Title: A Phase 1, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAK-228 (a Catalytic TORC1/2 Inhibitor) as Single Agent in Adult East Asian Patients with Advanced Nonhematological Malignancies

NCT Number: NCT03370302

SAP Approve Date: 28 August 2019

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
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- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C31008

A Phase 1 Study of TAK-228 in East Asian Patients with Advanced Nonhematological Malignancies

PHASE 1

Version: Final

Date: 28 August 2019

Prepared by:

PPD

Based on:

Protocol Version: Protocol Amendment No. 02

Protocol Date: 8 February 2018

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time 0 to time of last measurable concentration
$AUC_{0\text{-inf}}$	area under the plasma concentration-time curve from time 0 to infinity
AUC_{24}	area under the plasma concentration versus time curve from zero to 24 hours
BQL	below quantifiable limit
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CR	complete response
C_{trough}	observed concentration at the end of a dosing interval
CT	computed tomography
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GGT	Gamma glutamyl transferase
HDL-C	high-density lipoprotein cholesterol
HLT	heart lung transplantation
$lambda_z$	terminal disposition phase rate constant
LDL-C	low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	progressive disease
PK	pharmacokinetic(s)
PR	partial response
QD	once daily
QTcF	QT interval (msec) with Fridericia correction
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum of the longest diameter
$t_{1/2}$	terminal disposition phase half-life

TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
Vz/F	apparent volume of distribution during the terminal disposition phase
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives are:

- To evaluate safety and tolerability and to determine RP2D of TAK-228 administered daily (QD arm) or weekly (QW arm) to East Asian patients with advanced nonhematological malignancies.
- To characterize PK of TAK-228 in East Asian patients with advanced nonhematological malignancies

4.2 Secondary Objectives

The secondary objective is:

- To evaluate preliminary anti-tumor activity of TAK-228.

4.3 Exploratory Objectives

CCI [redacted]

4.4 Study Design

This study is a multicenter, open-label, phase 1 study of TAK-228 administered orally as a single agent in adult East Asian patients with advanced nonhematological malignancies for whom effective standard anticancer treatment is not available or is no longer effective.

The study will consist of 2 arms to evaluate the safety and tolerability, characterize the PK, and determine the RP2Ds of single-agent TAK-228 to be used for 2 schedules (daily and weekly) in East Asian patients.

1. QD (daily dosing schedule) arm: milled TAK-228 will be administered on an empty stomach, once daily, in repeated 28-day treatment cycles.

2. QW (weekly dosing schedule) arm: milled TAK-228 will be administered on an empty stomach in Cycle 1 and following a light meal in Cycle 2 and the subsequent cycles, weekly (ie, on Days 1, 8, 15, and 22), in repeated 28-day treatment cycles.

The 2 arms will enroll in parallel. Patient assignment to a specific schedule will be decided jointly by the investigator and sponsor with the aim of maximizing enrollment efficiency in the study.

During dose escalation, 2 planned dose levels of TAK-228 will be tested in each arm (2 mg and 4 mg in the QD arm; 20 mg and 30 mg in the QW arm) following standard 3+3 dose escalation rules. Dosing will increase to 4 mg in QD arm or 30 mg in QW arm, provided that the safety and tolerability of the starting dose has been demonstrated (Figure 4.a).

If a dose is deemed safe in any cohort based on 3+3 rules, then the cohort may be expanded to as many as 12 patients in total to further confirm safety, investigate PK and determine RP2D. At least 1 Japanese patient will be enrolled in each group of 3 patients during dose escalation. The total number of Japanese patients dosed at the RP2D level will be at least 6. On the basis of the geographic distribution of patients enrolled or any emerging safety data or PK, additional patients may be added, as needed, to further characterize the safety, tolerability, or PK in patients from a particular East Asian geographic region.

As Western population based RP2D have been defined as 4 mg for the QD schedule and the 30 mg QW schedule, the dose escalation schemas in the current study are designed to confirm Cycle 1 based RP2D in East Asian patients or determine an alternative appropriate lower dose. Escalation beyond 4 mg QD or 30 mg QW is not expected to be necessary in this study. However, if TAK-228 exposures are unexpectedly lower than anticipated in the East Asian populations, and no DLTs have occurred in the dose escalation parts, the TAK-228 dose may be escalated further after discussion between the investigators and the sponsor based on the available PK and safety data.

