Statistical Analysis Plan

NCT Number: NCT05020015

Title: A Phase 2, Open-label, Multicenter Study of the Safety and Efficacy of TAK-007 in Adult Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma

Study Number: TAK-007-2001

Document Version and Date: Version 2.0, 30 Aug 2024

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-007-2001

A Phase 2, Open-label, Multicenter Study of the Safety and Efficacy of TAK-007 in Adult Patients With Relapsed or Refractory B-cell Non-Hodgkin Lymphoma

Phase: 2

Version: 2.0

Date: 30 August 2024

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Based on:

Protocol Version: *Amendment 5*

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
Original version	09-Aug-2021	[Not Applicable]
Amendment 1		To make SAP consistent with Amendment 5 of the protocol, removal of Part 2 from the study

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AECI	adverse event of clinical interest
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable concentration
BLQ	below the limit of quantification
BOIN	Bayesian optimal interval
CAR	chimeric antigen receptor
CI	confidence interval
CK	cellular kinetic(s)
C_{last}	last measurable concentration
C_{max}	maximum observed concentration
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	percent coefficient of variation
ddPCR	Droplet Digital Polymerase Chain Reaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOB	date of birth
DOR	duration of response
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ECHO	echocardiogram
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level Scale
FACT-GP5	Functional Assessment of Cancer Therapy – General
FDG-PET	^{18}F-fluorodeoxyglucose–positron emission tomography
FL	follicular lymphoma
FLIPI	Follicular lymphoma international prognostic index
GvHD	graft-versus-host disease
HLA	anti-human leukocyte antigen
ICANS	immune effector cell-associated neurotoxicity syndrome
IL	interleukin
iNHL	indolent non-Hodgkin lymphoma
IPI	international prognostic index for diffuse large B-cell lymphoma
ITT	intention-to-treat
IRC	Independent Review Committee

LBCL	large B-cell lymphoma
LDH	Lactate dehydrogenase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin Lymphoma
NK	natural killer (cells)
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PP	per-protocol analysis set
PR	partial response
PT	Preferred Term (MedDRA)
Q1	25th percentile
Q3	75th percentile
r/r	relapsed or refractory
RCR	replication competent retrovirus
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCT	stem cell transplantation
SD	standard deviation
TEAE	treatment-emergent adverse event

1.0 OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objectives

- To evaluate the safety and tolerability of TAK-007 in adult patients with relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (NHL) to determine the recommended phase 2 dose (RP2D).

1.1.2 Secondary Objectives

- To evaluate secondary efficacy endpoints (overall response rate (ORR), complete response [CR], duration of response [DOR], progression-free survival [PFS], and overall survival [OS]).
- To further evaluate the safety and tolerability of TAK-007 in adult patients with r/r large B-cell lymphoma (LBCL) and indolent non-Hodgkin lymphoma (iNHL).
- To characterize cellular kinetics (CK) of TAK-007.
- To assess pharmacodynamics of TAK-007.
- To assess immunogenicity of TAK-007.

1.1.3 Exploratory Objectives

- To conduct CK/pharmacodynamics modeling to further evaluate the relationship between exposure and response (safety, efficacy, pharmacodynamics, and product attributes).
- To explore biomarkers of clinical response including predictive biomarkers, mechanism of action, mechanism of resistance, and product performance.

1.2 Endpoints

1.2.1 Primary Endpoints

- Incidence of adverse events (AEs) and clinically significant laboratory values and vital signs.

1.2.2 Secondary Endpoints

- ORR per investigator.
- CR investigator.
- DOR investigator.
- PFS investigator.
- OS.

- CK parameters (eg, maximum observed concentration [C_{max}], time of first occurrence of C_{max} [t_{max}], persistence (time of last measurable concentration above the lower limit of quantitation [t_{last}]), area under the concentration-time curve from time 0 to time of the last quantifiable concentration [AUC_{last}]), and other parameters as appropriate.
- Pharmacodynamic biomarker assessments utilizing B cell quantification and levels of cytokines in circulation over time.
- Prevalence and incidence of antidrug antibodies (ie, anti-human leukocyte antigen [HLA], anti-CAR).
- Prevalence and incidence of replication competent retrovirus (RCR) positive test results.

1.2.3 Exploratory Endpoints

- Characterization and evaluation of predictive biomarkers, as well as molecular mechanisms of action and resistance to TAK-007 utilizing (including but not limited to) quantitative and phenotypic evaluation of immune cells and cellular product characteristics, as well as HLA and KIR characterization.
- Assessment of circulating tumor DNA (ctDNA).
- Assessment of standardized uptake value, metabolic tumor volume, tumor volume computed tomography (CT)/magnetic resonance imaging (MRI), volumetric tumor assessment, and total lesion glycolysis assessed by ^{18}F-fluorodeoxyglucose–positron-emission tomography (FDG-PET) and volumetric tumor assessments by CT/MRI.

