Title: A Phase 1, Open-Label, Multicenter, Drug-Drug Interaction Study of TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients With Advanced Non–Small Cell Lung Cancer

NCT Number: NCT04051827

SAP Approve Date: 02 October 2020

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

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-788-1004

A Phase 1, Open-Label, Multicenter, Drug-Drug Interaction Study of TAK-788 and Midazolam, a Sensitive CYP3A Substrate, in Patients With Advanced Non–Small Cell Lung Cancer

PHASE 1

Date: 02 October 2020

Prepared by:

PPD

Based on:

Protocol Version: Amendment 02

Protocol Date: 03 September 2020

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND LISTINGS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_t	area under the plasma concentration-time curve from time 0 to time
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
HER2	human epidermal growth factor 2
ICH	International Council for Harmonisation
IRB	institutional review board
IV	intravenous
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PO	oral administration
PR	partial response
PT	preferred term

QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SGPT	serum glutamic pyruvic transaminase
SGOT	serum glutamic oxaloacetic transaminase
SoC	standard of care
SOC	System Organ Class
SOE	schedule of events
TEAE	treatment-emergent adverse events
TKI	tyrosine kinase inhibitors
t_{max}	time of first occurrence of maximum observed concentration
WBC	white blood count
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to characterize the effect of repeated oral administration (PO) of TAK-788 160 mg once daily (QD) on the single oral- and intravenous (IV) dose pharmacokinetics (PK) of midazolam.

4.2 Secondary Objectives

The secondary objective of this study is to assess the safety and tolerability of TAK-788 in patients with advanced non–small cell lung cancer (NSCLC).

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[redacted]

4.4 Study Design

This phase 1, open-label, multicenter, drug-drug interaction study will consist of 2 parts: Part A (Cycle 1: PK cycle) and Part B (Cycle 2 to Cycle 24: Treatment Cycles). The patient population will consist of adult patients with locally advanced or metastatic NSCLC that is refractory to standard available therapies. It is expected that approximately 26 patients will be enrolled in the study.

In Part A of the study, a fixed-sequence design over a single 30-day duration including 28 days of treatment with TAK-788 will be used (Protocol Table 6.a). After screening, eligible patients will be enrolled and will receive a single oral dose of midazolam 3 mg on Day 1 **and** Day 24 and a single IV dose of midazolam 1 mg as a 5-minute infusion on Day 2 **and** Day 25. Patients also will receive TAK-788 160 mg QD orally on Days 3 **through** Day 30 (see Protocol Table 8.a for standard dosing, and Protocol Table 8.b and Protocol Table 8.c for dose adjustments). Serial PK blood samples will be collected to measure plasma concentrations of midazolam and its metabolite 1-hydroxymidazolam in the absence and presence of TAK-788. In addition, TAK-788 PK blood sample will be collected prior dosing on Cycle 1 Day 24, 25, 26 and Cycle 2 Day 1 and post dosing on Day 24 to assess TAK-788 plasma concentrations and its active metabolites AP32960 and AP32914. Further, biomarker blood samples will be collected on Days 1 and 24

prior to dosing, to measure plasma concentrations of 4β-hydroxycholesterol and cholesterol, in addition circulating tumor DNA sampling which will be collected as part of assessments during Cycle 1, 3, and 5, and at the time of progressive disease assessments.

PK-Evaluable Population

Patients will be considered PK-evaluable if they meet **all** of the following criteria during study Part A, Cycle 1:

1. Received the protocol-specified dosing regimen without dose reductions prior to Day 26.
2. Experienced no dose interruptions within one week prior to Day 24.
3. Experienced no more than 1 day of dose interruption within the first 14 days of TAK-788 treatment.
4. Did not receive any excluded concomitant medications through the completion of PK sampling (Day 26).

Assessment of the PK-evaluable population will be conducted when dosing and safety (ie, vomiting) data become available and prior to study closure.

After completion of Part A, patients may continue into Part B to continue treatment with TAK-788 (Cycle 2 to Cycle 24: Treatment Cycles). Any patients who are not PK-evaluable in Part A may be eligible to continue into Part B.