If ≥2 of 6 patients experience a DLT at the starting dose level (ie, 2 mg in QD arm or 20 mg in QW arm), depending on the overall safety profile, the types 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 evaluate a lower dose or to terminate the study, following discussion between the investigators and the sponsor.

For either treatment arm, more conservative dose escalation, evaluation of intermediate doses, and expansion of an existing or previously tested dose level are all permissible following discussions and agreement between the investigators and the sponsor, if such measures are needed for patient safety or for a better understanding of the dose-toxicity and dose-exposure relationships of TAK-228.

Blood samples will be collected at prespecified time points in Cycle 1 Days 1, 2, 8, 15, 16, and 22 to characterize the PK of TAK-228 when given daily (QD) or weekly (QW). Blood samples will also be collected at prespecified time points during Cycle 2 Days 1 and 15 to characterize the PK of TAK-228 when given QW with light meals.

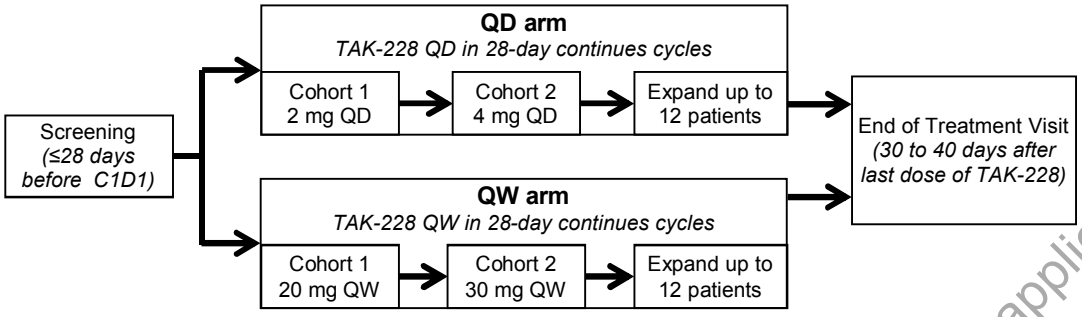
CCI [redacted]

Radiological tumor evaluations will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1) [1].

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [2].

Approximately 36 DLT-evaluable patients (approximately 18 patients in each arm) will be enrolled from approximately 4 study sites in East Asia. Enrollment is defined as the time of the first dose of TAK-228. Assuming a 20% dropout rate, approximately 23 patients will be needed for each arm to have approximately 18 DLT-evaluable patients; the total sample size for this study will be approximately 46.

Figure 4.a Study Overview Diagram



Abbreviations: C1D1=Cycle 1 Day 1, QD=once daily, QW=once weekly.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are:

- The number and percentage of patients with TEAEs.
- The number and percentage of patients with Grade 3 or higher TEAEs.
- The number and percentage of patients with serious TEAEs.
- Number of patients with DLTs during Cycle 1.
- The number and percentage of patients discontinuing study drug due to TEAEs.
- TAK-228 C_{max}, T_{max}, and AUC on Cycle 1 Days 1 and 15.

5.2 Secondary Endpoints

The secondary endpoint is:

- Clinical benefit rate defined as the proportion of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD) (SD of any duration).

5.3 Exploratory Endpoints

CCI

6.0 DETERMINATION OF SAMPLE SIZE

For each arm, dose escalation will be conducted according to a standard 3+3 dose escalation schema. There are 2 planned dose cohorts in each of 2 arms (QD arm and QW arm) in this study. For each 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 20% dropout rate, approximately 23 patients will be needed for each arm to have 18 DLT-evaluable patients; the total sample size for this study will be 46.

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 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.

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.

For the categorical variables, the count and proportions of each possible value will be tabulated. 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. Additional statistics will be tabulated for pharmacokinetic data (see Section 7.9.1).

A month is operationally defined to be 30.4375 days.

