Title: A Phase 1, Open-label Study of TAK-659 as a Single Agent in Adult East Asian Patients with Non-Hodgkin Lymphoma

NCT Number: NCT03238651

SAP Approve Date: 20 February 2020

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-659 C34007

A Phase 1, Open-label Study of TAK-659 as a Single Agent in Adult East Asian Patients with Non-Hodgkin Lymphoma

PHASE 1

Version: Final

Date: 20 February 2020

Prepared by:

PPD

Based on:

Protocol Version: Protocol Amendment No. 02
Protocol Date: 06 December 2018

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CMV	cytomegalovirus
CPK	creatine phosphokinase
CRF	case report form
ECG	electrocardiogram
FAS	full analysis set
GGT	γ-glutamyl transferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PK	pharmacokinetics
SAE	serious adverse event
SAP	statistical analysis plan
SDB	standard database
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary
Ae_{0-8}	amount of TAK-659 present in the urine from time zero to 8 hours postdose
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval
CL/F	apparent oral clearance after extravascular administration
CLr	renal clearance
C_{max}	Maximum observed plasma concentration
C_{trough}	trough concentration
fe_{0-8}	fraction of the administered dose present as TAK-659 in the urine from time zero to 8 hours postdose
$t_{1/2z}$	terminal disposition half-life
t_{max}	first time to reach C_{max}
ASCT	autologous stem cell transplant
CLL	chronic lymphocytic leukemia
CR	complete response
CT	Computed tomography
C_{trough}	observed concentration at the end of a dosing interval
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity

DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
FDG	fluoro-2-deoxy-D-glucose
FL	follicular lymphoma
HBV	hepatitis B virus
HCV	hepatitis C virus
IWG	International Working Group
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin lymphoma
ORR	overall response rate
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression-free survival
PR	Partial response
PTR	peak-trough ratio
Rac	accumulation ratio
RP2D	Recommended phase 2 dose
SD	stable disease
SPD	Sum of the product of the diameters
ECOG	Eastern Cooperative Oncology Group

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives are:

- To determine the safety, tolerability, and the MTD and/or RP2D of TAK-659 administered orally QD to East Asian patients with NHL who do not have an effective standard treatment available.
- To characterize the plasma and urine PK of TAK-659 in East Asian patients with NHL.

4.2 Secondary Objectives

The secondary objective is to evaluate preliminary efficacy of TAK-659 in patients with relapsed and/or refractory NHL.

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4.4 Study Design

This is an open-label, multicenter, phase 1 study of TAK-659 including a dose escalation part in adult East Asian patients with NHL and an expansion part in adult East Asian patients with relapsed and/or refractory NHL.

The dose escalation part of the study will enroll approximately 18 to 32 East Asian patients diagnosed with NHL for which no effective standard treatment is available. Assuming a dropout rate of 20%, this will ensure that 16 to 28 DLT-evaluable patients are enrolled in the dose escalation part. TAK-659 will be administered continuously, QD, in 28-day treatment cycles (Dosing Schedule A).Dose escalation will follow a standard 3+3 schema to determine the MTD and/or the RP2D. The initial TAK-659 dose will be 60 mg QD and will escalate to 80 mg QD, provided that the safety and tolerability of the 60 mg dose has been demonstrated. Dose escalation will continue until the MTD is reached or until an RP2D (if different from the MTD) for East Asian patients has been identified. More conservative dose escalation, evaluation of intermediate doses or regimens, and expansion of an existing dose level are all permissible following written confirmation of discussions between the sponsor and the investigators, if such

measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationships of TAK-659.

If ≥2 of 6 patients experience a DLT at 60 mg QD, depending on the overall safety profile, the type of AEs/DLTs observed, and following the examination of the preliminary PK results in relation to the PK data in the Western population, a decision will be made either to de-escalate the dose to 40 mg QD or to terminate the study following discussion between the investigator and the sponsor. If ≥2 of 6 patients experience a DLT at 80 mg QD, alternate dose regimens between 60 and 80 mg (ie, 80 mg 7 days on 7 days off [Dosing Schedule B]) will be evaluated as described below. The MTD and/or RP2D should be evaluated with a total of ≥6 DLT-evaluable patients. The RP2D will be determined on the basis of the totality of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. Intrapatient dose escalation is not allowed in this protocol.

