Title: Phase 2 Study of TAK-659 in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma After at Least 2 Prior Lines of Chemotherapy

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C34004

Phase 2 Study of TAK-659 in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma After at Least 2 Prior Lines of Chemotherapy

PHASE 2

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

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3.0 LIST OF ABBREVIATIONS

ABC	activated B-cell
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASH	American Society of Hematology
AST	aspartate aminotransferase
BCR	B-cell receptor
BCRP	breast cancer resistance protein
CFR	Code of Federal Regulations
CK	creatine kinase
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FAS	Full analysis set
FDA	United States Food and Drug Administration
FDG-PET	[^{18}F]fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
FL	follicular lymphoma
GCB	germinal center B-cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal

GM-CSF	granulocyte macrophage-colony stimulating factor
HbAc1	glycosylated hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemical; immunohistochemistry
IRB	institutional review board
IRC	independent radiologic review committee
ITAM	immunoreceptor tyrosine-based activating motifs
IV	intravenous; intravenously
IWG	International Working Group
KM	Kaplan Meier
LDH	lactate dehydrogenase
LLN	Lower limit of normal
LOCF	Last observation carried forward
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PJP	*Pneumocystis jiroveci* pneumonia
PK	pharmacokinetic(s)
PLT	platelets
PO	per os; by mouth (orally)
PR	partial response
PTE	pretreatment events
QD	once daily
QTc	rate-corrected QT interval (msec) of electrocardiograph

QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RDI	Relative dose intensity
RBC	red blood cell
R-CHOP	cyclophosphamide+doxorubicin (hydroxydaunomycin)+vincristine (Oncovin)+prednisone with rituximab
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SSC	study steering committee
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TEAE	treatment-emergent adverse events
ULN	upper limit of the normal range
US	United States
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is to assess the efficacy of TAK-659 as measured by IRC assessed ORR in patients with DLBCL (Stage 2).

4.2 Secondary Objectives

Key Secondary Objective:

The key secondary objective is to assess CR rate per IRC in patients with DLBCL (Stage 2).

Secondary Objectives:

- To select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1) and assess efficacy using ORR per IRC (Stage 2).
- To assess ORR per IRC at 3, 6, and 9 cycles in patients with DLBCL (Stage 2).
- To assess DOR and duration of CR per IRC in patients with DLBCL (Stage 2).
- To assess ORR per IRC in the subgroup of patients with germinal center B-cell (GCB) DLBCL (Stage 2).
- To assess ORR per IRC in the subgroup of patients with DLBCL transformed from indolent non-Hodgkin lymphoma (NHL) (Stage 2).
- To assess PFS per IRC in patients with DLBCL (Stage 2).
- To assess OS in patients with DLBCL (Stage 2).

4.3 Additional Objectives

- To assess the safety and tolerability of TAK-659 in the patient population under study (Stages 1).
- To assess the number of responding patients proceeding to ASCT or allogeneic stem cell transplant.
- To collect TAK-659 plasma concentration–time data to contribute to population PK and exposure–response analyses (Stages 1).

4.3.1 Exploratory Objectives

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4.4 Study Design

This is an open-label, multicenter, phase 2 study to evaluate the efficacy and safety of TAK-659 as a single agent in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least 2 prior lines of chemotherapy. Eligible patients will also be ineligible for autologous stem cell transplant (ASCT) or be patients for whom ASCT has failed.

This study will start with a lead-in dose exploration phase (Stage 1) during which two TAK-659 dose regimens will be evaluated in two patient cohorts (Cohorts A and B). Patients in Cohort A will receive a daily dose of 100 mg TAK-659 continuously throughout the study. In Cohort B, patients will follow a ramp-up dosing schema leading to a full dose of 100 mg QD TAK-659. Patients will initially receive 60 mg QD TAK-659 for one cycle of 28 days, and if tolerated well, will then receive 80 mg QD TAK-659 for the next cycle, and subsequently 100 mg QD TAK-659 in the 3rd cycle and beyond. At the end of each cycle during the ramp-up, patients will be assessed for their suitability to dose-escalate to the next level based on safety and tolerability.

