Title: A Phase 1b, Dose Escalation Study to Determine the Recommended Phase 2 Dose of TAK-659 in Combination With Bendamustine (±Rituximab), Gemcitabine, Lenalidomide, or Ibrutinib for the Treatment of Patients With Advanced Non-Hodgkin Lymphoma After At Least 1 Prior Line of Therapy

NCT Number: NCT02954406

SAP Approve Date: 06 September 2019

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- Named persons or organizations associated with the study.
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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C34005

A Phase 1b, Dose Escalation Study to Determine the Recommended Phase 2 Dose of TAK-659 in Combination With Bendamustine (±Rituximab), Gemcitabine, Lenalidomide, or Ibrutinib for the Treatment of Patients With Advanced Non-Hodgkin Lymphoma After At Least 1 Prior Line of Therapy

PHASE 1b

Version: 1.0

Date: 06 September 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 03

Protocol Date: 15 November 2018

Approval Signatures

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
ΔAUC	change in area under the concentration-time curve
AE	adverse event
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_τ	area under the concentration-time curve during a dosing interval
AUC_τ/Dose	steady-state, dose-normalized area under the concentration-time curve during a dosing interval
BCR	B-cell receptor
BCRP	breast cancer resistance protein
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
C_{max}	maximum observed concentration
CO_2	carbon dioxide
CPK	creatine phosphokinase
CR	complete response
ctDNA	circulating tumor DNA
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
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDG	fluoro-2-deoxy-D-glucose
FL	Follicular Lymphoma
GGT	gamma glutamyl transferase
IWG	International Working Group
LDH	lactate dehydrogenase
MAD	maximally administered dose
MedDRA	Medical Dictionary for Regulatory Activities
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)

Abbreviation	Term
PET	positron emission tomography
PK	pharmacokinetic(s)
PR	partial response
PTR	peak-trough ratio during a dosing interval, at steady state
QD	once daily
Rac	accumulation ratio
SPD	Sum of Product of Diameters
$t_{1/2}$	terminal disposition half-life
t_{max}	first time to reach maximum (peak) plasma concentration
TTP	Time-to-progression
WHO	World Health Organization

1.0 OBJECTIVES

1.1 Primary Objectives

The primary objective is to determine the maximum tolerated dose (MTD) or the recommended Phase 2 dose (RP2D) for TAK-659 when administered in combination with each of the combination partners (bendamustine, bendamustine + rituximab, gemcitabine, lenalidomide, and ibrutinib).

1.2 Secondary Objectives

The secondary objectives are:

- To characterize the PK of TAK-659 when administered with each of the combination partners. To observe the preliminary efficacy of different combination drugs with TAK 659 (Cohorts A-E) in patients with advanced NHL who have relapsed and/or are refractory after ≥1 prior line of therapy (for patients in Cohort B expansion with FL/marginal zone lymphoma (MZL), ≤1 prior line of therapy).

1.3 Additional Objectives

The additional objective is to evaluate safety and tolerability of TAK-659 in combination with each of the 5 cohorts.

1.4 Exploratory Objectives

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1.5 Study Design

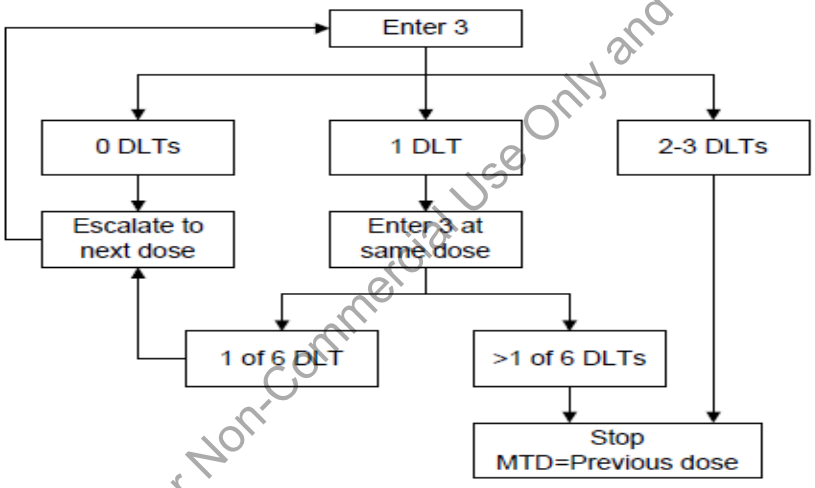
This is a phase 1b, dose escalation study of TAK-659 in combination with 1 of 5 combination partners (bendamustine, bendamustine+rituximab, gemcitabine, lenalidomide, and ibrutinib) in adult patients with advanced NHL after at least 1 prior line of therapy. The primary objective of the study is to determine the MTD or the RP2D of TAK-659 when administered with each of the combination partners.