- Dosing Schedule B: TAK-659 will be administered QD for 7 consecutive days followed by another 7 days of rest and repeated again (ie, 7 days "on" and 7 days "off"), for a cycle duration of 28 days. The starting dose of 80 mg QD was the maximum administered dose in Dosing Schedule A (2 out of 4 patients presented a DLT in the continuous dosing regimen). However, the alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable per emerging data.

The expansion part of this study will begin once the RP2D has been determined. The expansion part will proceed with dosing of TAK-659 at the RP2D in 28-day cycles. The patient population will consist of East Asian patients with FL or MZL who are relapsed and/or refractory after at least 2 prior of chemotherapy and who must be ineligible for or refusal to hematopoietic stem cell transplant. It is expected that a minimum of 12 response-evaluable patients will be enrolled. Assuming a 20% dropout rate, a total of approximately 15 patients will be enrolled. The objectives of the expansion part are to evaluate the longer-term safety and tolerability of TAK-659 administered at the RP2D, to characterize the PK of TAK-659, and to evaluate the preliminary efficacy of TAK-659 in relapsed and/or refractory FL/MZL as measured by ORR and other efficacy variables, including CR rate, DOR, and PFS.

At least 1 Japanese patient will be enrolled in each cohort in the dose escalation part. The total number of Japanese patients dosed at the RP2D (either the MTD or a lower dose as determined) will be at least 6 including the dose escalation and expansion parts to ensure adequate characterization of PK and safety in Japanese patients.

On the basis of the geographic distribution of patients enrolled and emerging PK and safety data, additional patients may be added, as needed, to further characterize the PK, safety, and tolerability in a particular East Asian geographic region. On the basis of emerging efficacy data, additional groups or patients with FL/MZL may be added to further explore efficacy.

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

treatment-related AEs. AEs will be assessed, and laboratory values, vital signs, ophthalmic exams, 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 4.03, effective date 14 June 2010. DLTs are defined in the study protocol.

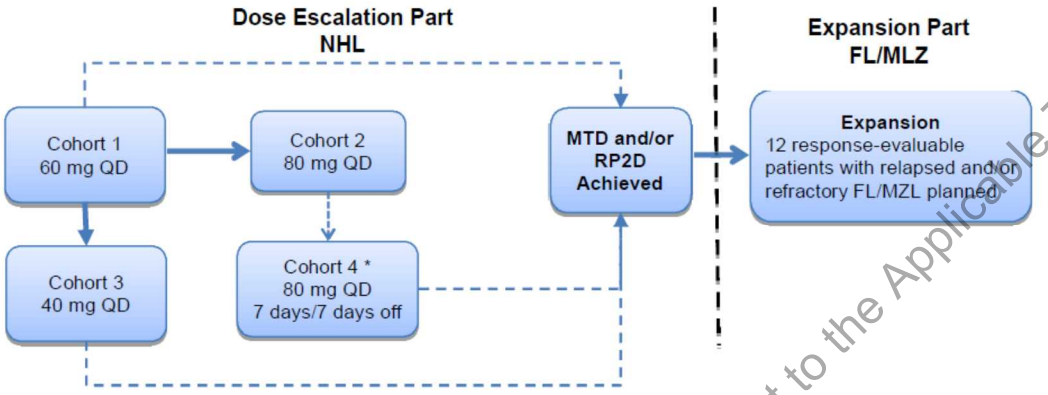
Intensive PK samples (serial blood samples and 2 urine samples) will be collected during Cycle 1 in all patients in the dose escalation part to permit detailed characterization of TAK-659 plasma PK and urine PK across different dose levels. Sparse PK samples will be collected in expansion patients to contribute to population PK and exposure-response analyses. If fewer than 6 Japanese patients are dosed at the RP2D in the dose escalation part, then additional intensive PK samples will be collected during Cycle 1 in a subset of Japanese patients in the expansion part. In total, intensive PK sampling will be performed in at least 6 Japanese patients dosed at the RP2D (either the MTD or a lower dose) among the dose escalation and expansion parts combined to ensure adequate characterization of plasma and urine PK in Japanese patients. Archived and/or freshly biopsied tumor samples may be analyzed to identify potential patient selection markers or to identify biomarkers of response and resistance to TAK-659.