2.0 STUDY DESIGN

This phase 2, open-label, multicenter study will investigate the safety and efficacy of TAK-007 administered IV in adult patients with r/r B-cell NHL, including LBCL and iNHL, who have failed ≥2 prior systemic therapies. Eligible patients are required to have previously received an anti-CD20 monoclonal antibody (mAb) and chemotherapy regimen.

At the beginning of the study, the dose escalation phase will be conducted to assess the acute safety profile, CK, and pharmacodynamics of the TAK-007 cell product at 2 dose levels (200×10^6 [±30%] and 800×10^6 [±25%] CD19 CAR$^+$ viable natural killer [NK] cells per patient). Previous clinical experience with CD19 CAR NK cells suggests that both proposed dose levels are likely to be clinically active [1]. A sequential dose escalation guided by Bayesian optimal interval (BOIN) design ([2], [3], [4]) will be used, followed by expansion cohorts to select the recommended phase 2 dose (RP2D).

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

No longer applicable to the study as of Protocol Amendment 5.

3.2 Multiplicity Adjustment

No longer applicable to the study as of Protocol Amendment 5.

4.0 SAMPLE-SIZE DETERMINATION

The primary analysis for the study does not involve any statistical inference. Consequently, the sample size was determined based on feasibility considerations instead of a formal statistical evaluation. Approximately 42 patients at dose levels of either 200×10^6 (±30%) or 800×10^6 (±25%) CD19-CAR+ viable NK cells per patient will be enrolled.

5.0 ANALYSIS SETS

5.1 Intent-to-treat (ITT) Set

All enrolled patients in the TAK-007 study. This set will primarily be used for disposition.

5.2 Safety Analysis and Modified Intent-to-treat (mITT) Set

Patients who have received TAK-007 administration. This set will be used for safety analyses (safety set), and efficacy analysis to inform RP2D.

5.3 Response-Evaluable Analysis Set

Patients who have received TAK-007 administration, have had measurable disease at baseline, and at least 1 posttreatment radiologic assessment of disease response. This set will primarily be used for sensitivity analyses of efficacy endpoints, ORR and CR.

5.4 CK Analysis sets

CK Analysis Set (CKAS): All patients who have received TAK-007 administration and have at least 1 plasma sample obtained and analyzed.

CK Evaluable Population: All patients who have received TAK-007 administration and have a sufficient data to estimate 1 or more CK parameters.

Concertation analyses will be based on the CKAS.

5.5 Pharmacodynamic Analysis Set

Patients from the safety analysis set who have a baseline and at least 1 postbaseline sample assessment, will be used for pharmacodynamics analyses.

5.6 Per-Protocol (PP) Set

The PP set will include all enrolled patients who do not have a major protocol violation. All decisions to exclude patients from the PP set will be made prior to the database lock.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline values are defined as the last observed value prior to the first dose of lymphodepleting chemotherapy unless specified otherwise.

All p-values reported will be 2-tailed (unless specified otherwise) and rounded to 3 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. Standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals (CI)s intervals will be presented using the same number of decimal places as the parameter estimate.

Where applicable, variables will be summarized descriptively by study visit. For the categorical variables, the counts and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses.

Screen failure subjects will be grouped and listed at the end.

The primary analysis will be conducted and documented in a clinical study report (CSR) after all dosed patients in the study have had the opportunity to be assessed for response and safety for at least 6 months after TAK-007 administration. Additional analyses may occur after the primary analyses have been completed. These additional analyses will be descriptive. The data cutoff for final analysis for the CSR addendum will be conducted after all dosed patients have had the opportunity to complete long-term follow-up or if the study has been terminated by the sponsor.

All the endpoints (by dose levels in dose escalation, and by disease cohorts and dose regimens in expansion cohorts) will be summarized separately, unless specified otherwise.

6.1.1 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which they were collected unless otherwise specified. These visit designators are predefined values that appear as part of the visit tab in the electronic case report form (eCRF).

6.1.2 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits:

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of lymphodepleting chemotherapy. Otherwise, the 15th of the month will be used.
- If only the year is present, and it is the same as the year of the first dose of lymphodepleting chemotherapy, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.
- If only the year is present, and it is not the same as the year of the first dose of lymphodepleting chemotherapy, the 15th of June will be used, unless other data indicates that the date is earlier.

6.1.3 Conventions for Partial or Missing Adverse Event Dates

AEs with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known but day is missing:
  - If month and year are the same as month and year of TAK-007 infusion date, then impute to the TAK-007 infusion date.
  - If month and year are different than month and year of TAK-007 infusion date, then impute to first day of the month.
- If year is known but day and month are missing:
  - If year is same as year of TAK-007 infusion date, then TAK-007 infusion date will be used instead.
  - If year is different than year of TAK-007 infusion date, then 1st of January of the year will be imputed.
- If all are missing, then the start date is imputed with TAK-007 infusion date.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the stop dates to ensure the stop date does not occur before start date.

AEs with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing:
  - If YYYY < year of TAK-007 infusion date, then 31st of December will be imputed.
  - If YYYY = year of TAK-007 infusion date, then 31st of December will be imputed.
  - If YYYY > year of TAK-007 infusion date, then 1st of January will be imputed.
- If all are missing, then impute date to 31st of December, in the year of TAK-007 infusion.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date. If subject dies, then use death date for AE stop date.

