NT-I7 when administered after CAR T-cell Therapy on the expansion of lymphocytes, CAR T-cells, and serum cytokines in vivo, below exploratory outcome measures will be performed by NIT. Data will be transferred from vendors to NIT directly and there will be no data transfer to Amarex.

- Flow cytometry-based comprehensive immunophenotyping of T cells, T-cell subtypes and myeloid subsets in peripheral blood. Additional markers may include, but are not limited to, Ki-67
- Quantitative DNA PCR and/or FACS for measuring CAR T-cell expansion
- Serum cytokine profiling
- Single cell RNA sequencing (scRNA-seq) of peripheral blood before NT-I7 administration, on D35 +/- 2 days (i.e., approximately 2 weeks after NT-I7 administration), and at the time of relapse
- LBCL immunophenotyping pre-treatment (before CAR T-cell Therapy infusion) and at the time of relapse
- Polyfunctional analyses to assess the number and percentage of CAR T-cell and non-transduced T cells that are able to express and secrete various cytokines and chemokines before NT-I7 administration and on D35 +/- 2 days

8.5.2 To correlate baseline and post-treatment responses as assessed by plasma minimum residual disease (MRD) and compared to SoC FDG PET-CT imaging

To correlate baseline and post-treatment responses as assessed by MRD and compared to SoC FDG PET-CT imaging for dose expansion cohort, MRD, and compared to SoC FDG PET-CT imaging will be performed by NIT. Data will be transferred from vendors to NIT directly and there will be no data transfer to Amarex.

9. APPENDIX 1 SCHEDULE OF EVENTS

Figure 9-1 Schedule of Assessments

Phase 1b														
Treatment Week / Visit	Screening	SoC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14days	± 7 days
Lymphodepletion		X												
CD19 CAR T-cell infusion ¹⁷			x											
NT-17							X							
Informed consent ¹	X													
Verify eligibility criteria	X						X							

Phase 1b														
Treatment Week / Visit	Screening	SoC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14days	± 7 days
Prior cancer treatment and disease history including relapsed/refractory status ¹⁹	X													
Disease assessment by 2014 IWG Criteria for lymphoma and Whole body FDG-PET/CT scan		X						X					X	Per CAR-T SoC
Bone marrow biopsy and aspirate ²¹	X													
Physical exam	X	X		X	X	X	X	X	X	X	X	X	X	
Demographics	X													
Medical history	X													
ECOG performance status	X			X			X			X			X	

Phase 1b														
Treatment Week / Visit	Screening	SoC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14days	± 7 days
Vital signs ³	X		X	X	X	X	X	X	X	X	X	X	X	
Height ⁴	X													
Weight	X		X	X	X	X	X	X	X	X	X	X	X	
AEs/SAEs Assessment ⁵	X		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications ²	X		X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG ⁶	X			X			X			X			X	
Cardiac Enzymes (Troponin (Tnl or TnT) and CK-MB) ⁶	X			X			X			X			X	
Echocardiogram ²²	X ²²			X ⁶			X ⁶			X ⁶			X ⁶	

Hematology ⁷	X	X	X	X	X	X	X	X	X	X	X			X	
Serum chemistry ⁸	X			X	X	X	X	X	X		X	X	X	X	

Phase 1b														
Treatment Week / Visit	Screening	SoC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14days	± 7 days
Coagulation parameters	X			X			X			X			X	
Thyroid Function Tests ⁹	X			X			X			X			X	
Urine or Serum Pregnancy Test ¹⁰	X			X			X			X			X	
Lymphocyte Subset Panel ¹⁸			X	X	X	X	X	X	X	X			X	
Urinalysis ¹¹	X			X		X	X	X		X	X		X	

Phase 1b														
Treatment Week / Visit	Screening	SoC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho-depletion (LD)	CD19 CAR T-cell infusion Day 0 ¹⁴	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after LD	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14days	± 7 days
Fresh or archival biopsy (Fresh – optional) Archival – required if available ¹⁶	X													
Immunogenicity (NT-17 ADA)							X		X		X	X	X	
Pharmacokinetics ¹²														
Refer to Table 5 for PK sampling														
Immunophenotyping ¹³		X			X	X	X	X	X	X			X	
FACS/PCR		X			X	X	X	X	X	X			X	
Serum cytokine profiling		X			X	X	X	X	X	X			X	
scRNA-seq						X			X				X	