If the patient experiences any drug-related adverse events that require dose modification (inclusive of dose held and dose reduction) per protocol in a given dose cycle, dose escalation will not proceed to the next level. If the AE(s) resolves, the patient may then restart dose escalation in the next cycle either at the same dose or a reduced dose according to the protocol-defined dose reduction criteria. In case dose reduction is not required, when the patient resumes the study drug at the same dose, dose escalation to the next dose level and further to the full dose of 100 mg QD TAK-659 may be pursued if no recurrence of the same AE(s) or any other AEs leading to dose modification is observed in the next cycle of treatment. However, if the same AE(s) or different AE(s) requiring dose modification occur in two consecutive cycles at the same dose level, further dose escalation is not allowed. If the patient resumes the study drug at a reduced dose per protocol, no dose re-escalation is recommended. Approximately 20 patients are expected to be enrolled into each cohort, with a total of ~40 patients planned for Stage 1.

Upon completion of Stage 1, the dose exploration analysis will occur. Based on the posterior probability of response comparison between the 2 cohorts, one TAK-659 dose regimen will be selected to proceed to Stage 2. During this analysis, if both Stage 1 regimens are determined to be ineffective, termination of the study without proceeding to Stage 2 may be considered. However, other considerations should be taken into account when making this development decision including, but not limited to, sample size, relevant data from other TAK-659 trials, and applicable patient enrichment or selection strategy that justifies further evaluation of TAK-659 in this setting.

During the Stage 2 efficacy evaluation phase, it is expected that approximately 82 patients will be enrolled. Once enrolled, patients will be administered TAK-659 orally in 28-day treatment cycles according to the selected dose regimen of TAK-659 from Stage 1. After approximately 40 patients have been enrolled in Stage 2 and have had the opportunity to receive at least 3 cycles of

study treatment and have at least 1 posttreatment response evaluation, an interim analysis will be performed to assess futility. The study may either stop for futility or continue as planned.

In Stage 2, patients will be administered TAK-659 orally according to the dose regimen selected in Stage 1. Efficacy will be assessed using the IWG revised response criteria for malignant lymphoma (the modified 2007 IWG criteria [1] and the 2014 [Lugano] criteria [2]). Dedicated computed tomography (CT) scans (chest, neck, abdomen, and pelvis) will be performed at Baseline; at the end of Cycles 1, 3, and 6; every 3 cycles up to 24 cycles; and every 6 cycles thereafter. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans will be performed at baseline and at the end of Cycles 1, 3, and 6 if positive at baseline, or when clinically indicated during the study. The primary endpoint of this study is ORR, defined as the proportion of patients with CR or PR as determined by independent central review of radiology by an IRC according to the modified 2007 IWG criteria.

AEs will be assessed, and laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of TAK-659. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0, effective date 27 November 2017 [3].

Patients on TAK-659, including those who achieve a CR, may receive study drug until they experience PD or unacceptable toxicities. Patients who discontinue study for reasons other than PD will be followed for PFS every 3 months after the last dose of study drug until PD, the start of alternative therapy, or conclusion of the study, whichever occurs first. All patients, after the last dose of study drug, will be followed for OS every 3 months until death or conclusion of the study, whichever occurs first.

Patients may discontinue therapy at any time. Patients will attend the End-of-Treatment (EOT) visit 28 days (+10) after receiving their last dose of TAK-659 or before the start of subsequent anticancer therapy, whichever occurs first, to permit the detection of any delayed treatment-related AEs.

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5.0 ANALYSIS ENDPOINTS

Primary:

- ORR as assessed by IRC according to modified 2007 IWG criteria for malignant lymphoma.

Key secondary: CR rate as assessed by IRC according to the modified 2007 IWG criteria.

Secondary:

- ORR per IRC according to the 2014 IWG (Lugano) criteria (Stage 2).
- CR rate per IRC according to the 2014 IWG (Lugano) criteria (Stage 2).
- ORR per IRC to select the Stage 2 dose regimen of TAK-659 from the lead-in dose exploration phase (Stage 1).
- ORR per IRC at 3, 6, and 9 cycles, respectively (Stage 2).
- DOR and duration of CR per IRC (Stage 2).
- ORR per IRC in patients with GCB DLBCL (Stage 2).
- ORR per IRC in patients with DLBCL transformed from indolent NHL (Stage 2).
- PFS per IRC (Stage 2).
- OS (Stage 2).