During dose escalation, the dose of TAK-659 will be escalated (planned 2 dose levels of escalation: 60 and 100 mg) according to a 3+3 dose escalation scheme; all 5 combination partners will be administered at a fixed dose and regimen.

It is expected that approximately 100 patients (approximately 20 in each of the 5 treatment groups) will be enrolled in the study.

Once enrolled in the study, patients will be assigned to one of 5 treatment groups comprising TAK-659 in combination with bendamustine, bendamustine+rituximab, gemcitabine, lenalidomide, or ibrutinib. The starting dose of TAK-659 will be 60 mg QD. Dose escalation will follow a standard 3+3 escalation scheme, and dosing will increase to 100 mg QD provided that the safety and tolerability of the 60 mg dose has been demonstrated. Intermediate dose levels between 60 and 100 mg (eg, 80 mg) or dose levels below the starting dose of 60 mg (eg, 40 mg) also may be evaluated if appropriate. Dose escalation will continue until the MTD is reached, or until TAK-659 100 mg QD (the maximally administered dose [MAD]) is determined to be safe and tolerable, or until an RP2D, if different from the MTD or MAD, is identified on the basis of the safety, tolerability, and preliminary PK and efficacy data (if available) observed in Cycle 1 and beyond. Approximately 6 additional patients will be enrolled at the MTD/MAD/RP2D for each combination for further safety evaluation.

The dose escalation rule is as below.



The dose of each combination drug will remain constant while the TAK-659 dose escalation takes place. The doses of the combination drugs will be as follows:

Bendamustine: 90 mg/m^2 administered intravenously (IV) over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles.

Bendamustine+rituximab: 90 mg/m^2 bendamustine administered IV over 10 or 60 minutes (depending on which formulation is used) on Days 1 and 2 of a 21-day cycle, up to 8 cycles, and 375 mg/m^2 rituximab administered IV per local guidelines and labeling on Day 1 of a 21-day cycle, up to 8 cycles.

Gemcitabine: 1000 mg/m^2 IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle.

Lenalidomide: 25 mg PO QD for Days 1 to 21 of a 28-day cycle.

Ibrutinib: 560 mg PO QD of a 28-day cycle.

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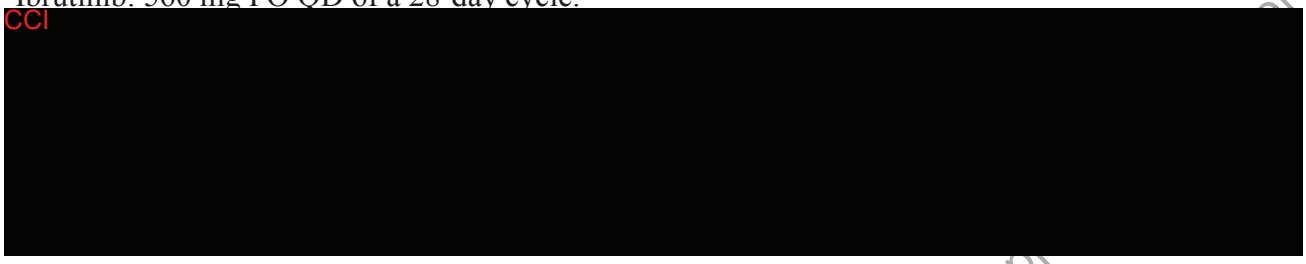

For all dose escalation cohorts (including the safety expansion in the MTD/MAD/RP2D cohorts), serial blood samples will be collected at prespecified time points for up to 24 hours after TAK-659 dosing on Cycle 1 Days 1 and 15 to characterize the plasma PK of TAK-659 when administered with each of the combination partners. In addition, blood samples for plasma PK will be collected at the same time points for cytokine/chemokine assessments on Cycle 1 Day 8.