Phase 1b														
Treatment Week / Visit	Screening	SoC Baseline		Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 9	Week 15 ¹⁵	Survival Follow-up
Scheduling Window	Within	Lympho- depletion (LD)	CD19 CAR T-cell	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 63	Day 100	Every 90 Days post-NT-17
	28 days	3 days	2 to 11 days after	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14days	± 7 days
Polyfunctional CAR-T cell, T cells		X			X			X				X		
MRD (Ig-HTS) ²⁰		X		X		X		X				X		

¹Written consent must be obtained prior to performing any protocol specified procedure.

²Prior medications – Record all medications (prescription and over-the-counter [OTC]) taken within 30 days of Screening visit. Concomitant medications – Enter all medications (prescription and OTC) taken between Consent through Day 100. Follow-up anti-cancer therapies should continue to be recorded during survival follow-up.

³Vitals (blood pressure, heart rate, respiratory rate, temperature) to be collected in a standardized manner in a sitting position after the subject has rested comfortably for ~5 minutes.

⁴Height is measured on the first visit during Screening only.

⁵Adverse event recording including immune related adverse events will commence from the time of consent through Day 100.

⁶Duplicate ECGs, at least 5 minutes apart, and serum cardiac enzyme levels (Troponin (TnI or TnT) and CK-MB) must be obtained at Screening, Days 1, 21, 42, and 100.

⁷Hematology includes complete blood count (CBC) with differential, including but not limited to red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with differential (neutrophil count including lymphocyte, monocyte, eosinophil, basophil counts and bands), absolute neutrophil count (ANC), and platelet count.

⁸Chemistry includes (but is not limited to) sodium, potassium, calcium, phosphorus, chloride, magnesium, bicarbonate, blood urea nitrogen (BUN) or urea, serum creatinine, glucose, uric acid, albumin, total protein, alkaline phosphatase, lactate dehydrogenase, bilirubin (indirect and direct), aspartate serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum pyruvic transaminase (ALT/SGPT).

⁹Thyroid function testing: thyroid-stimulating hormone (TSH), free Triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)

¹⁰Serum pregnancy test to be performed at the Screening visit for all females except those surgically sterile or 1 year postmenopausal. Subsequent serum or urine pregnancy tests could be performed as noted or per the Investigator's discretion. A serum or urine pregnancy test must be performed within 72 hours of the first dose of NT-17. Tests completed > 72 hours must be repeated prior to NT-17 dosing.

¹¹Urinalysis (a urine dipstick may be used) at scheduled visits.

¹²For sampling details of PK, please refer to Table 5Table 5. Additional information on handling and shipping are provided in the *Laboratory Manual*.

- 13** Whole blood will be collected for the multispectral immunophenotyping to obtain absolute cell counts for CD4+ and CD8+ T-cell and other cell types as necessary.
- 14** SoC CD19 CAR T-cell infusion will be given within 2 to 11 days after lymphodepletion therapy. The day CAR T-cell therapy is given will be considered the Baseline Visit, Day 0. All baseline samples for correlative analyses will be collected on the Day 0 Baseline Visit. All baseline samples for correlative analyses will be collected on the Day 0 Baseline Visit.
- 15** End of Study Visit: Should the patient withdraw or be withdrawn from the study early, then all procedures and assessments should be completed in this column for the End of Study visit.
- 16** Tumor tissue should be tested per the site's local standard of care to confirm disease status, and this should be noted on the site's pathology report. It is recommended for the subject to have a biopsy at time of progression. Biopsy at CR is optional.
- 17** The date CAR-T Therapy cells were collected, number of cells collected, and number of cells infused should be documented on the CAR-T Therapy administration eCRF.
- 18** Lymphocyte panel to include: Absolute CD3+ cells, %CD3, Absolute CD4+ cells, %CD4, Absolute CD8+ cells, %CD8, CD4/CD8 ratio.
- 19** Cancer History to include documentation of double- or triple- hit, double- or triple- hit, double- or triple- hit, double- or triple- hit, and International Prognostic Index (IPI) at enrollment.
- 20** Minimum Residual Disease will be completed during the Dose Expansion only.
- 21** Screening bone marrow biopsy aspirate samples are required for submission in Dose Expansion for subjects with bone marrow involvement only. Prior bone marrow biopsy results should be updated into the EDC for those without bone marrow involvement. Bone marrow biopsy aspirate samples are not required for submission in Dose Escalation.
- 22** Echocardiogram is only performed at screening in cases of abnormal ECG or abnormal serum levels of cardiac enzymes where additional cardiac follow-up is needed to confirm eligibility.