6.1.4 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month.
- If year is known, but day and month are missing, then 1st of January of the year will be imputed.
- If all is missing, then impute date to date of birth (DOB).
- If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB).

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed.
- If year is known, but day and month are missing:
  - If YYYY < year of TAK-007 infusion date, then 31st of December will be imputed.
  - If YYYY = year of TAK-007 infusion date, then 31st of December will be imputed.
  - If YYYY > year of TAK-007 infusion date, then 1st of January will be imputed.
- If all is missing, then impute date to 31st of December in the year of TAK-007 infusion.

Imputing missing concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If a subject dies, the death date will be used for the concomitant therapies stop date. After the imputation, all imputed dates will be checked against the start dates to ensure stop date did not occur before start date. If the imputed stop date occurs prior to start date, then the imputed date will be the same as the start date.

6.1.5 Conventions for Partial or Missing Subsequent Medication/Therapy Dates

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing:
  - If the onset month and year are the same as the month and year of TAK-007 infusion date, the day of TAK-007 infusion date + 1 will be imputed.
  - If the onset month and year are not the same as the month and year of TAK-007 infusion date, the first day of the month will be imputed.

- When only a year is present:
  - If the onset year is the same as the year of TAK-007 infusion date, the date of TAK-007 infusion date + 1 will be imputed.
  - If the onset year is not the same as the year of TAK-007 infusion date, the first day of the year is imputed.
- If no components of the onset date are present, the date of TAK-007 infusion date + 1 will be imputed.

6.1.6 Conventions for Partial or Missing Death Dates

- If death year and month are available, but day is missing:
  - If the year and month for the last date known to be alive are the same as the year and month of death date, death date will be the day after the last date known to be alive.
  - If the year and month for the last date known to be alive is earlier than the death date, death date will be the first day of the death month.
- If both month and day are missing for death date or a death date is completely missing, do not impute, and censor the subject survival time at the last date known to be alive.

6.2 Disposition of Subjects

The number of subjects screened, enrolled, treated with lymphodepleting chemotherapy and treated with TAK-007 will be summarized. The number of subjects in each analysis set will be provided. The reasons for discontinuing treatment and discontinuing study will also be summarized.

The summary will be presented by dose levels, by disease cohorts, and overall for the study.

The percentages will be based on the number of patients in the ITT population, except for the number of subjects screened.

For the screening phase, the clinical eligibility criteria that were not met by patients will also be tabulated. The number of subjects enrolled by country and site will also be summarized.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Baseline Characteristics

Demographics will be summarized by dose levels, by disease cohorts, and overall for the study using the ITT and mITT populations. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and other parameters, as appropriate. Age will be calculated from date of birth to date of informed consent.

Throughout this study, baseline assessments are defined as those performed at the closest time on or prior to the start of lymphodepleting chemotherapy, unless specified otherwise.

Disease characteristics will also be summarized in a similar fashion including disease diagnosis at initial diagnosis and study entry, follicular lymphoma international prognostic index (FLIPI) score (FL only) at study entry, international prognostic index for diffuse large B-cell lymphoma (IPI, LBCL only) at study entry, progression of disease within 24 months of starting induction chemoimmunotherapy (POD24) (iNHL only), molecular classification status (ABC or GCB) at study (LBCL only), bone marrow involvement at initial diagnosis and study entry, extranodal involvement at initial diagnosis and study entry, Ann Arbor stage at initial diagnosis and study entry, and baseline Eastern Cooperative Oncology Group (ECOG) status. Time since initial diagnosis will also be summarized.

Continuous variables will be summarized by means, medians, standard deviations, and ranges; categorical variables will be summarized by counts and percentages. Other variables may also be included in this analysis by categorizing the continuous variables or re-categorizing existing categorical variables.

6.4 Medical History and Concomitant Medications

Medical history and concomitant medications will be analyzed in the ITT analysis set. A general medical history will be listed for all patients, with medical history defined as any start date prior to informed consent.

Concomitant medications will be coded by generic term using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications from screening through the end of the on-study period will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO generic drug term and sorted in decreasing frequency based on the number of reports. A patient who has been administered several medications with the same preferred medication name will be counted only once. The preferred medication name will be used.

6.5 Any Prior Interventions

6.5.1 Prior Anti-cancer Therapy

Types of prior anticancer therapy will be summarized by dose levels, by disease cohorts and overall, along with number of lines, and best response to the most recent anticancer chemotherapy.

The status of refractory and relapsed as the response to last line of therapy, status of refractory and sensitive as the response to last line of chemotherapy, treatment history (primary refractory disease or never in CR) will also be summarized.

6.5.2 Other Prior Interventions

A listing of prior surgery or procedure will be provided.

Types of prior radiotherapy and best response to the most recent prior radiotherapy will be summarized.

Types of prior stem cell transplant and source of stem cells will also be summarized.