Disease status will be assessed using the Internation Working Group (IWG) revised criteria for patients with malignant lymphoma, based on investigator assessment. Computerized tomography (CT) scans (with contrast) of the chest, abdomen, and pelvis (neck should be included if appropriate) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans extending from neck to mid-thigh will be performed in all patients to follow the disease as indicated in the Schedule of Events (Appendix A, Protocol Amendment 3). Repeat FDG-PET scans may be performed during the study only when the screening FDG-PET scan is positive. For patients with a negative screening FDG-PET scan, additional scans may be performed on study if clinically indicated for occurrence of PD per local standard of care.

As this is a phase I study using a standard 3+3 methodology to allocate patients to the next dose level, no randomization is planned for this study. This is an open-label study. No blinding/ unblinding methodology is required.

Patients in the dose escalation cohorts who are withdrawn from treatment during Cycle 1 for reasons other than DLTs will be replaced.

2.0 ANALYSIS ENDPOINTS

2.1 Primary Endpoints:

Maximum tolerated dose (MTD) (dose escalation).

Recommended phase 2 dose (RP2D) (dose escalation).

2.2 Secondary Endpoints:

- TAK-659 PK parameters, including maximum observed concentration (Cmax), time of first occurrence of Cmax (Tmax), and area under the plasma concentration-time curve during a dosing interval (AUCτ) by dose escalation cohort.
- Overall response rate (ORR)
- Duration of response (DOR)
- Time to progression (TTP)

2.3 Additional Endpoints:

- Percentage of patients with AEs and drug related AEs, respectively.
- Percentage of patients with ≥Grade 3 AEs and drug related ≥Grade 3 AEs, respectively.
- Percentage of patients with serious adverse events (SAEs) and drug related SAEs, respectively.
- Percentage of patients who discontinued due to AEs.
- Clinically significant laboratory values.
- Clinically significant vital sign measurements.
- Other TAK-659 PK parameters, including apparent oral clearance, peak-trough ratio, accumulation ratio, and trough concentration by dose escalation cohort.

2.4 Exploratory Endpoints:

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3.0 DETERMINATION OF SAMPLE SIZE

The dose escalation of this study will use a 3+3 design. With the exception of the bendamustine combination arm, the combination partner's dose will be the dose according to the manufacturer's label. The dose of bendamustine will be based on its use in previous combination studies [1,2]. The planned doses of TAK-659 are 60 and 100 mg. For each combination arm, 9 to 12 DLT-evaluable patients will be needed for the dose escalation portion. In addition, for each arm, another 6 patients will be needed for safety expansion. Assuming a 10% dropout rate, 20 patients will be needed for each arm; therefore, the total sample size for this study, including all 5 arms, will be 100.

4.0 METHODS OF ANALYSIS AND PRESENTATION

4.1 General Principles

Statistical analyses will be performed separately for the following five combination arms. Within each combination arm (cohort), analysis will be done by TAK-659 dose escalation cohort and overall in pooled data across dose escalation levels. In addition, data collected within each cohort will be analyzed across NHL subtypes, and for some tables, separately within DLBCL and within FL.

The following specifies each combination (cohort):

- TAK-659+bendamustine (cohort A).
- TAK-659+bendamustine+rituximab (cohort B).
- TAK-659+gemcitabine (cohort C).
- TAK-659+lenalidomide (cohort D).
- TAK-659+ibrutinib (cohort E).

No formal statistical hypothesis testing will be performed. 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 listings and tabulations as needed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

Baseline values are defined as the last observed value before the first dose of study medication.

All statistical analyses will be conducted using SAS® Version 9.2, or higher.

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.

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.

The summary tables will include escalation cohort, overall for dose escalation phase, and by expansion cohort and overall for expansion phase and overall for both phases as appropriate.

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

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4.2 Definition of Study Visit Windows

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

4.3 Conventions for 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 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 study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

4.4 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, then 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.
- If the start date has a specified year, but the day and month are missing, then 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.
- 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, then the event will not be considered treatment emergent.

4.5 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/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, then 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 study drug
   - and
   - on or before the month and year of the date of the last dose of any study drug plus 28 days.
2. 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 study drug
   - and
   - on or before the year of the date of the last dose of any study drug plus 28 days.
3. 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 study drug, then 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 study drug plus 28 days to be included.

4.6 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 some 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 one dose of study drug, have sites of measurable disease at Baseline, and have one post-Baseline disease assessment will be used for analyses of response. Investigators will assess responses using the IWG criteria for malignant lymphoma.

- 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 dose of TAK-659, and 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.