10. APPENDIX 2

10.1 Planned by-subject listings

DISPOSITION/WITHDRAWALS
PROTOCOL DEVIATIONS
SUBJECTS EXCLUDED FROM ANALYSIS POPULATIONS
DEMOGRAPHIC DATA
PRIOR AND CONCOMITANT MEDICATIONS
PRIOR ANTICANCER TREATMENT
MEDICAL HISTORY
DRUG CONCENTRATION DATA
INDIVIDUAL EFFICACY RESPONSE DATA
AE LISTINGS
INDIVIDUAL LABORATORY MEASUREMENTS
VITAL SIGN
ELECTROCARDIOGRAM
ECOG
ECHOCARDIOGRAM
PHYSICAL EXAMINATION
BIOPSY
NT-17 SERUM CONCENTRATION (PK)
CAR-T PK ANALYSIS
IMMUNOGENICITY
OTHER SAFETY DATA
OTHER LISTINGS

10.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS

POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS

CONCOMITANT MEDICATION USAGE

EFFICACY SUMMARIES

SAFETY SUMMARIES AE SUMMARIES

LABORATORY

VITAL SIGNS

MEDICAL HISTORY

ELECTROCARDIOGRAM

ECOG

NT-I7 SERUM CONCENTRATION (PK)

CAR-T CONCENTRATION (PK)

IMMUNOGENICITY

OTHER SAFETY

11. REFERENCES

1. ASA Ethical Guidelines for Statistical Practice (2016)
2. The Royal Statistical Society: Code of Conduct (2014)
3. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
4. ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3(R1), 2013)
5. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)
6. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9(R1), 2017)
7. Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics Guidance for Industry (U.S. Department of Health and Human Services, April 2015)

12. VERSION HISTORY

This is the second version of this document.

Version	Version Date	File Name	Description of Changes
1.0	15 Nov 2021	20211115_NIT112_SAP_Final v1.0 (part 1) - signed.pdf	Original Version
2.0	14 Aug 2023	20230814_NIT112_SAP_Final v2.0_clean	Editorial changes were made per version 8.0 of the protocol. Details are listed in Section 13.
3.0	18 July 2023	20240722_NIT112_SAP_Final v3.0_clean	Editorial changes were made per version 11.0 of the protocol and eTMF review comments from NIT. Details are listed in Section 13.

13. SUMMARY OF CHANGES

Below is the list of changes compared with the first version.

Table 13-1: Summary of Changes from v1.0 to v2.0

Version	Section #	Section Title	Changes
2.0	Throughout	All	Protocol date and version number have been updated.
2.0	Throughout	All	Editorial changes were made per version 8.0 of the protocol.
2.0	Throughout	All	Minor adjustments for typos and formatting.
2.0	Throughout	All	Language updated to refer to all SoC CD19 CAR T-cell Therapies throughout protocol.
2.0	2.1	Design Review	Language removed for safety follow-up visits. Clarified follow-up in survival based on SoC for CAR T-cell Therapy.
2.0	2.1	Design Review	Clarified the active study will end when the last subject completes the Day 100 End of Treatment
2.0	2.1	Design Review	‘Subjects will be closely monitored and asked to stay within 1 hour radius of the location where they received treatment per treating physician’s discretion’ has been removed.
2.0	2.1	Design Review	Schema graphic has been updated to include D21 for MRD.
2.0	2.1	Design Review	Yescarta and Breyanzi administration and prescribing practices have been included.
2.0	2.1	Design Review	Schema graphic has been updated to include D21 for MRD.
2.0	2.5.3	Exploratory Objectives	Updated Area Under Curve CAR T-Cell expansion to Days 22-100.