The IRC will evaluate the assessments above using both the modified 2007 IWG criteria for malignant lymphoma and the 2014 IWG (Lugano) criteria. Unless otherwise specified, evaluations using the 2007 IWG criteria will be the primary analyses, and evaluations using the 2014 IWG (Lugano) criteria will be the sensitivity analyses.

Additional:

- Percentage of patients who experience AEs, Grade ≥3 AEs, serious AEs, discontinuations for AEs, and clinical laboratory values and vital sign measurements outside the normal range (Stages 1 and 2).
- Percentage of patients proceeding to ASCT or allogeneic stem cell transplant out of all patients who achieve a best response of PR or CR on study.
- TAK-659 plasma concentration–time data (Stages 1 and 2).

Exploratory:

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6.0 DETERMINATION OF SAMPLE SIZE

For the lead-in dose exploration portion (Stage 1) of the study, assuming a historical control rate of 20% for ORR, at least 20 patients per dosing regimen are required to determine if either dosing regimen A or dosing regimen B is more effective.

For Stage 2 efficacy evaluation phase of the study, assuming a historical control rate of 20% for ORR and a TAK-659 ORR of 37%, this study will need to enroll at least 82 patients in Stage 2 to achieve 91% power at a 1-sided alpha level of 0.025, using an exact binomial test. After approximately 40 patients have been enrolled in Stage 2 and have had the opportunity to receive at least 3 cycles of treatment and have at least 1 posttreatment response evaluated, the interim analysis will be performed. The interim analysis will assess futility, and the study may either stop for futility (if posterior probability of ORR<20% is greater than the threshold of 0.75) or continue as planned.

7.0 METHODS OF ANALYSIS AND PRESENTATION

The study was terminated early without entering into the Stage 2 efficacy evaluation phase. The analyses described in this section are only for the stage 1 lead-in dose exploration phase.

7.1 General Principles

In general, summary tabulations will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data.

All statistical analyses will be conducted using SAS® Version 9.3, or higher.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated.

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

7.1.1 Definition of Study Days

Study Day 1 is defined as the date on which a patient is administered their first dose of the medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.2 Conventions for Handling Missing Data

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

7.1.2.1 Missing/Partial Dates in Screening Visit

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

1. 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 study drug. Otherwise, the fifteenth will be used.
2. If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the 15th of January will be used.
3. If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

7.1.2.2 Missing/Partial Dates in Adverse Events/Concomitant Therapies/Subsequent Therapies

Every effort will be made to avoid missing/partial dates in on-study data.

7.1.2.3 Missing/Partial Dates in Adverse Events

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

- If the start date has a month and year but the day is missing, the event will be considered treatment emergent if the month and year of the start date of the event are:
  - On or after the month and year of the date of the first dose of study drug

    and
- on or before the month and year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
- If the start date has a year, but the day and month are missing, the event will be considered treatment emergent if the year of the start date of the event is:
  - On or after the year of the date of the first dose of study drug

    and
  - on or before year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
- If the start date of an event is completely missing then the event is assumed to be treatment emergent.

However, if the end date is complete or partially missing but it is clear that the end date is before the first dose of study drug, the event will not be considered treatment emergent.

7.1.2.4 Missing/Partial Dates in Concomitant Therapies

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

1. If the start date has a month and year but the day is missing, the therapy will be considered concomitant if the month and year of the start date are:
   - On or after the month and year of the date of the first dose of study drug

     and
   - on or before the month and year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.

2. If the start date has a year, but the day and month are missing, the therapy will be considered concomitant if the year of the start date is:
   - On or after the year of the date of the first dose of study drug

     and
   - on or before the year of the date of the last dose of any study drug plus 28 days, or the start date of subsequent anticancer therapy, whichever occurs first.
3. If the start date of a therapy is completely missing then the therapy is assumed to be concomitant.

However, if the end date is complete or partially missing but it is clear that the end date is before the first dose of study drug, the therapy will not be considered concomitant.