6.6 Efficacy Analysis

The mITT set will be used to inform the RP2D. The analyses of primary and secondary endpoints will be summarized by dose levels in the dose escalation cohorts, and by disease cohorts and dose regimens in expansion cohorts.

In the event a patient undergoes a stem cell transplantation (SCT) or any other anticancer therapy (excluding localized radiotherapy and surgery) while on study, the patient's best response will be derived only based on evaluation before SCT or initiation of a new therapy, whichever occurs earlier. All patients who do not meet the criteria for an objective response by the analysis cutoff date will be considered non-responders within the response-related analyses.

6.6.1 Primary Endpoint Analysis

No longer applicable to the study as of Protocol Amendment 5.

6.6.2 Secondary Efficacy Endpoint(s) Analysis

6.6.2.1 ORR by Investigator

ORR by investigator will be calculated by dose levels in the dose escalation cohorts, and by disease cohorts and dose regimens in expansion cohorts. 95% exact CI will be provided.

The subject incidence of best response (CR, partial response [PR], stable disease, progressive disease [PD]) by investigator will also be calculated, along with the 95% exact CI.

6.6.2.2 CR by Investigator

CR rate is defined as the incidence of CR as best response to treatment. CR by investigator will be presented along with the calculated 95% CI based on the binomial distribution.

6.6.2.3 DOR by Investigator

DOR is defined only for patients who experience objective response (CR or PR) and is the time from the date of first documented objective response to the date of first documented disease progression or death, whichever comes first. Patients not meeting the criteria for progression or death will be censored at the last disease assessment. Duration of response will be derived using disease assessments obtained on study prior to initiation of new anticancer therapy. Detailed handling rules for missing assessments and censoring for the analysis of DOR are presented in Table 1.

Table 1 Handling of Missing Assessments and Censoring for DOR Primary Analysis

Situation	Date of progression or censoring	Outcome
PD documented at a scheduled visit or between scheduled visits prior to initiation of new anticancer therapy	Date of progression	Event

PD or death documented after at least two missing tumor assessments	Date of last adequate assessment [a]	Censored
New anticancer therapy (excluding SCT and localized radiotherapy/surgery) started before documented progression or death	Date of last adequate assessment prior to initiation of anticancer therapy (excluding SCT and localized radiotherapy/surgery)	Censored
SCT started before documented progression or death	Date of SCT	Censored
No documented PD or death	Date of last adequate assessment	Censored
Lost to follow-up or withdrawal of consent	Date of last adequate assessment	Censored

[a] The date of the last assessment with response assessment as CR, PR or stable disease which was made before a censoring reason occurred.

Kaplan-Meier plots, estimates and median values (if estimable) along with their 2-sided 95% CIs, will be computed. Estimates of the proportion of event-free patients at 3-month intervals will be provided.

6.6.2.3.1 Sensitivity Analysis

Additional sensitivity analyses may also be performed based on the alternations of the handling of missing assessment and censoring in Table 2, on the basis of 1 alteration at a time, not on combined alterations unless otherwise specified. A sensitivity analysis combing the first 2 rows in Table 2 may also be conducted.

Table 2 Handling of Missing Assessments and Censoring for DOR Sensitivity Analysis

Situation	Date of progression or censoring	Outcome
PD or death documented after at least two missing tumor assessments	Date of progression or death	Event
New anticancer therapy started before documented progression or death	Date of documented disease progression or death	Event
PD documented between scheduled visits prior to initiation of new anticancer therapy	Date of next scheduled assessment	Event
New anticancer therapy started before documented progression or death	Date of initiation of anticancer therapy	Censored

6.6.2.4 PFS by Investigator

PFS in the mITT set is defined as the time from TAK-007 administration to the date of disease progression or death from any cause, whichever comes first. PFS in the ITT set is defined as the time from enrollment to the date of disease progression or death from any cause, whichever comes first. Patients who do not have disease progression or die will be censored at the last disease assessment. Patients who do not have postbaseline disease assessment prior to new anticancer therapy in the absence of death will be censored at the date of TAK-007 administration (mITT set) or enrollment (ITT set). Detailed handling rules for missing assessments and censoring will follow Table 1. Sensitivity analysis may be performed following censoring rules similarly as defined in Section 6.6.2.3.1.

Kaplan-Meier plots, estimates, and median values (if estimable) along with their 2-sided 95% CIs, will be computed. Estimates of the proportion of event-free patients at 3-month intervals will be provided.

6.6.2.5 OS

OS in the mITT set is defined as the time from TAK-007 administration to the date of death. OS in the ITT set is defined as the time from enrollment to the date of death. Patients who do not die will be censored at the last contact date.

Kaplan-Meier plots, estimates and median values (if estimable) along with their 2-sided 95% CIs, will be computed. Estimates of the proportion of event-free patients at 3-month intervals will be provided.

6.6.3 Subgroup Analyses

Subgroup analyses of the primary endpoint is no longer applicable with Protocol Amendment 5. Subgroup analyses may be performed for secondary endpoints CR, DOR, PFS and OS, if deemed appropriate.