7.1.1 Data Presentation

In general, data will be presented as follows:

QD Arm:

Dose Escalation			Dose Expansion	Dose Escalation + Expansion	
TAK-228 2 mg QD N=3	TAK-228 3 mg QD N=3	TAK-228 4 mg QD N=3	TAK-228 3 mg QD N=xx	TAK-228 3 mg QD N=xx	Total N=xx

QW Arm:

TAK-228 20 mg QW N=3	TAK-228 30 mg QW N=3	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 the medication. Other study days are defined relative to the Study Day 1 with Day -1 being the day prior to Study Day 1.

7.1.3 Conventions for Partial Adverse Event/Concomitant Medication Dates

Missing or incomplete start dates will be imputed based on the algorithm described below:

- If the start date has month and year but day is missing, the adverse event will be considered treatment-emergent or the therapy concomitant if both the month and year of the start date are on or after the month and year of the date of the first dose of TAK-228 and on or before the month and year of the date of the last dose of TAK-228 plus 30 days.
- If the start date has year, but day and month are missing, the adverse event will be considered treatment -emergent or the therapy concomitant if the year of the start date is on or after the year of the date of the first dose of TAK-228 and on or before the year of the date of the last dose of TAK-228 plus 30 days.

7.1.4 Conventions for Other Partial Dates

Missing or incomplete dates recorded during the screening visits (e.g date of initial diagnosis) will be imputed based on the algorithm described below:

- 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.
- 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 1st of January will be used.
- 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.

7.2 Analysis Sets

7.2.1 Safety Analysis Set

The safety set includes all patients who receive at least 1 dose of study drug, and will be used for all safety analyses (except for DLT analysis) and efficacy analyses.

7.2.2 Pharmacokinetics Analysis Set

Pharmacokinetic set includes patients with sufficient dosing and PK data to reliably estimate 1 or more PK parameters. PK analyses will be performed using the PK population.

7.2.3 DLT-evaluable Set

DLT-evaluable set: patients who have received at least 75% of planned doses of TAK-228 in Cycle 1 (21 doses for the QD arm and 3 doses for QW arm) unless interrupted by study drug-related AEs and have sufficient follow-up data considered by sponsor and investigator to determine whether DLT occurred.

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 characteristics consist of: age, sex, ethnicity, Asian sub-category, baseline weight and height, smoking history, country. Age will be calculated from date of birth to date of informed consent. No inferential statistics will be carried out.

Baseline characteristics assessments consist of: baseline ECOG performance status, primary diagnosis, stage of disease at study entry, months since initial diagnosis.

A separate table will summarize the count and proportions of patients with prior surgery, prior radiation, prior systemic anticancer therapies, number of prior regimens and best response to most recent systemic treatment.

7.5 Medical History and Concurrent Medical Conditions

No summary for medical history and concurrent medical conditions.

7.6 Medication History and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO generic name for the safety population.

7.7 Study Drug Exposure and Compliance

7.7.1 Study Treatments

Cycles consist of 28 days for all treatment arms. In QD arm, TAK-228 will be administered QD (every day of a 28-day treatment cycle). In QW arm, TAK-228 will be administered once weekly (on Days 1, 8, 15, and 22 of a 28-day treatment cycle).

7.7.2 Extent of Exposure

Summaries and descriptive statistics of duration of treatment in weeks ((last dose date – start dose date + 1)/7), total number of cycles administered, actual cumulative dose, planned cumulative dose and relative dose intensity will be summarized by dose level in each treatment arm for patients in the safety population.

Number of cycles administered = A treated cycle is defined as a cycle in which the patient received any amount of TAK-228. This is defined as Actual Dose greater than zero for at least one of the dosing day in the cycle for TAK-228.

Actual cumulative dose (mg) = Sum of all doses (mg) administered to a subject during the treatment period.

Relative dose intensity = cumulative dose / planned cumulative dose.