When the start date is complete and is before the first dose, and the concomitant medication is not ongoing but the end date is missing completely or partially, a similar algorithm should be used to assess whether the end date is before the last dose of study drug plus 28 days to be included.

7.1.3 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. C1D1 (cycle 1 day 1) values are generally considered pre-dose, unless explicitly stated values are post-dose, C1D1 values are considered baseline values if available. Screening values are considered baseline values if C1D1 value is unavailable.

7.1.4 Windowing of Visits

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

7.1.5 Withdrawals, Dropouts, Loss to Follow-up

Patients who dropout or withdraw for any reason will not be replaced.

Time to event parameters (DOR, PFS, 1-year OS) will be censored if patients withdraw, drop out, or are lost to follow-up before documentation of the event of interest (progressive disease/death). Rules for censoring are detailed in section 7.8.3.1.

7.2 Analysis Sets

DLBCL Population

The DLBCL population includes all patients who have a confirmed DLBCL diagnosis and who receive at least 1 dose of TAK-659. The DLBCL population will be used for primary and secondary efficacy analysis, and for additional efficacy analyses.

Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all patients who receive at least 1 dose of TAK-659. The mITT will be used for the sensitivity analyses for the efficacy analyses.

Per-Protocol Population

The per-protocol population includes all patients who receive at least 1 dose of TAK-659 and who have measurable disease at Baseline and no other major protocol deviations that could potentially affect tumor response.

Safety Population

The safety population includes all patients who receive at least 1 dose of TAK-659. The safety population will be used for all baseline characteristics, safety analyses, and exposure analysis.

Response-Evaluable Population

The response-evaluable population includes all patients who receive at least 1 dose of TAK-659 and have measurable disease at Baseline and at least 1 postbaseline disease assessment. The response-evaluable analysis set will be used for sensitivity analyses of efficacy endpoints that are related to response, such as ORR, CR, and DOR.

7.3 Disposition of Patients

Disposition of patients includes the number and percentage of patients in each population, presented by dosing regimen (Cohorts A and B) and total. The primary reason for discontinuation of study drug as well as study termination will be summarized.

All percentages will be based on the number of patients in the safety population.

Summary of number of patients by region, country, and site (for posting)

7.3.1 Significant Protocol Deviations

Protocol deviations will be identified either through manual lists or using programmed algorithms. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment. Protocol deviations applicable to all study parts and protocol deviations specific to each study part will be identified. A listing will be generated for significant protocol deviations, which will include, but will not be limited to, at least 1 of the following:

- Any inclusion/exclusion criteria not met by an enrolled patient.
- Use of or administration of excluded and/or restricted medications, not in accordance with the study protocol.
- Study procedures not performed as per the clinical study protocol that may confound interpretation of primary clinical study objectives and/or affect patient safety.
- Dispensing of incorrect treatment and/or incorrect dose of clinical study medication.

- Any occasion that withdrawal criterion is met but the patient is not withdrawn.

7.4 Demographic and Other Baseline Characteristics

Patient demographics will be summarized by dosing regimen (Cohorts A and B) and in total. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, and weight.

Age will be calculated from date of birth to date of informed consent.

Demographic data will also be presented in a by-patient listing.

No inferential statistics will be generated.

7.4.1 Baseline Disease Characteristics

Baseline disease primary diagnosis and disease subtype, years since initial diagnosis, Ann Arbor staging, and Eastern Cooperative Oncology Group (ECOG) performance status, molecular classification (GCB vs. Non-GCB), number of nodal sites, bulky disease (Y/N), extranodal involvement, bone marrow involvement, and IPI score will be summarized by dosing regimen (Cohorts A and B) and in total.

7.5 Medical History and Concurrent Medical Conditions

Medical history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the end date relative to signing Informed consent (whether it is before or ongoing).

7.6 Medication History and Concomitant Medications

Prior therapies will be summarized by the numbers and percentages of patients who received prior anticancer therapy, prior radiation, prior transplant, number of lines of prior anticancer therapies, and best response to the last prior anticancer therapy and dosing regimen (Cohorts A and B) and in total.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term for the safety population, from the first dose of study treatment and through 28 days after the last dose of study medication drug, or to the start of subsequent anticancer therapy, whichever occurs first.