2.0	2.5.3	Exploratory Objectives	Moved ORR analysis from primary to exploratory objectives, as the addition of two other CAR-T therapies renders current ORR statistical analysis plan obsolete.
2.0	2.5.3	Exploratory Objective	Exploratory objective about pharmacokinetics has been updated to all SoC CD19 CAR T-cell Therapies throughout SAP.
2.0	2.6.3	Exploratory Outcome Measure	ORR analysis has been moved from primary to exploratory objectives, as the addition of two other CAR-T therapies renders current ORR statistical analysis plan obsolete.
2.0	2.6.3	Exploratory Outcome Measure	Exploratory endpoint about CAR T-cell pharmacokinetics has been updated to secondary endpoint.
2.0	3	Sample Size Calculation	Sample size justification has been revised. And original statistical power calculation for ORR has been removed.
2.0	4	Interim Analysis	Interim Analysis section has been added. 'An interim analysis will be performed after the completion of the Dose Escalation' has been clarified. 'DSMC will review the data from the interim analysis and determine the recommended phase 2 dose' has been clarified.
2.0	6.4	Analysis Population	All Enrolled Subjects has been added.
2.0	7.2	Duplicate Data	Wording has been added for replicate ECGs as: 'In cases where additional ECGs are performed at the same visit, the Duplicate ECGs measurements will be used for the analysis.'
2.0	7.3.2	Handling of Missing data for safety evaluations	This section has been newly added.

2.0	7.7	Subgroups	Subgroup analysis has been updated. Stratification factors for those who received Kymriah, Breyanzi, and Yescarta and those whose End of Study visit occurs < 100 days or ≥ 100 days have been added.
2.0	8.1.3	Demographics and Baseline Characteristics	Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term (PT).
2.0	8.2.2	Analysis of Secondary Outcome Measures	Section title wording has been updated
2.0	8.2.2.6	Quantitative DNA PCR and/or FACS for CAR-T PK analysis	This section has been newly added.
2.0	8.3.1	Adverse Event	'AE will be classified by SOC and PT according to CTCAE version 5 except grading of CRS and ICANS which will be based on ASTCT guidelines'
2.0	8.3.1	Adverse Event	'Adverse events with Grade 3 or higher' and 'Related adverse events with Grade 3 or higher' will be summarized.
2.0	8.3.1	Adverse Events	'Severe adverse events by CTCAE grade' has been removed.
2.0	8.3.1	Adverse Events	'f) Adverse events leading to treatment discontinuation' has been updated to 'Adverse events leading to study discontinuation'.

2.0	8.3.2	Laboratory Evaluations	Added Thyroid Function and Lymphocyte Subset Panel to with cell types to include in the panel.
2.0	8.3.3.2	Individual Subject Changes (Shift tables)	Shift table will be using CTC AE grades and PI's lab interpretation
2.0	8.3.4	Electrocardiogram (ECGs)	Wording has been updated for Electrocardiogram (ECGs) analysis
2.0	8.3.6	ECOG Performance Status	A shift table has been planned to compare the change from baseline to the worst post-baseline value.
2.0	8.4	Analysis of Exploratory Outcome Measures	This section has been newly added.
2.0	8.4.2-8.4.4	Analysis of Exploratory Outcome Measures	External data related information has been included.
2.0	8.4.1.4	The Pharmacokinetic profile of NT-I7	'PK parameters to be calculated' have been updated
2.0	9	Schedule of Event	Schedule of Assessment has been updated

Below is the list of changes compared with the second version.

Table 13-2: Summary of Changes from v2.0 to v3.0

Version	Section #	Section Title	Changes
3.0	Throughout	All	Protocol date and version number have been updated.
3.0	Throughout	All	Editorial changes were made per version 11.0 of the protocol.
3.0	Throughout	All	Minor adjustments for typos and formatting.
3.0	Throughout	All	Headers and footers have been updated.
3.0	1.0	Introduction	Protocol version and ASA Ethical guidelines have been displayed as separate bullets
3.0	2.1	Design Overview	Below wording has been removed: ‘Starting at DL4, if a DLT was not observed at the first subject after the 3-week DLT period ended, then the second and third subjects in the cohort could be enrolled simultaneously. DLT was not observed in Dose Level 4. Given that NT-I7 has not shown an increase in the development of CRS or ICANS, all subjects in subsequent Dose Levels can enroll simultaneously. Given that NT-I7 has not shown an increase in the development of CRS or ICANS, all subjects in subsequent Dose Levels can enroll simultaneously.’