TAK-228 QD (every day of a 28-day treatment cycle)

Average daily dose (mg/day) is defined as:

Sum of all doses (mg) actually received (cumulative dose) / duration of treatment in days

Planned cumulative dose is defined as:

*(duration of treatment in days * initial dose at start of treatment)*

Relative dose intensity for TAK-228 (%) is defined as:

*(Cumulative dose / planned cumulative dose) * 100*

TAK-228 QW (Days 1, 8, 15 and 22 of a 28-day cycle)

Relative dose intensity for TAK-228 (%) is defined as:

*Cumulative dose (mg) / [Number of planned dose from start dose date to last dose date*30mg] * 100*

Planned dose =[(Date of first dose in last cycle + 28 days – date of first dose) / 7] * 30 mg/week

7.7.3 Action on Drug

Action on study drug (e.g. dose reduced due to AE) will be summarized by each cycle (Cycles 1-6) and total, for each dose level in each arm in the safety population.

7.8 Efficacy Analysis

Analysis of efficacy measures will be descriptive. All efficacy analyses will be based on safety set.

7.8.1 Primary Efficacy Endpoint(s)

Not applicable

7.8.2 Secondary Efficacy Endpoint(s)

Secondary efficacy endpoint is clinical benefit rate defined as the proportion of patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD) (SD of any duration). Best overall response is defined as the best response reported by the investigator; ordered from best to worst: Complete Response, Partial Response, Stable Disease, Progressive Disease. The best response can also be Not Evaluable (NE) or No assessment performed if this is the only investigator assessment of objective response available for the patient. Best overall response is defined as the best response recorded after the first dose of study drug until subsequent therapy.

The number and percentage of patients in each best response category (CR, PR, SD, Progressive Disease, Unable to Assess, Unknown, or no post baseline response assessment) will be summarized by dose level in each arm. In addition, overall response (CR+PR) will be summarized.

Data listings will present the tumor measurements from CT or MRI (including changes from baseline), change/percent change from baseline in sum of the longest diameter (SLD), change/percent change from nadir in SLD, non-target disease assessment, new lesion assessment and disease response assessment at each response assessment and the best overall response. Duration of response and duration of SD will also be presented in data listings.

Duration of Response (DOR)

The duration of objective response will be calculated for those patients with a best response of CR or PR, and is defined as the number of days from the start date of CR, or PR (whichever response is achieved first) until progressive disease or until the last response assessment if there is no progressive disease.

Duration of Stable Disease

The duration of stable disease will be calculated for those patients with a best response of SD.

The duration of SD is the number of days from cycle 1 day 1 until progressive disease or until the last response assessment if there is no progressive disease.

7.8.3 Additional Efficacy Endpoint(s)

Not Applicable

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

All PK analyses will be performed using the PK analysis set.

Data Handling

All BLQ values occurring prior to C_{max} are replaced by "0" and all BLQ concentrations occurring after C_{max} will be treated as missing. Embedded BLQ values (between two measurable

data points) occurring before/after C_{max} will be handled on a case by case basis. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, will be set to missing at the discretion of the pharmacokineticist. No sample and no result values will always be treated as missing data. For the estimation of mean concentration in plots and tabular summaries, BLQ values will always be replaced by zero.

All TAK-228 plasma concentrations obtained in the present study, including sparse sampling data from Cycle 2, may be combined with data from other studies in which the PK of TAK-228 has been characterized for the purposes of population PK analyses. If conducted, the results of population PK analyses will be presented in a separate report.

TAK-228 Plasma Concentration Tables

Descriptive statistics (i.e. number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, geometric mean, geometric coefficient of variation, median, minimum, and maximum) will be used to summarize the plasma TAK-228 concentrations by nominal (scheduled) time post-dose in Cycle 1 (Days 1 and 15) for each arm.

Concentration values will be excluded from the summary statistics and flagged with code in the concentration tables when blood draw time deviations are greater than 20% of nominal time calculated relative to the time of dosing.

TAK-228 Plasma Concentration Figures

Linear and semi-logarithmic plots of the mean (±SD) TAK-228 plasma concentration versus scheduled sampling time will be provided separately for each PK visit (Cycle 1 Day 1 and Cycle 1 Day 15) and each treatment arm (QD arm and QW arm). Plots will be grouped by dose level.