7.7 Study Drug Exposure and Compliance

The study drug will be dosed continuously, QD, in 28-day cycles.

The exposure to TAK-659 will be characterized by total amount of dose taken in mg, total number of doses taken, relative dose intensity (RDI, %), number of treated cycles, numbers and

percentages of patients who had ≥1, ≥2, …, ≥6, and ≥12 treated cycles for patients by dosing regimen (Cohorts A and B) and total in the safety population.

RDI (%) will be presented overall, by cycle, and by study days 1-28 and study days 29-56. Overall RDI is defined as 100 x (total dose received in mg) / (initial prescribed dose per day x number of treated days). Where the number of treated days is defined as (reference end date for study drug – reference start date for study drug) + 1.

For RDI by cycle, the same formula is used as overall RDI, but the number of treated days is derived differently. Cycle RDI is defined as 100 x (total dose received in mg in cycle) / (initial prescribed dose per day x number of treated days in cycle). Where the number of treated days in cycle is defined as (last dose date of a cycle – first dose day of cycle) + 1, however, if a patient discontinues during the cycle then use date of drug discontinuation – first dose day of cycle + 1.

RDI by study day will have a slightly different calculation than overall or by cycle. Study days 1-28 RDI will be defined as 100 x (total dose received in mg up to study day 28) / (initial prescribed dose per day x 28). Study days 29-56 RDI will be defined as 100 x (total dose received in mg between study days 29 through 56) / (initial prescribed dose per day x 28).

Prescribed dose is determined by the dose level to which a patient is enrolled at the onset of the study. Patients in Stage 1 Cohort B will have their prescribed dose determined by the first scheduled dose of the relevant cycle.

The extent of exposure will be summarized by dosing regimen (Cohorts A and B) and in total.

Action on study drug will be summarized by each cycle (Cycles 1- 6), sum of the remainder of cycles, and dosing regimen (Cohorts A and B) and in total.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

There is no primary efficacy endpoint for the stage 1 lead-in dose exploration phase of the study

7.8.2 Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints defined for Stage 2 are not applicable due to the early termination of the study.

The overall response rate (ORR) and Complete Response Rate from Stage 1 will be summarized by dosing regimen (Cohorts A and B) based on the DLBCL population. Overall response is defined as a best response of CR or PR. ORR is the percentage of patients who have overall responses. The summary will be based upon the investigator response assessment. There was no IRC review of the responses. The number and percentage of patients falling into each response category (CR, PR, SD, PD) will also be tabulated descriptively. Estimates of the ORR will be presented with 2-sided 95% exact binomial confidence intervals (CIs).

7.8.3 Additional Efficacy Endpoint(s)

Additional time to event data (DOR, PFS, and OS) will be analyzed by the Kaplan-Meier method and results will be summarized by the 25th, 50th, and 75th percentiles for survival times with associated 2-sided 95% CIs. The corresponding Kaplan-Meier curves will also be plotted.

DOR is defined as the time from the date of first documentation of a response (PR or CR) to the date of first documented PD.

PFS is defined as the time from date of first study drug administration to the day of first documented PD or death due to any cause, whichever occurs first.

OS is defined as the time from the first dose date to the date of death. Patients without documentation of death at the time of the analysis will be censored at the date when they were last known to be alive.

7.8.3.1 Censoring Method for Efficacy Analysis of Progression-Free-Survival

The efficacy analysis for PFS will be based on the DLBCL population. The approach regarding handling of missing response assessments and censoring based on US Food and Drug Administration (FDA) guidance is presented in Table 7.a.