The following baseline covariates may be used in the subgroup analyses. Subgroup analysis may also be performed in FL patients only.

- Gender: male, female
- Age at baseline: <65, ≥65; <75, ≥75 years
- Disease type in LBCL cohort: High grade B cell lymphoma, diffuse large B-cell lymphoma (DLBCL)-not otherwise specified (NOS), transformed DLBCL, primary mediastinal B cell lymphoma (PMBCL), others
- Disease type in iNHL cohort: FL, marginal zone lymphoma (MZL), subtypes of MZL (extranodal MZL, nodal MZL, splenic MZL)
- Response to last line of therapy: refractory, relapsed

  - Refractory is defined as patients who experienced disease progression as best response to last line of therapy or had stable disease after last line of therapy with duration of stable disease no longer than 6 months.
  - Relapsed is defined as patients who had a CR or PR from last line of prior therapy and relapsed prior to the study.
- Response to last line of chemotherapy: refractory, sensitive
  - Refractory is defined as patients who never achieved CR or PR after the last line of chemotherapy.
  - Sensitive is defined as patients who achieved CR or PR after the last line of chemotherapy.
- Treatment history: primary refractory disease, never in CR
  - Primary refractory is defined as patients who experienced disease progression as best response to first line therapy or had stable disease after the first line therapy with duration of stable disease no longer than 6 months from the last dose of therapy.
  - Never in CR is defined as patients who never achieved CR to any line of prior therapy.
- Prior autologous stem cell transplantation: Yes, No
- Prior allogeneic stem cell transplantation: Yes, No
- Type of Prior CD19 therapy: CD19 Targeted Therapy, CD19 CAR-T, CD19 T-Cell Engager
- Number of prior lines of systemic treatment: 2, ≥3
- Disease stage at study entry: I or II, III or IV
- Disease stage at initial diagnosis: I or II, III or IV
- LBCL cohort:
  - IPI risk category at study entry: 0-2, 3-5
  - IPI risk category at initial diagnosis: 0-2, 3-5
- FL cohort:
  - FLIPI score at study entry: 0-2, 3-5
  - FLIPI score at initial diagnosis: 0-2, 3-5
- History of bone marrow involvement: Yes, No
- Tumor burden by metabolic tumor volume at baseline: ≤median, >median
- Lactate dehydrogenase (LDH) at baseline: <500 U/L, ≥500 U/L
- Extranodal disease at baseline: Yes, No
- Beta-2 microglobulin: ≤3 mg/L, >3 mg/L

- Cell of origin in LBCL cohort: germinal center B-cell-like subtype, activated B-cell-like subtype
- Rearranged MYC plus BCL2, BCL6 or both in LBCL cohort: double or triple hit, not double or triple hit
- POD24 in iNHL cohort: Yes, No
    - POD24 is defined as disease progression within 24 months from the start of systemic chemo-immunotherapy or during CD20 mAb maintenance.
- Time to progression in LBCL cohort: <12 month, <24 month and ≥12 month, ≥24 month
    - Time to progression is defined as time between start of first-line chemo-immunotherapy treatment until first disease progression.
- PRIMA-PI score for FL at study entry: high-risk, intermediate-risk, low-risk
    - High-risk is defined as Beta-2 microglobulin > 3mg/L
    - Intermediate-risk is defined as Beta-2 microglobulin ≤ 3mg/L with bone marrow involvement at baseline
    - Low-risk is defined as Beta-2 microglobulin ≤ 3mg/L without bone marrow involvement at baseline

6.7 Safety Analysis

6.7.1 Adverse Events

The safety set will be used for all safety analyses.

Treatment-emergent adverse events (TEAE) are defined as any AE that begins on or after the start date of lymphodepleting chemotherapy.

The incidence and percentages of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the International Council for Harmonisation Medical Dictionary for Regulatory Activities (MedDRA) and by grade according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [5]. In addition, grading of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) will follow the American Society for Transplantation and Cellular Therapy (ASTCT) guidelines [6], grading of acute graft-versus-host disease (GvHD) will follow the recommendations by the Mount Sinai Acute GvHD International Consortium [7], and grading of chronic GvHD will follow the 2014 National Institutes of Health (NIH) Consensus [8]. For each set of grading criteria, a later version of the criteria may be applied.

Tabulated AEs will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade ≥3 TEAEs.
- Grade ≥3 drug-related TEAEs.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of patients).
- Serious adverse events (SAEs).
- Drug-related SAEs.
- Deaths.
- Drug-related deaths.
- Adverse events of clinical interest (AECIs) as defined in Section 6.7.2.

Additionally, any TEAE leading to treatment discontinuation (lymphodepleting chemotherapy or TAK-007) will be summarized. A listing will be provided.

AEs that begin on or after the date of signed informed consent but before the start date of lymphodepleting chemotherapy will be provided in a listing.