3.0	2.1	Design Overview	Below wording has been added: ‘No DLTs were observed in Dose Level 1-5. There was no subject at any dose level who experienced the first ADR between 14 days to 21 days after NT-I7 administration. Starting at Dose Level 6, if a DLT is not observed in the first subject after 2 weeks, then the second and third subjects can be dosed simultaneously.’
3.0	2.1	Design Overview	Wording has been updated to 'up to 15 subjects in the Dose Expansion phase will be enrolled at approximately 20 study centers'.
3.0	2.1	Design Overview	Wording has been updated, 'In all DLs that followed the 3+3 design in DL31-5, subjects were dosed in a 3-week staggered fashion'.
3.0	2.5, 2.6	Secondary/ Exploratory Objectives/ Outcome Measures	Added more structure to clarify whether specific objectives belong to the Dose Escalation or Dose Expansion phase, or both.
3.0	4	Interim Analysis	Wording has been updated to 'A Data Safety Monitoring Committee (DSMC) will make decisions for dose escalation or dose-de-escalation in the Dose Escalation phase and determine the RP2D.' instead of 'An independent Data Safety Monitoring Committee (DSMC).
3.0	4.4	Metrics to be Calculated for the Interim Analysis	NT-I7 PK and immunogenicity outcome measures have been added in interim analysis metrics

3.0	6.4	All Enrolled Subjects	'All enrolled subjects' has been removed.
3.0	6.4	DLT Population	DLT Population has been added.
3.0	7.1	Baseline Definition	Baseline definition of safety parameters has been specified as 'the last available value before NT-17 treatment'. Baseline definitions of DOR, PFS/OS, NT-17 PK/ADA, and CAR-T expansion have been added.
3.0	7.4	Multicenter Clinical Trials	Updated number of study sites permitted from "up to 6" to "approximately 20".
3.0	7.8.4	Time to PFS/OS	Time to Event has been updated to 'Time to PFS/OS' as 'Date of Event – Date of CAR-T administration + 1'.
3.0	7.8.5	Duration of Response	Formula of duration of response has been included

3.0	8.1.4	Prior and Concomitant Medications	Prior medication definition has been specified as 'medication with an end date prior to NT-17 administration'. Concomitant medication definition has been added as 'any medication taken on or after the date of NT-17 administration'. All prior and concomitant medications will be summarized by Anatomical Therapeutic Classification (ATC) class (2nd level, chemical subgroup) and preferred term (PT). Subjects will only be counted once within each ATC-2 code and within each preferred name.
3.0	8.2.2.2, 8.2.2.3	Progression Free Survival (PFS) Overall Survival (OS)	Hyperlinks have been fixed to avoid '(Error! Reference source not found)'.
3.0	8.3.7	Echocardiogram	Echocardiogram assessment has been added. A by-subject listing has been planned for Echocardiogram.
3.0	8.3.8	Cardiac Enzymes	Cardiac enzymes have been removed as this will be included as one of laboratory values.
3.0	8.2.2.6	Immunogenicity Assessment	Summary statistics of raw data for each parameter will be presented by dose levels (DLs) and time point.
3.0	8.4.2	Immunogenicity Assessment	Incidence of anti-drug antibody (ADA) to NT- 17 during the study relative to baseline will be summarized.

3.0	2.6.4 8.5.2	Exploratory Outcome Measures for Correlative Analysis	Changed Plasma Immunoglobulin High-Throughput Sequencing (Ig-HTS) to Plasma Minimal Residual Disease (MRD).
3.0	9	Appendix 1 Schedule of Events	Schedule of Event and footnote changes were made per version 9 of the protocol.
3.0	10.1	Planned by-subject listings	ECG, vital signs, ECOG, physical examination, medical history, concomitant medications, prior anti-cancer treatment, biopsy, echocardiogram, NT-I7 PK, CAR-T PK, and Immunogenicity have been added as planned by-subject listings.
3.0	10.2	Planned Summary Tables	Medical history, ECG, ECOG, NT-I7 PK, CAR-T PK, and Immunogenicity have been added as planned summary tables.