Table 7.a Handling of Missing Response Assessment and Censoring for Progression-Free Survival Analysis Based on US Food and Drug Administration Guidance

Situation	Date of Progression or Censoring	Outcome
No baseline and/or no post baseline assessment	First dose date	Censored
Disease progression documented between scheduled visits	Date of disease progression	PFS event
No documented disease progression or death	Date of last adequate assessment*	Censored
Treatment discontinuation for undocumented disease progression after the last adequate assessment	Date of last adequate assessment*	Censored
Alternate antineoplastic therapy started prior to disease progression	Date of last adequate assessment* prior to the start of subsequent antineoplastic therapy	Censored
Death before first assessment	Date of death	PFS event
Death between adequate assessment visits	Date of death	PFS event
Death or disease progression after more than 1 missed visit	Date of last adequate assessment prior to multiple missing visits*	Censored

Abbreviation: PFS = progression-free survival.

* Adequate assessment is defined as there is sufficient radiographic data to evaluate a patient's disease status.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Plasma concentrations of TAK-659 will be listed by patient, dosing cycle and day, and nominal and actual time point for each dosing regimen (Cohorts A and B).

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Safety Analysis

Safety evaluations will be based on the incidence, severity, relatedness, and type of AEs, and by changes from baseline in the patient's clinical laboratory results. These analyses will be performed using the safety population.

7.10.1 Adverse Events

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary for the purpose of summarization. All AEs will be summarized by the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI CTCAE).

Treatment-emergent AEs will be tabulated where treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment and up to 28 days after the last dose of study medication, or until the start of subsequent antineoplastic therapy, whichever occurs first. Treatment-emergent AEs will be tabulated by dosing regimen (Cohorts A and B), according to the MedDRA by system organ class (SOC), and preferred terms (PT) and will include the following categories, for Stage 1 Cohorts A and B.

- Treatment-emergent AEs (SOC and PT, PT).
- Drug-related treatment-emergent AEs (SOC and PT, PT).
- Grade 3 or higher treatment-emergent AEs (SOC and PT, PT).
- Grade 3 or higher drug-related treatment-emergent AEs (SOC and PT, PT).
- The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥10% of all patients in the safety population) (PT).
- Treatment-Emergent AEs leading to discontinuation (PT).
- Drug-Related Treatment-Emergent AEs leading to discontinuation (PT).
- Serious Treatment-emergent AEs (SOC and PT).
- Drug-related Serious treatment-emergent AEs (SOC and PT).

Patients with the same AE more than once will have the maximum intensity of that event counted within each body system, and once within each preferred term.

An overall summary treatment-emergent AE table will include numbers and percentages of patients who had any treatment-emergent AE, drug-related treatment-emergent AE, grade 3 or higher treatment-emergent AE, grade 3 or higher drug-related treatment-emergent AE, serious AE (SAE), drug-related SAE, treatment-emergent AE resulting in discontinuation, drug-related treatment-emergent AE resulting in discontinuation and on-study deaths.

7.10.2 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (e.g., less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier.

If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

The actual values of laboratory test results and percent change from baseline will be summarized according to the scheduled sample collection time point by Stage 1 (Cohorts A and B separately),

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTC for toxicity from baseline to post baseline worst on study CTC grade, if available. Parameters to be tabulated will include:

Hematology:

Hematocrit
Hemoglobin
Leukocytes with differential
Neutrophils (ANC)
Platelet (count)
Lymphocytes (absolute lymphocyte count [ALC])
Lymphocyte subsets (CD4, CD8, CD4:CD8 ratio)

Serum chemistry:

Albumin
Alkaline phosphatase (ALP)
ALT
Amylase
AST
Bilirubin (total)
Blood urea nitrogen (BUN)
Calcium
Carbon dioxide (CO_2)
Creatinine
Creatine kinase (CK)
Chloride
γ-Glutamyl transferase (GGT)
Glucose
Glycosylated hemoglobin (HbA1c)
Lactate dehydrogenase (LDH) (including LDH isozymes)
Lipase
Magnesium
Phosphate
Potassium
Sodium
Total protein
Urate

Urinalysis:

Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

Mean laboratory values over time will be plotted for key lab parameters, including Hb, leukocytes, ALC, ANC, platelets, and liver function tests (ALT, AST, ALP, total bilirubin), LDH (with isozymes), phosphate, creatinine, CK, lipase and amylase.

7.10.3 Vital Signs

The actual values of vital sign parameters including oral temperature, heart rate, systolic and diastolic blood pressure, and oxygen saturation, will be summarized over time for each dose level and overall. Change of vital signs from baseline values will also be summarized over time.