6.7.2 Adverse Events of Clinical Interest

The sponsor has designated some AEs as being of clinical interest. Since there are no commercially available CAR-NK therapies, TEAEs of clinical interest are based on adverse reactions reported with commercially available CAR-T therapies and common adverse reactions related to lymphodepleting chemotherapy. Rates of all AECIs are expected to be lower in patients treated with TAK-007 compared to rates in patients treated with CAR-T therapies. AECIs related to lymphodepleting chemotherapy are expected to have comparable rates to those described in the cyclophosphamide and fludarabine product labeling.

The list of AECIs includes:

- CRS:
  - Hemophagocytic lymphohistiocytosis (HLH)
  - Macrophage activation syndrome (MAS)
- ICANS (including encephalopathy, seizures, confusion, somnolence, aphasia, and cerebral edema)
- Tumor lysis syndrome (TLS)
- GvHD
- Hypersensitivity reactions/Infusions reactions
- Myelosuppression (including neutropenia, opportunistic infections, thrombocytopenia, bleeding, and anemia)
- Second primary malignancies

These TEAEs of clinical interest are defined using Standardised MedDRA Queries (SMQs), High Level Terms (HLTs), and/or individual PTs, as clinically appropriate.

The analyses of TEAEs of clinical interest will be conducted using the safety analysis set, as similar fashion described in Section 6.7.1.

6.7.3 Other Safety Analysis

Descriptive statistics for the actual values of clinical laboratory parameters will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters. Shift tables for laboratory parameters will be generated for changes in NCI CTCAE grade from baseline to worst postbaseline value.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and electrocardiograms (ECGs) will be tabulated by scheduled time point. ECOG performance scores will also be summarized using shift tables.

6.7.4 Extent of Exposure and Compliance

The exposure to fludarabine and cyclophosphamide will be characterized by total amount of dose received (mg), total number of doses received, and relative dose intensity using safety set. The number and percentage of patients whose dose was modified or discontinued will be summarized.

The relative dose intensity (%) is defined as: 100 × (total dose received)/(total dose intended). Total dose intended is the summation of the intended doses on Days -5, -4 and -3.

The exposure to TAK-007 will be characterized by total number of NK cells in prepared product, total number and percentage of transduced CAR+ cells in prepared product, total number of NK cells infused to patients, total number and percentage of transduced CAR+ cells infused to patients, and viability in the prepared product using safety set.

The exposure will be summarized separately by dose levels and disease indications.

6.8 CK, Pharmacodynamic, and Other Analyses

6.8.1 CK Analyses

CK Sample Collection and Analysis:

Blood samples will be collected at pre-dose and 1 hour (±15 minutes) after TAK-007 administration on Day 0, Day 1, Day 3, Day 5, Day 7, Day 10, Day 14, Day 21, Day 28/Month 1, Month 2, Month 3, Month 4 and Month 6 for primary analysis and analyzed for TAK-007 transgene copies per genomic DNA by Droplet Digital Polymerase Chain Reaction (ddPCR) and TAK-007 CAR+ NK cell number by flow cytometry.

Summary Statistics:

Individual blood level of TAK-007 (as transgene copies per genomic DNA) and TAK-007 cell number (as CAR+ NK cells/μL) versus time data will be listed by dose level or indication. Individual blood level of TAK-007 and TAK-007 cell number versus actual time profiles will be

plotted on both linear and semi logarithmic scales for each subject. Blood levels of TAK-007 and TAK-007 cell number will be summarized by nominal time point for each dose level and indication using the following descriptive statistics includes n, arithmetic mean, SD, percent coefficient of variation (CV%), median, minimum and maximum. Blood level of TAK-007 and TAK-007 cell numbers will be reported to 3 significant figures in summary statistics except for CV% which will be reported to 1 decimal place. Sample side (N) will be presented as an integer.

Blood level of TAK-007 and TAK-007 cell number concentrations that are below the limit of quantification (BLQ) will be set to zero for calculation of summary statistics.

Noncompartmental Analysis:

CK parameters will be estimated using noncompartmental methods by Phoenix® WinNonlin® (Certara L.P., Princeton, NJ) Version 8.0 or higher. In addition, separate population-based CK analysis may be performed using NONMEM 7 (ICON plc, Dublin, Ireland). The actual sampling and dose duration times will be used for the calculation of CK parameters.

As permitted by data, CK parameters will be estimated from the blood level of TAK-007 and TAK-007 cell number versus time profiles using the CK analysis set as the following.

Table 3 Cellular Kinetic Parameters Estimated Using Noncompartmental Analysis

CK Parameter	**Definition**
C_{max}	Maximum observed concentration
T_{max}	Time to maximum observed concentration
AUC_{last}	Area under the concentration versus time curve (AUC) from time 0 to the last quantifiable measurement, calculated using the linear trapezoidal rule
$AUC_{(0-28)}$	AUC from time 0 to Day 28 post dose
$AUC_{(0-90)}$	AUC from time 0 to Month 3 post dose
C_{28}	Concentration at Day 28
C_{last}	The last quantifiable measurement
T_{last}	The last quantifiable time point

For the calculation of CK parameters, all BLQ will set to missing except that prior to the first measurable value will be set to zero. The BLQ values that are between measurable values will be set to missing.