Part B of the study will consist of 28-day treatment cycles in which patients will continue to receive TAK-788 until completion of Cycle 24, or until progressive disease (PD), intolerable toxicity, or another discontinuation criterion is met, whichever is sooner.

During each treatment cycle, the TAK-788 dose may be reduced based on dose modification guidelines to 120, or 80 mg QD in patients who do not tolerate the 160 mg dose (see Protocol Section 8.2). However, any patient who experiences dose reduction prior to Day 26 in Part A Cycle 1 will not be considered as a PK-evaluable patient. The study will include a 30 day follow-up period after end of treatment (EOT). Safety and tolerability will be evaluated during the study by AE monitoring, clinical laboratory tests, vital signs, and physical examinations until 30 days after EOT. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

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Number of Patients

Approximately 26 patients with locally advanced or metastatic NSCLC will be enrolled in this study from 4 to 6 clinical sites to achieve approximately 12 PK-evaluable patients for assessment of the effect of repeated doses of TAK-788 on the PK of midazolam. Study regions will be provided in the study manual.

5.0 ANALYSIS ENDPOINTS

5.1.1 Primary Endpoints

The primary endpoints of this study are midazolam PK parameters in the presence and absence of TAK-788, to include the following:

- The geometric mean ratios and 90% CI of C_{max} and AUC_{∞} for midazolam administered orally with TAK-788 and when orally administered as midazolam alone.
- The geometric mean ratios and 90% CI of C_{max} and AUC_{∞} for midazolam administered intravenously with TAK-788 and when intravenously administered as midazolam alone.

The primary endpoints will be analyzed in the Part A analysis.

5.1.2 Secondary Endpoints

The secondary endpoints of the study to assess the safety and tolerability TAK-788, are as follows:

- Adverse events (AEs).
- Clinical laboratory tests (hematology, and clinical chemistry).
- Vital signs.

The secondary endpoints will be analyzed for Part A, and Part B safety and efficacy update.

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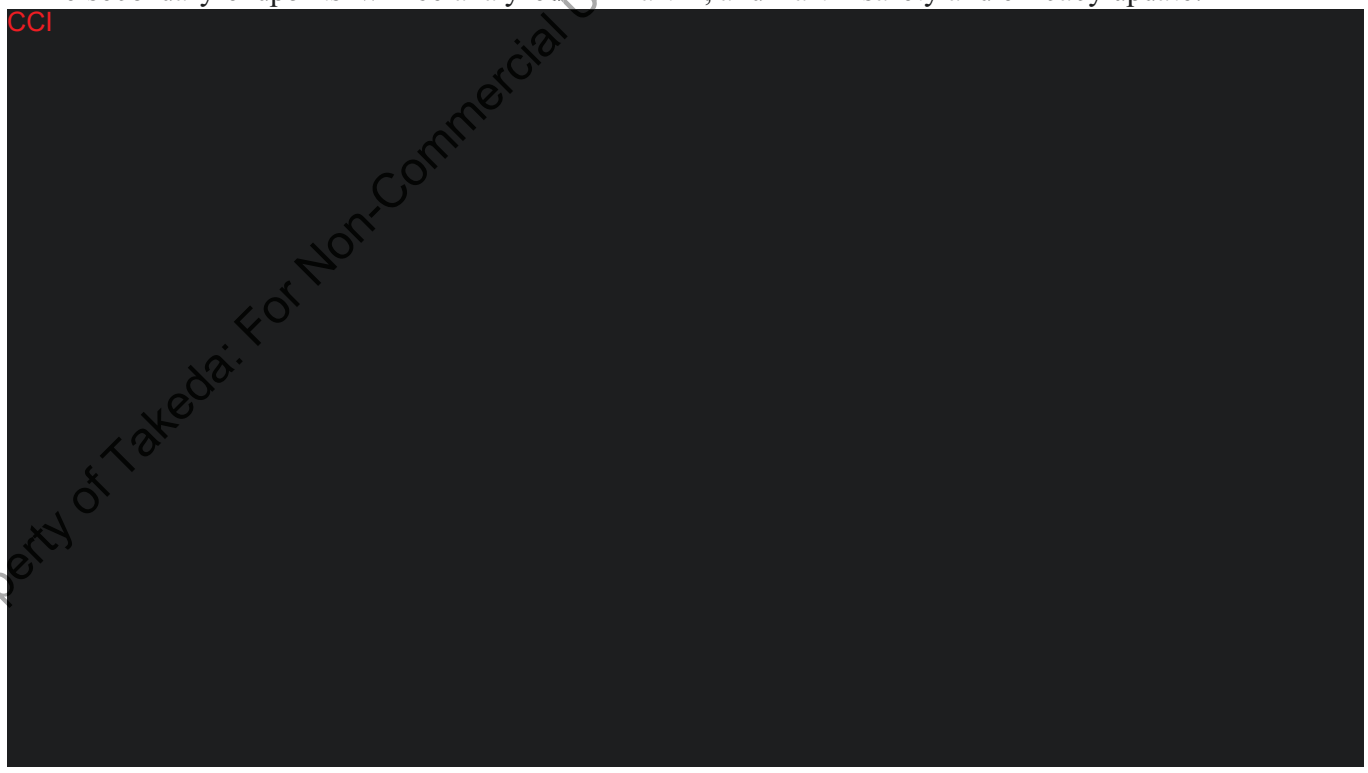