Serum samples will be collected pretreatment and posttreatment, and the levels of circulating cytokines/chemokines/serum proteins in serum will be measured. Whole blood samples will be collected pretreatment during Cycle 1, and the levels of circulating immune cells will be measured.

Buccal epithelial cells will be collected, and DNA may be analyzed for germline polymorphisms in genes encoding drug-metabolizing enzymes and/or transporters involved in the metabolism or disposition of TAK-659 (e.g., CYP2D6). Germline DNA may also be used as a comparator for analysis of tumor mutations and genetic changes.

Evaluation of disease response will be performed as described in the protocol, using the IWG 2007 modified response criteria for malignant lymphoma based on investigator assessment. An imaging modality (e.g., computed tomography [CT] with contrast and fluoro-2-deoxy-D-glucose [FDG]-positron emission tomography [PET] if appropriate) will be used to follow sites of measurable disease during the study treatment. Radiographic images will be maintained at the site. Based on efficacy data observed, the sponsor can elect to have central collection of disease assessment images. In the event of antitumor response, the sponsor may request electronic images for those patients who demonstrate tumor reduction.

The study design is detailed below:



FL=follicular lymphoma MTD=maximum tolerated dose, MZL=marginal zone lymphoma, NHL=non-Hodgkin lymphoma, QD=once daily, RP2D=recommended phase 2 dose.
*The alternative dose of 60 mg may be tested if the 80 mg intermittent regimen is deemed not tolerable.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are:

- Percentage of patients with treatment-emergent AEs (TEAEs).
- Percentage of patients with Grade 3 or higher TEAEs.
- Percentage of patients with serious TEAEs.
- Percentage of patients with DLTs during Cycle 1 (dose escalation part only).
- Percentage of patients discontinuing study drug because of TEAEs.
- Percentage of patients with clinically significant abnormal laboratory values.
- Percentage of patients with clinically significant abnormal vital sign measurements.
- TAK-659 C_{max} on Cycle 1 Days 1 and 7 or 15 by dose.
- TAK-659 t_{max} on Cycle 1 Days 1 and 7 or 15 by dose.
- TAK-659 AUC_{τ} on Cycle 1 Days 1 and 7 or 15 by dose.
- Renal clearance (CL_R) on Cycle 1 Day 7 or 15 by dose.

5.2 Secondary Endpoints

The secondary endpoints are:

- Overall response rate (ORR) in the expansion part.
- CR rate in the expansion part.
- Duration of response (DOR) in the expansion part.
- Progression-free survival (PFS) in the expansion part.

The investigators will perform response assessments using modified International Working Group (IWG) 2007 criteria for malignant lymphoma, which will be the main analysis for the efficacy endpoints.

5.3 Additional Endpoints

Additional endpoints are:

- Apparent oral clearance (CL/F), CL_R as a percentage of CL/F, peak-trough ratio (PTR), accumulation ratio (Rac), and observed concentration at trough on Cycle 1 Day 7 or 15 by dose.
- Plasma concentration-time data contributing to population PK and exposure response analyses.

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6.0 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine sample size were performed for this study. It is estimated that 16 to 28 DLT-evaluable subjects will be enrolled in the dose escalation part. The actual number of patients may vary depending on the actual doses being tested. Assuming a 20% dropout rate, 18 to 32 patients will be enrolled in the dose escalation part.