If a patient deviated substantially from the protocol-defined study procedures, including but not limited to dosing, dose timing, sample collection, and concomitant medications, CK parameters will be included in the listings but excluded from the descriptive statistics and statistical evaluations, with appropriate footnotes.

Individual CK parameters will be listed and also summarized as permitted by data by part, cohort and indication using descriptive statistics: the n, arithmetic mean, SD, CV%, minimum, median, maximum, and geometric mean and geometric CV%. T_{max} will be summarized by n, minimum, median, and maximum only.

CK parameters will be reported to 3 significant figures in summary statistics except for CV% and geometric CV%, which will be reported to 1 decimal place.

Descriptions of population CK modeling methods and data analysis will be documented and reported in a separate brief report.

6.8.2 Pharmacodynamic Analyses

Changes in average B cell counts from baseline will be summarized. The frequency and percentage of patients with B cell aplasia will be summarized before and after TAK-007 administration by scheduled time point using the pharmacodynamic analysis set. B cell aplasia is defined as <50 B cell/ul of blood

Concentration data of interleukin (IL)-15 and soluble immune factors in circulation (eg, interferon gamma, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, tumor necrosis factor alpha, granulocyte-macrophage colony-stimulating factor) in plasma will be tabulated using summary statistics over scheduled time point. Individual and mean concentration-time profiles may also be plotted.

Additional analysis may be performed as appropriate and will be reported outside the CSR.

6.9 Immunogenicity Analyses

Frequency and percentage of patients with detectable anti-HLA (including donor specific anti-HLA antibodies) and anti-CAR antibodies will be summarized by scheduled time point using the safety analysis set. Impact of anti-HLA and anti-CAR immunogenicity on CK parameters, safety and efficacy may be assessed, as appropriate based on the available data.

6.10 RCR Analyses

Frequency and percentage of patients with positive RCR test results will be summarized by scheduled time point before and after TAK-007 administration using safety analysis set.

6.11 Exploratory Analyses

6.11.1 Population CK-Pharmacodynamic Analysis

The relationship between TAK-007 systemic exposure and safety, efficacy, and pharmacodynamic response (eg, B cell aplasia, time to B cell recovery, changes in cytokines/chemokines) will be evaluated to understand the CK-pharmacodynamic relationship of TAK-007. These data will be reported outside the CSR.

6.11.2 Biomarker Analyses

Exploratory biomarker analyses will be separately defined in biomarker analysis plan and the results of these analyses may be reported separately from the CSR.

6.11.3 Imaging Analyses

As data permit, the metabolic tumor volume measures including standard uptake value, lesion volumes and total lesion glycolysis as assessed by FDG-PET will be summarized at baseline. Analyses to understand the relationship between metabolic tumor volume and patients response may be evaluated.

6.11.4 Patient-Reported Outcome Analyses

No longer applicable to the study as of Protocol Amendment 5.

6.11.5 Healthcare Resource Utilization Analyses

No longer applicable to the study as of Protocol Amendment 5.

6.12 Statistical Considerations for Dose Escalation

A sequential dose escalation guided by BOIN design ([2], [3], [4]) will be used followed by expansion cohorts to select the RP2D.

During the dose escalation, only patients who received TAK-007 will be considered as dose-limiting toxicity (DLT)-evaluable. Each dose level will enroll at least 3 patients. The target toxicity rate for the maximum tolerated dose (MTD) is $\phi = 0.25$, and the maximum sample size is 12 total patients for dose escalation. As shown in Table 4, the BOIN design uses the following rule to guide dose escalation/ de-escalation:

- If the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose level; if the current dose is the highest dose, treat the new patients at the highest dose.
- If the observed DLT rate at the current dose is > 0.298, de-escalate the dose to the next lower dose level; if the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary (as shown in Table 4), at which point the dose escalation will be terminated for safety.
- Otherwise, stay at the current dose.
- Repeat above until the maximum sample size of 12 is reached, or until the number of evaluable patients treated at the current dose reaches 6 and the decision according to above is to stay at the current dose.

For the purpose of overdose control, doses j and higher levels will be eliminated from further examination if $Pr(p\_j > 0.25 \mid data) > 0.95$ and at least 3 evaluable patients have been treated at dose level j, where p_j is the true DLT rate of dose level j, j= 1, 2.

Table 4 Dose Escalation/De-escalation Rule for the BOIN Design

Number of Evaluable Patients Treated at Current Dose	1	2	3	4	5	6
Escalate if # of DLT ≤	0	0	0	0	0	1
De-escalate if # of DLT ≥	1	1	1	2	2	2
Eliminate if # of DLT ≥	NA	NA	3	3	3	4

DLT: dose-limiting toxicity

"# of DLT" is the number of patients with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of patients. "NA" means that a dose cannot be eliminated before treating 3 evaluable patients.

Enrollment into the lower dose level may be continued during exploration of the higher dose level in the dose escalation phase, if deemed appropriate by the sponsor and the investigators. In this case, if additional DLT are identified during additional patients enrolled, the dose escalation decision will be re-examined using the cumulative DLT rate at this dose level.