7.10.4 12-Lead ECGs

A summary of ECG abnormalities will be presented by visit. ECG intervals (QT and Bazette's and Friderichia's corrected QT intervals [QTcB and QTcF], PR, QRS, and heart rate) will be summarized at each scheduled time point, along with mean change from baseline to each post treatment time point.

7.11 Dose Exploration Analysis

Dose exploration analysis will occur at the end of Stage 1. Assuming a historical control rate of 20% for ORR, 20 patients per dosing regimen are required to determine the dosing regimen for the phase 2 efficacy evaluation (Stage 2) portion of the study. Response data from both dosing regimens will be analyzed with a Bayesian model assuming prior of Beta(0.1,0.1) for each ORR. Dosing regimen A will be claimed ineffective if the posterior probability of ORR_A <20% is greater than the threshold of 0.75, likewise for dosing regimen B. If both regimens are deemed to be ineffective, termination of the study without proceeding to stage 2 may be considered. Other considerations for making this decision should be taken into account, including but not limited to sample size limitation, relevant data from other TAK-659 trials, and applicable patient enrichment or selection strategy that justifies further evaluation of TAK-659 in this setting. If only one dosing regimen is determined to be ineffective, then the other dosing regimen is chosen as the dosing regimen for the remaining portion of the study. If neither dosing regimen is claimed to be ineffective, then regimen A will be chosen if the posterior probability of $ORR_A > ORR_B$ is greater than the threshold of 0.55, likewise dosing regimen B will be chosen if the posterior probability of $ORR_B > ORR_A$ is greater than 0.55. If both the posterior probability of $ORR_A > ORR_B$ and the posterior probability of $ORR_B > ORR_A$ are ≤0.55, clinical and safety factors will be considered to choose the dosing regimen for Stage 2.

Consideration of an alternative dose regimen other than the two TAK-659 dose regimens evaluated in Stage 1 is permissible if supported by the Stage 1 data. For example, if the ramp-up dose schema (dose regimen B) is chosen based on the Bayesian model (see above) but majority of patients treated with dose regimen B fail to dose escalate beyond 60 mg QD TAK-659 following the dose escalation criteria, 60 mg QD TAK-659 may be considered as the dose for Stage 2. The Stage 1 data as well as other relevant supportive data from other trials of TAK-659 will be reviewed and discussed by the SSC. The stage 2 dose regimen of TAK-659 will be selected based on the recommendation by SSC upon agreement with the sponsor.

For tabulation of this analysis, the ORR for Cohorts A and B will be displayed, along with the number and percentage of patients falling into each response category (CR, PR, SD, PD) by cohort.

7.12 Interim Analysis

Since the study was terminated early without proceeding to Stage 2, the interim analysis is not applicable.

7.13 Changes in the Statistical Analysis Plan

All the planned analyses for Stage 2, including the interim analysis, as described in the protocol amendment 2 (dated 24 April, 2018) were removed, since the study was terminated early without proceeding to Stage 2.

8.0 REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. Journal of Clinical Oncology 2007;25(5):579-86.
2. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. Journal of Clinical Oncology 2014;32(27):3059-68.
3. Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services Series v5.0. 27 November 2017.

9.0 DATA LISTINGS

The below subject-level listings will be generated:

- Disposition (date of first dose, date of last dose, number of cycles, reason for discontinuation of study treatment).
- Demographics.
- Concomitant Medications.
- Medical history.
- TAK-659 Exposure and Compliance.
- Target Lesions.
- Non-Target Lesions.
- New Lesions.
- Imaging Assessments (CT, FDG-PET, MRI).
- Lymphoma Symptoms.
- Investigator response assessment.
- Best Overall response.
- Adverse Events.
- TEAEs of grade 3 or higher (including day within each cycle based on the AE onset dates).
- TEAEs leading to study drug discontinuation.
- Serious AEs (all SAEs regardless of treatment emergent AE status).
- Deaths.
- All Lab Parameters.
- Plasma drug concentration.
- Ophthalmic findings.
- Significant protocol deviations.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	02-Apr-2019 12:57 UTC