For the expansion part, a minimum of 12 response-evaluable patients will be enrolled to allow adequate assessment of safety and a preliminary assessment of efficacy. Assuming a 20% dropout rate, approximately 15 patients will be enrolled in the expansion part. The actual number of patients enrolled may increase on the basis of emerging data to allow a sufficient number of PK/safety-evaluable patients per country or in the East Asian race group or to further assess efficacy in a specific subtype or group of patients with FL or MZL. The probability of observing at least 4 responders in the 12 response-evaluable patients is 0.775 if the true TAK-659 response rate is 40% (can be considered the true positive rate); the probability of observing at least 4 responses in the 12 response-evaluable patients is 0.205 if the true TAK-659 response rate is 20% (can be considered the false positive rate). See Table 6.a for more details.

Table 6.a Probabilities of observing the minimum number of responders given true response rates, assuming a total of 12 response-evaluable patients

Number of Responders	TAK-659 True Response Rate			
	0.2	0.3	0.4	0.5
≥2	0.725	0.980	1	1
≥3	0.442	0.917	0.997	1
≥4	0.205	0.775	0.985	1
≥5	0.073	0.562	0.943	0.999
≥6	0.019	0.335	0.842	0.996
≥7	0.004	0.158	0.665	0.981

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4.

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of the study drug administration. Cycle 1 Day 1 values are considered pre-dose. Screening values are used for baseline values if a Cycle 1 Day 1 value is unavailable.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 available efficacy and safety data will be included in data tabulations and listings as needed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

Means, medians, min and max will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 or 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.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count 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.

Screen failure subjects and reasons for screen failure will be grouped.

A month is operationally defined to be 30.4375 days.

7.1.1 Data Presentation

In general, data will be presented as follows

TAK-659 40 mg QD N=xx	TAK-659 60 mg QD N=xx	TAK-659 80 mg QD N=xx	TAK-659 QD Total N=xx

TAK-659 80 mg 7 days off/ 7 days on N=xx	TAK-659 100 mg 7 days off/ 7 days on N=xx	TAK-659 Total 7 days off/ 7 days on N=xx	TAK-659 Total N=xx

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of study drug. 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.

7.1.3 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screen 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 TAK-659. 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 TAK-659, the fifteenth 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.
3. If only the year is present, and it is not the same as the year of the first dose of TAK-659, the fifteenth of June will be used, unless other data indicates that the date is earlier.

7.1.4 Conventions for Missing Adverse Event Dates

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 TAK-659.

    and
  - on or before the month and year of the date of the last dose of TAK-659 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 TAK-659.

    and
  - on or before year of the date of the last dose of TAK-659 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 TAK-659, the event will not be considered treatment emergent.

7.1.6 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 the start date has a month and year but the day is missing, the event will be considered concomitant 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 TAK-659.

    and
  - on or before the month and year of the date of the last dose of TAK-659 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 concomitant if the year of the start date of the event is:
  - On or after the year of the date of the first dose of TAK-659.

    and
  - on or before the year of the date of the last dose of TAK-659 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 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 TAK-659, the event 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 TAK-659 plus 28 days to be included.

7.2 Analysis Sets

The Analysis Sets (Analysis Populations) will include the following:

- Safety analysis set: patients who have received at least 1 dose of study drug will be used for all safety analyses and for efficacy analyses.
- PK analysis set: patients with sufficient dosing and PK data to reliably estimate 1 or more PK parameters will be used for PK analyses.
- Response-evaluable analysis set: patients who have received at least 1 dose of study drug, have sites of measurable disease at baseline, and have as least 1 post-baseline disease assessment will be used for analyses of response.
- DLT-evaluable analysis set: patients who have met the minimum treatment and safety evaluation requirements of the study or who experience a DLT during Cycle 1. The

minimum treatment and safety evaluation requirements are met if in Cycle 1 the patient is treated with at least 75% of planned doses of TAK-659, is observed for ≥1 cycle following the dose on Cycle 1 Day 1, and is considered to have sufficient safety data by both the sponsor and the investigators to conclude that a DLT did not occur.

7.3 Disposition of Subjects

The date first subject signed ICF, date of last subject's last visit/contact, date of last subject's last procedure for collection of data for primary endpoint, MedDRA Version, WHO Drug Dictionary Version, and SAS Version will be generated in a summary table.