Linear and semi-logarithmic plots of the mean (±SD) TAK-228 plasma concentration versus actual sampling time will be provided separately for each treatment group (QD arm by dose level and QW arm by dose level) and grouped by study visit (Cycle 1 Day 1 and Cycle 1 Day 15 overlay plots).

Linear and semi-logarithmic plots of individual plasma concentration versus actual sampling time will be generated by treatment group (QD arm by dose level and QW arm by dose level) and Day (1 and 15).

Linear mean (±SD) TAK-228 pre-dose or trough concentration versus time plots will generated for the QD arm and the QW arm.

TAK-228 Plasma Concentration Listings

All individual patient plasma concentration data will be listed by treatment arm.

Pharmacokinetic Parameter Calculation

TAK-228 PK parameters will be calculated on Cycle 1 Days 1 and 15 during the dose escalation and expansion portions of the study by noncompartmental analysis with WinNonlin® Professional Version 7.0 or higher (Certara USA, Inc., Princeton, NJ) using the linear log

trapezoidal method, unless otherwise stated. Actual sampling times (calculated relative to the last study drug administration) will be used for PK parameter calculations. Nominal times will be used only when actual times are not available. For concentration-time profiles in which the terminal elimination phase cannot be reliably estimated, derived PK parameters will be flagged and excluded from summary statistics. Reasons for unreliable estimation include R^2adj < 0.8 for the log-linear regression and AUC percent extrapolated (%AUCextrap) ≥ 20 %.

Pharmacokinetic Parameters

Data permitting, the following single-dose PK parameters will be calculated for TAK-228 by noncompartmental analysis:

Cycle 1 Day 1 and Cycle 1 Day 15:

Cmax, tmax, AUClast, AUC24, t1/2, CL/F, Vz/F

Cycle 1 Day 1, only:

AUCinf

Cycle 1 Day 15, only:

Accumulation ratio calculated based on Cmax (RA Cmax)

Accumulation ratio calculated based on AUC24 (Rac AUC24 for QD and Rac AUC168 for QW)

Ctrough

For the QW Arm, the additional parameter AUC168 will be calculated on Cycle 1 Day 1 and Cycle 1 Day 15.

Additional supplementary parameters will be presented in a separate table:

Adjusted-R2, number of points used in the λz calculation, λz upper, λz lower, λz, tlast, %AUCextrap

Pharmacokinetic Parameter Tables

PK parameters will be summarized using descriptive statistics (i.e. number of patients, arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation, median, minimum value, and maximum value) for each arm and day.

Pharmacokinetic Parameter Figures

Box plots of dose-adjusted exposure parameters (e.g. AUCinf, AUC24 or AUC168 and Cmax) vs. the planned doses administered by Arm (QD or QW) in East Asians from this study (total of 2 box plots per PK parameter) will be presented. Individual subject values, mean and median value and the upper and lower whiskers (1.5 × Interquartile Range [IQR]) will be displayed on the plot with outliers (if any) shown as individual round markers.

Pharmacokinetic Parameter Listings

Individual PK parameters will be listed by arm.

Cross-Study Comparison Tables and Figures

A comparison of PK in Asian patients from this study (C31008) will be made to results from PK in a Western population (Study MLN0128-1004). A summary PK table will be generated. For the comparison with single-agent 2 mg QD dose in this study (C31008), the PK parameters for the 4 mg QD dose in Western patients (MLN0128-1004) will be dose-normalized.

Mean (±SD) (linear; log-linear) concentration-time curves: for the QD or QW schedule, mean concentration-time profiles in Western patients (MLN0128-1004) following a single dose of TAK-228 will be overlayed with Day 1 TAK-228 concentration-time profiles in East Asians (C31008) by dose level and arm (QD or QW).

Mean (±SD) (linear; log-linear) pre-dose or trough concentration-time curves for Asian subjects from Study C31008 and for Western subjects from Study MLN0128-1004 overlayed by dose level and arm (QD or QW).