Separate expansion cohorts for LBCL and iNHL with approximately 15 patients each may be initiated for dose level(s) selected based on the dose escalation part, to further evaluate the safety, tolerability, efficacy and cellular kinetics and allow the selection of the RP2D to be used in the rest of the study.

6.13 Interim Analysis and Criteria for Early Termination

No longer applicable to the study as of Protocol Amendment 5.

6.14 Data Monitoring Committee

No longer applicable to the study as of Protocol Amendment 5.

7.0 REFERENCES

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7. Harris AC, Young R, Devine S, Hogan WJ, Ayuk F, Bunworasate U, et al. International, multicenter standardization of acute graft-versus-host disease clinical data collection: a report from the Mount Sinai GVHD international Consortium. Biol Blood Marrow Transplant. 2016; 22(1):4-10.
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8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

NA

9.0 APPENDIX

SAS version 9.4 or higher will be used for the analysis.

10.0 CHANGES FROM THE PREVIOUS VERSION OF THE SAP

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
1.0 OBJECTIVES AND ENDPOINTS		Removed all objectives and endpoints associated with Part 2 of the study.	Part 2 of the study was removed with protocol amendment 5.
2.0 STUDY DESIGN		Removed portion which summarized design for Part 2.	Part 2 of the study was removed with protocol amendment 5.
3.0 STATISTICAL HYPOTHESIS AND DECISION RULES		Removed this section as the study no longer has a formal hypothesis with the removal of Part 2.	Part 2 of the study was removed with protocol amendment 5.
4.0 SAMPLE-SIZE DETERMINATION	**The primary analysis for the study does not involve any statistical inference. Consequently, the sample size was determined based on feasibility considerations instead of a formal**	Removed the calculation for Part 2 and included additional details around the primary analysis.	Part 2 of the study was removed with protocol amendment 5.

	statistical evaluation. Approximately 42 patients at dose levels of either 200 × 10^6 (±30%) or 800 × 10^6 (±25%) CD19-CAR+ viable NK cells per patient will be enrolled.		
5.4 CK ANALYSIS SET	**CK Analysis Set (CKAS):** All patients who have received TAK-007 administration and have at least 1 plasma sample obtained and analyzed. **CK Evaluable Population: All patients who have received TAK-007 administration and have a sufficient data to estimate 1 or more CK parameters.**	Provided additional details about the CK analysis sets	More clearly define the CK populations
6.1 General Considerations	The primary analysis will be conducted and documented in a **clinical study report (CSR)** after all dosed patients in the study have had the opportunity to be assessed for response and safety for at least 6 months after TAK-007 administration. **AEs** with start dates that are completely or partially missing will be analyzed as follows:	Updated language to correct use of acronyms	Align this section with the rest of the document
6.2 Disposition of Subjects		Removed mention of Part 2.	Part 2 of the study was removed with protocol amendment 5.
6.3 Demographics and Other Baseline Characteristics		Removed mention of Part 2.	Part 2 of the study was removed with protocol amendment 5.
6.6 Efficacy Analysis		Removed analyses associated with Part 2.	Part 2 of the study was removed with protocol amendment 5.
6.6 Efficacy Analysis	In the event a patient undergoes a stem cell transplantation (SCT) or	Included additional details that subjects will not be censored at localized	Patients will not be censored if they received anticancer therapy which

	any other anticancer therapy **(excluding localized radiotherapy and surgery)** while on study…	radiotherapy or surgery.	is deemed to not affect the disease of interest.
6.6.3 Subgroup Analyses	**• Type of Prior CD19 therapy: CD19 Targeted Therapy, CD19 CAR-T, CD19 T-Cell Engager**	Included additional subgroup around type of Prior CD19 therapy	
6.7 Safety Analysis		Removed mention of Part 2.	Part 2 of the study was removed with protocol amendment 5.
6.7.1 Adverse Events		Removed summaries specific to the time between lymphodepleting chemotherapy and TAK-007 Administration, and solely after TAK-007 administration	
6.8.1 CK Analyses	**If a patient deviated substantially from the protocol-defined study procedures, including but not limited to dosing, dose timing, sample collection, and concomitant medications, CK parameters will be included in the listings but excluded from the descriptive statistics and statistical evaluations, with appropriate footnotes.**	Updated analyses to align with protocol amendment 5	
6.11 Exploratory Analysis		Removed analysis of Time to Next Therapy	Align with protocol amendment 5
6.11.4 Patient-Reported Outcome Analyses		Removed all PRO Analyses as these were specific to Part 2.	Part 2 of the study was removed with protocol amendment 5.
6.11.5 Healthcare Resource Utilization Analyses		Removed all healthcare resource utilization analyses as these were specific to Part 2.	Part 2 of the study was removed with protocol amendment 5.
6.13 Interim Analysis and Criteria For Early Termination		Removed as the interim analysis was specific to Part 2.	Part 2 of the study was removed with protocol amendment 5.
6.14 Data Monitoring Committee		Removed as the DMC was specific to Part 2.	Part 2 was removed with protocol amendment 5.

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