The number of patients who were screening failures and reasons for screen failures will be summarized.

The number of patients in the safety population, in the pharmacokinetics population, in the DLT evaluable population, and the reason study drug was discontinued will be summarized.

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

7.4 Demographic and Other Baseline Characteristics

Summaries of demographic and baseline characteristics will be presented for subjects in the safety set.

The demographic data to be evaluated will include age, sex, race, ethnicity, Asian sub-category, baseline height and weight, smoking history, country. Age will be calculated from date of birth to date of informed consent. No inferential statistics will be generated.

Baseline characteristics including lymphoma disease subtype, months since initial diagnosis, staging, Eastern Cooperative Oncology Group (ECOG) performance status.

A separate table will summarize the numbers and percentages of patients who received prior therapy, including prior anticancer, prior transplant, if the patient received, prior radiation, prior surgery, and best response to the last prior anticancer therapy.

7.5 Medication History and Concomitant Medications

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 treatment, or to the start of subsequent anticancer therapy, whichever occurs first.

7.6 Study Drug Exposure and Compliance

7.6.1 Study Treatments

Cycles consists of 28 days for all treatment arms. In QD arm, TAK-659 will be administered QD (every day of a 28-day treatment cycle). In intermittent dosing arm, TAK-659 will be

administered QD for 7 consecutive days followed by another 7 days of rest and repeated again (ie, 7 days "on" and 7 days "off"), for a cycle duration of 28 days.

7.6.2 Extent of Exposure

The exposure to TAK-659 will be characterized by total amount of dose taken in mg, total number of dose taken, relative dose intensity (%), number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, ≥6, and ≥12 treated cycles in the safety population.

Relative dose intensity (RDI) (%) will be presented for cycles 1, 2, …, 6 and overall. Overall RDI is defined as 100 x (total dose received in mg) / (initial prescribed total dose in mg for treated days

For TAK-659, the initial prescribed total dose in mg for treated days is defined as below:

- For QD dosing regimen: 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 intermittent dosing regimen (7 days on /7 days off, or 14 days on/7 days off): initial prescribed dose per "on" day x number of treated "on" days, where an "on" day is defined as a day on which a non-zero dose is prescribed, and the number of treated "on" days is defined as the total number of "on" days among the number of treated days.
  - For 7 days on/7 days off: let q1 be the quotient and r1 be the remainder after dividing the number if treated days by 14. The total number of "on" days=q1*7+r1 if r1<7, otherwise the total number of "on" days=(q1+1)*7.
  - For 14 days on/7 days off: let q2 be the quotient and r2 be the remainder after dividing the number if treated days by 21. The total number of "on" days=q2*14+r2 if r2<14, otherwise the total number of "on" days=(q2+1)*14.

For Relative Dose Intensity by cycle, the same formula is used as overall relative dose intensity, but the number of treated days is derived differently. 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.

Prescribed dose is determined by the dose level to which a patient is enrolled at the onset of the study.

7.6.3 Action on Drug

Action on study drug (eg. Dose reduced due to AE) will be summarized by each of cycle (Cycles 1- 6), sum of the remainder cycles, and total, summarized by dose.

The reason for dose modification (omission, delay, reduction) of study drug will be summarized by each cycle and overall based on the safety analysis set.

7.7 Efficacy Analysis

Analysis of efficacy measures will be descriptive. All efficacy analyses will be based on investigator assessments. Investigators will assess responses using the IWG criteria for lymphoma.

7.7.1 Primary Efficacy Endpoint(s)

There is no primary efficacy endpoint for the study.

7.7.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include ORR, CR rate, DOR, and PFS. No formal statistical tests will be performed for these secondary endpoints. Analyses for these endpoints will be done for expansion patients only. PFS will be summarized using the safety population. All other secondary efficacy endpoints will be summarized using the Response-Evaluable population.