Box plots of exposure parameters (e.g. AUCinf, AUC24 or AUC168 and Cmax) vs. Population (i.e. QD and QW in East Asians from this study C31008 and in Western patients from Study MLN0128-1004) by the planned dose administered and Arm (QD or QW) with a total of 4 box plots per PK parameter. Individual subject values, mean and median value and the upper and lower whiskers (1.5 × Interquartile Range [IQR]) will be displayed on the plot with outliers (if any) shown as individual round markers. For the comparison with the 2 mg QD dose in East Asians in this study C31008, the mean concentration-time profile data and trough data for the 4 mg QD dose in Western patients (milled API, fasted state) will be dose-normalized.

7.9.2 Pharmacodynamic Analysis

Genetic polymorphism data collected in this study will be pooled with similar data collected in other studies of TAK-228 for population assessment of the impact of genetic polymorphisms on the PK of TAK-228. The results of these analyses will not be presented in the clinical study report for this study and will be reported separately at a later time.

7.10 Other Outcomes

Not applicable

7.11 Safety Analysis

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.

7.11.1 Adverse Events

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.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or later (based on version at time of database lock). Treatment-emergent AEs are defined as: AEs that occur after the first dose of TAK-228 and within 30 days after the last dose of TAK-228.

Treatment-emergent AEs will be tabulated by MedDRA system organ class and preferred term and will include the following categories

- Treatment-emergent adverse events
- Most commonly reported TEAEs (at least 10% in any arm, sorted by preferred term)
- Grade 3 or higher TEAEs
- Drug-related TEAEs
- Grade 3 or higher drug-related TEAEs
- Serious TEAEs
- Drug-related treatment emergent serious AEs
- TEAEs resulting in study drug discontinuation
- TEAEs resulting in dose reduction
- TEAEs resulting in dose interruption
- Most frequent non-serious TEAEs (> 5% of patients in any arm sorted by preferred term)

Patients reporting the same event more than once will have that event counted only once within each system organ class, and once within each preferred term.

A by-subject listing of DLTs in Cycle 1 will be generated.

7.11.2 Clinical Laboratory Evaluations

Whenever available, laboratory values will be assigned toxicity grades using the NCI CTCAE version 4.03. The number and proportion of patients with grade 3 or higher will be summarized for the following laboratory tests:

- Hematology: Hemoglobin increased, Lymphocyte count decreased, Neutrophil count decreased, Platelet count decreased, White blood cell count decreased.
- Chemistry: Alanine aminotransferase (ALT) increased, Alkaline phosphatase increased, Aspartate aminotransferase (AST) increased, Bilirubin (total) increased, Cholesterol high, Creatinine increased, Gamma glutamyl transferase (GGT) increased, Calcium - decreased, Calcium – increased, Glucose – decreased, Glucose – increased, Potassium – decreased,

Potassium – increased, Magnesium – decreased, Magnesium – increased, Sodium – decreased, Sodium – increased, Triglycerides – increased, Albumin – decreased, Phosphate – decreased, Amylase – increased.

7.11.3 Vital Signs

Vital sign results (diastolic and systolic blood pressure, pulse, temperature, and oxygen saturation and body weight) will be summarized by dose level in each arm 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.

7.11.4 12-Lead ECGs

ECG results (QT, QTcF, PR interval, QRS interval, Ventricular Rate) will be summarized by dose level in each arm 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.

All QT values will be converted to QTcF using Fridericia's correction:

$$QT_F = \frac{QT}{\sqrt[3]{RR}} \text{ (sec)}$$

[Note: RR (sec) = 60 / ventricular rate in beats/minute].

7.12 Interim Analysis

Not applicable

7.13 Changes in the Statistical Analysis Plan

8.0 REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
2. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 14 June 2010.

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.
- Study drug exposure.
- TEAEs leading to study drug discontinuation.
- TEAEs resulting in dose modifications.
- Serious AEs.
- On-study deaths (defined as death that occurs between the first dose of study drug and 30 days after the last dose of study drug (adverse events with an outcome of death)).
- DLTs during Cycle 1.
- Pharmacokinetic concentrations.
- Pharmacokinetic parameters.
- Efficacy (target lesions, non-target lesions, investigator assessment of response, best response).
- Significant protocol deviations.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	29-Aug-2019 18:47 UTC