4.7 Disposition of Subjects

Dispositions of patients include the number and percentage of patients in each analysis population, and will be presented by each combination arm and overall, as well as by escalation cohort and overall. The primary reason for study termination will also be summarized similarly in this table. All percentages will be based on the number of patients in the safety population. A listing will present data concerning patient disposition. Screen failures will be summarized in separate tables/listings.

4.8 Demographic and Other Baseline Characteristics

Demographics will be summarized for each escalation cohort andoverall for dose escalation phase. Demographic data will also be presented in a by-patient listing. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, height, weight, and primary diagnosis. Age will be calculated from date of birth to date of informed consent. No inferential statistics will be generated.

Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

Baseline characteristics including baseline disease primary diagnosis, years since initial diagnosis, staging, Eastern Cooperative Oncology Group (ECOG) performance status, will be summarized.

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

4.9 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 status (whether it is resolved or ongoing).

4.10 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.

Concomitant medications will also be presented in a by-patient listing.

Concomitant procedures will not be coded, but will be presented in a by-patient listing.

4.11 Study Drug Exposure and Compliance

4.11.1 Extent of Exposure:

The exposure to TAK-659, and to each of the other study drugs, will be characterized by total amount of dose taken in mg, total number of doses taken, relative dose intensity (%), number of treated cycles, numbers and percentages of patients who had ≥1, ≥2, …, ≥6, and ≥12 treated cycles for patients in the safety population. A treated cycle is defined as a cycle in which the patient received any amount of study drug.

Relative dose intensity (RDI) (%) will be presented overall and by cycle. 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 relative dose intensity, 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 date of cycle) + 1, however, if a patient discontinues during the cycle then use (date of drug discontinuation – first dose date of cycle) + 1.

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

The extent of exposure to TAK-659 and to each of the combination partner study drugs (as applicable to the escalation cohort) will be summarized by escalation dose within each cohort and overall for the cohort.

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

4.12 Action on Drug:

Action on study drug will be summarized by each of cycle (Cycles 1- 6, post-Cycle 6), sum of the remainder cycles, and total, for each dose escalation within each cohort and overall for each cohort.

4.13 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.

4.14 Primary Efficacy Endpoint(s)

There is no primary efficacy endpoint for the study.

4.15 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoints include ORR, DOR and TTP. No formal statistical tests will be performed for these secondary endpoints. Analyses for these endpoints will be done for each of the 5 combination arms separately and by dose level. All secondary efficacy endpoints will be summarized using the Response-Evaluable population.

ORR is based on the best overall response recorded from the enrollment in the study until progression or end of study. The percentage of subjects from the response-evaluable population and experiencing objective response (based on investigator confirmed CR or PR) at the time of analysis defines ORR.

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.

TTP is defined as the time from the date of first study drug administration to the date of first documented PD or relapse in the response evaluable population.

Antitumor activity of TAK-659 will be based on best overall response. Investigators will assess individual responses using the IWG criteria for lymphoma. Data listings will present the tumor measurements from imaging, including changes from Baseline, disease response category, and as appropriate, tumor marker measurements. Waterfall plots will visualize the best change from baseline in lesion shrinkage across dose cohorts.

The number and percentage of patients falling into each response category (eg, CR, PR, SD) will be tabulated descriptively for each escalation dose within the cohort and overall for each cohort. Estimates of the CR+PR rate will be presented with 2-sided 95% exact binomial CIs.

ORR will be tabulated by baseline factors if applicable. The prognostic factors will include, but will not be limited to age, number and types of prior therapy, TTP from diagnosis or prior therapy, prior autologous transplant, and International Prognostic Index score. Waterfall plots representing the best percent change from baseline of the sum of the product of diameters (SPD) across the lesions of patients from each dose escalation cohort will be provided. These will be colored by best objective response.

DOR and TTP will be censored at the last response assessment that is SD or better for patients who do not experience progression.

4.16 Additional Efficacy Endpoint(s)

Not applicable

4.17 Pharmacokinetic/Pharmacodynamic Analysis

4.17.1 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 PK parameters of TAK-659. Plasma concentrations of TAK-659 will be determined by validated liquid chromatography tandem mass spectrometry assay methods.

For each combination arm, plasma TAK-659 concentrations will be summarized by nominal (scheduled) time postdose and grouped by dose cohort and dosing cycle and study day (except for those 2 to 4 hours postdose PK samples collected on Cycle 1, Day 8). Summary statistics will be reported at nominal sampling times with at least 2 patients in the PK evaluable population; means will be reported if the number of observations above the lower limit of quantitation (NALQ) is ≥ 50% of the number of patients. The summary statistics will consist of: N, mean (SD), coefficient of variation (CV), geometric mean, CV of geometric mean, median, min, max. Arithmetic mean, geometric mean, median, min, and max will be reported on at least 2 non-missing values, while the SD and CV will be reported on at least 3 non-missing values. Plasma concentrations that are BLQ will be set to zero for calculation of summary statistics, except for geometric means, where BLQ values will be considered missing. 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) on both linear and semi-logarithmic scales.