- ORR is defined as the proportion of patients who achieved Complete Response (CR) and Partial Response (PR) (determined by the investigator) in the response-evaluable population.
- CR rate is defined as the proportion of patients who achieved Complete Response (CR, determined by the investigator) in the response-evaluable population.
- DOR is defined as the time from the date of the first documented response to the date of first documented Progression of Disease (PD) by the investigator.
- PFS is defined as the time from the date of first study drug administration to the day of first documented PD or death due to any cause, whichever occurs first, by the investigator.

Antitumor activity of TAK-659 will be based on best overall response. Investigators will assess responses using the IWG 2007 criteria for lymphoma.

Response rate will be tabulated by baseline factors if applicable.

7.7.3 Additional Efficacy Endpoint(s)

Not applicable

7.8 Pharmacokinetic/Pharmacodynamic Analysis

7.8.1 Pharmacokinetic Analysis

The PK population will be used for the description of the plasma PK profile of TAK-659 and for the estimation of plasma and urine PK parameters of TAK-659. The plasma and urine concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry assay methods.

Descriptive statistics (number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, median, minimum, and maximum) will be used to summarize the plasma concentrations.

For dose escalation cohorts, plasma TAK-659 concentrations will be summarized by time postdose and grouped by dose cohort and dosing cycle and day. For sparse PK collected in expansion, plasma TAK-659 concentrations will be summarized for the predose time points on Cycle 1 Days 1, 15 and 22, and Day 1 of Cycle 2, 3 and 4. For dose escalation cohorts, mean and individual plasma TAK-659 concentration data will be plotted over time and grouped by dose cohort and dosing cycle and day (Cycle 1, Days 1 and 15). Plasma concentration-time data from dose escalation cohorts will be used to calculate single-dose (Cycle 1 Day 1) and multiple-dose (Cycle 1 Day 15) plasma PK parameters and multiple-dose (Cycle 1, Day 15) urine PK parameters of TAK-659 by noncompartmental methods. These parameters will include, but not be limited to, C_{max}, t_{max}, C_{trough}, AUC_{last}, AUC_{τ}, CL/F, PTR, and Rac. Urine PK parameters to be calculated in dose escalation cohorts will include, but not be limited to, $Ae_{0\text{-}8}$, $fe_{0\text{-}8}$, and CLr. Plasma and urine PK parameters of TAK-659 will be summarized by dose escalation cohort, dose expansion cohort, and by dosing cycle and day. Dose proportionality of TAK-659 PK will be evaluated by visual inspection of plots of individual PK parameter values versus dose. If data permit, regression analysis using a power model will also be used to assess dose proportionality.

TAK-659 plasma PK data from dose escalation and expansion cohorts, along with data from other studies, may contribute to population PK analyses and exposure-response analyses for pharmacodynamic, safety, and efficacy endpoints. If applicable, the specifics of the population PK and exposure-response analyses will be described in separate analysis plans, and results will be reported separately from the clinical study report.

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7.9 Safety Analysis

AEs will be summarized using the safety analysis set.

Safety will be evaluated by the frequency of AEs, severity and types of AEs (whether the AEs are related to study drug, and whether they are serious AEs or not), and by changes from Baseline in patients' vital signs, weight, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

7.9.1 Adverse Events

The incidence of DLT will be tabulated for each dose group. In addition, to assess the relationship between toxicities and TAK-659 dose, the preferred terms for individual toxicities will be summarized by their frequency and intensity for each dose group. The DLT-evaluable set will be used for the analysis of DLT.

Safety will be evaluated by the frequency of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to study drug and reasons for discontinuation will be tabulated. TEAEs that occur after administration of the first dose of study drug and through 28 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, will be tabulated.

AEs will be tabulated according to the MedDRA and will include the following categories:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- The most commonly reported treatment-emergent AEs (ie, those events reported by more than 10% of all patients).
- SAEs.
- Non-serious treatment-emergent adverse events reported by >5% of patients in any dose level. 5% cutoff will be applied before any rounding.
- Treatment-emergent AEs leading to study drug discontinuation.

Descriptive statistics for the actual values of clinical laboratory parameters and/or change from baseline in clinical laboratory parameters will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Descriptive statistics for the actual values and/or change from baseline of vital signs and weight over time will be tabulated by scheduled time point.

Shift tables for lab parameters will be generated based on changes in NCI CTCAE grades from baseline to the worst post-baseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst post-baseline values, may be used to understand the TAK-659 safety profile.

All concomitant medications collected from Screening through the study period will be classified to preferred terms according to the WHO drug dictionary.

Additional safety analysis may be performed to most clearly enumerate rates of toxicities to further define the safety profile of TAK-659.

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. Drug-related treatment-emergent AEs will also be summarized by the National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI CTCAE) V4.03 intensity.

All deaths occurring on-study will be displayed (regardless of treatment-emergent AE status). An on-study death is defined as a death that occurs between the first dose of study drug and 28 days of the last dose of study drug.

7.9.2 Clinical Laboratory Evaluations

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE v4.03. The number and proportion of patients with shifts in NCI CTCAE toxicity grades from baseline to the worst post baseline toxicity grade.

Parameters to be tabulated include:

Hematology	**Serum Chemistry**	
Hematocrit	Albumin	γ-glutamyl transferase (GGT)
Hemoglobin	Alkaline phosphatase (ALP)	Glucose
Leukocytes with differential	ALT	Lactate dehydrogenase (LDH)
Neutrophils (ANC)	AST	(including LDH isozymes)
Platelet (count)	Amylase	Lipase
Lymphocytes (absolute lymphocyte count [ALC])	Bilirubin (total)	Magnesium
	Blood urea nitrogen (BUN)	Phosphate
Lymphocyte subsets (CD4, CD8, CD4:CD8 ratio)	Calcium	Potassium
	Carbon dioxide (CO_2)	Sodium
	Chloride	Total protein
	Creatinine	Urate
	Creatine phosphokinase (CPK)	

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 Hgb, WBC, lymphocytes, ANC, platelets, and liver function tests (ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin), LDH, creatinine, lipase and amylase for all patients.

7.9.3 Vital Signs

Vital sign results (diastolic and systolic blood pressure, pulse, temperature, and oxygen saturation and body weight) will be as follows:

- Baseline value.
- Minimum post-baseline value.
- Maximum post-baseline value.

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

7.9.4 12-Lead ECGs

ECG intervals (QT and Bazette's and Friderichia's corrected QT intervals [QTcB and QTcF], PR, QRS, and heart rate) will be summarized as follows:

- Baseline value.
- Minimum post-baseline value.
- Maximum post-baseline value.

Changes to the minimum and maximum post-baseline values will be calculated relative to the baseline value.

In addition, the number and percent of patients with increases >30 ms and >60 ms from pre-dose in QTcF will also be summarized.

7.9.5 Other Observations Related to Safety

Ophthalmology and CMV

Any ophthalmic and CMV findings that are determined to be abnormal, clinically significant by the investigators will be listed.

7.10 Interim Analysis

Not applicable

7.11 Changes in the Statistical Analysis Plan

None

8.0 REFERENCES

None

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).
- Populations (can be included with disposition listing).
- Demographics.
- Baseline characteristics.
- Prior therapy.
- Concomitant medications.
- Tumor measurements (tumor measurements from imaging, including changes from baseline, disease response category, and as appropriate, tumor marker measurements).
- Study drug exposure.
- TEAEs.
- TEAEs of grade 3 or higher (cycle date information for the AE onset and end dates will be included).
- TEAEs leading to study drug discontinuation.
- TEAEs resulting in dose modifications.
- Serious AEs (all SAEs regardless of treatment emergent AE status).
- On-study deaths (defined as death that occurs between the first dose of study drug and 28 days after the last dose of study drug (adverse events with an outcome of death)).
- DLTs during Cycle 1.
- Pharmacokinetic concentrations.
- Pharmacokinetic parameters.
- Best overall response (will include prognostic factors as collected in the baseline characteristics: age, number and types of prior therapy, prior autologous transplant, and International Prognostic Index score).
- Laboratory results and change from baseline.
- Ophthalmic findings.
- CMV findings.
- Significant protocol deviations.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	24-Feb-2020 16:14 UTC