Plasma concentration-time data will be used to calculate single-dose (Cycle 1 Day 1) and multiple-dose (Cycle 1 Day 15) plasma PK parameters of TAK-659 by noncompartmental methods. These parameters will include, but not be limited to, C_{max}, t_{max}, AUC_{τ}, C_{trough}, CLss/F, PTR, and Rac. Plasma PK parameters of TAK-659 will be summarized by dose escalation cohort, dose expansion cohort, and by dosing cycle and day.

TAK-659 plasma PK data from dose escalation 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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4.18 Other Outcomes

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4.20 Safety Analysis

AEs will be summarized using the safety analysis set.

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

Safety will be evaluated by the frequency of AEs, severity and types of AEs, 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.

4.21 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 presented in a by-patient listing. Treatment-emergent AEs 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 according to the MedDRA by system organ class, high level terms and preferred terms and will include the following categories, for each combination arm and overall as well as for escalation cohort, safety expansion and overall.

Categories of AEs:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
  - Relatedness to TAK-659 alone
  - Relatedness to each of the combination partners alone
  - Relatedness to TAK-659 and the combination partner
- 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)
- Serious adverse events (SAEs)

Listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

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, once within each high level term, 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.

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, and on-study deaths.

By-patient listing of grade 3 or higher treatment-emergent AE will also be provided, where the cycle day information for the AE onset and end dates will be included in the listing.

4.22 Serious Adverse Events

The number and percentage of subjects experiencing at least 1 treatment emergent serious AEs (SAEs) will be summarized by MedDRA primary system organ class, high-level term, and preferred term. Drug-related SAEs will be summarized similarly.

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of treatment emergent AE status).

4.23 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up 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.

4.24 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug will be presented. All AEs resulting in discontinuation of study drug occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status).

4.25 Dose Limiting Toxicities (DLTs)

A by-patient listing of DLTs in Cycle 1 will be presented by dose level for patients in the DLT-evaluable population.

In addition, to assess the relationship between toxicities and TAK-659 dose, the preferred term of individual toxicities will be summarized by their frequency and intensity for each combination arm, and by dose level of TAK-659 within each combination arm.

4.26 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 dose escalation cohort, overall for dose escalation phase, safety expansion cohort and overall. Laboratory data will also be presented in listings. Unscheduled laboratory test results will be listed and included in laboratory shift tables.

Shift tables will be constructed for laboratory parameters to tabulate changes in NCI CTCAE v4.03 for toxicity from baseline to post baseline worst on study CTCAE grade, if available. 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	Lipase
Platelet (count)	Amylase	Magnesium
Lymphocytes (absolute lymphocyte count [ALC])	Bilirubin (total)	Phosphate
	Blood urea nitrogen (BUN)	Potassium
Lymphocyte subsets (CD4, CD8, CD4:CD8 ratio)	Calcium	Sodium
	Carbon dioxide (CO_2)	Total protein
	Chloride	Urate
	Creatinine	
	Creatine phosphokinase (CPK)	

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

By-patient listings to be presented include hematology, clinical chemistry, urinalysis, clinically significant laboratory values and ophthalmology.

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).

4.27 Vital Signs

The actual values of vital sign parameters including diastolic and systolic blood pressure, heart rate, temperature, and oxygen saturation, will be summarized over time by each combination arm and overall as well as by escalation cohort and overall in dose escalation phase, safety expansion and overall. Change of vital signs from baseline values will also be summarized over time. Vital sign values will also be presented in a by-patient listing.

4.28 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. ECG data will be presented in a by-patient listing.

4.29 Other Observations Related to Safety

Not applicable

4.30 Interim Analysis

Not applicable

4.31 Changes in the Statistical Analysis Plan

5.0 REFERENCES

1. Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. J Clin Oncol 2005;23(15):3383-9.
2. Vacirca JL, Acs PI, Tabbara IA, Rosen PJ, Lee P, Lynam E. Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma. Ann Hematol 2014;93(3):403-9.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	06-Sep-2019 14:02 UTC