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6.0 DETERMINATION OF SAMPLE SIZE

It is anticipated that approximately 26 patients will be enrolled in this study to obtain approximately 12 PK-evaluable patients. The sample size calculation was based on the expected 2-sided 90% CI for the difference in the paired, log-transformed AUC_∞ mean values for midazolam in the absence and presence of TAK-788. CCI [redacted] Assuming that the AUC_∞ ratio for midazolam in the presence versus absence of TAK-788 is 1, with a sample size of 12, the 90% CI for the AUC_∞ ratio is expected to be 0.82 to 1.23 on the basis of the variance assumptions. Assuming that the AUC_∞ ratio for midazolam in the presence versus absence of TAK-788 is X, with a sample size of 12, the 90% CI for the AUC_∞ ratio is expected to be 0.82X to 1.23X on the basis of the variance assumptions.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

The primary PK and safety analyses will be conducted after all patients complete Cycle 1 (Part A) of the study. Unless otherwise specified, the methods described in this section apply only to the primary analyses. A safety and efficacy update will be conducted after all patients complete Part B of the study. The details of the methods for the safety and efficacy update are described in Section 7.14.

In general, summary tabulations will include the number of observations, (arithmetic) mean, standard deviation (SD), geometric mean and coefficient of variation (%CV) for PK related parameters, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, unless specified otherwise. 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 (CIs) about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

The PK parameters will be summarized with a precision of 3 significant digits, while time of first occurrence of maximum observed concentration (t_{max}) is presented with the number of relevant decimal places to specify the sampling time. Percent CV and frequency percentages will be presented as integers.

Summary statistics will be calculated by time point, if applicable.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.1 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

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

7.1.1 Study Definitions

A patient is considered to be enrolled when the first dose of study drug has been administered. Study start date is defined as the date of first dose of study drug for the first enrolled and drug administered patient.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a patient is administered their first dose of the 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. Study day will be calculated relative to the date of the first dose of study drug.

Study days prior to the first dose of study drug will be calculated as: Date of assessment/event – Date of first dose of study drug.

Study days on or after the first dose of study drug will be calculated as: Date of assessment/event – Date of first dose of study drug + 1.

7.1.3 Definition of Baseline Values

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration. Baseline is defined as the last non-missing measurement prior to the administration of first dose of the study drug.

7.1.4 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. The analysis of PK data and determination of PK parameters will be based on the actual elapsed time post dose relative to the first dosing.

7.1.5 Imputations for Missing Dates

7.1.5.1 Imputation Rules for Missing Initial Cancer Diagnosis Date and Start Date and Stop Date for Selected Prior Anti-Cancer Therapies

In general, an initial diagnosis date will be imputed first and then used to adjust the imputation of the corresponding prior treatment start date when necessary.

Initial Diagnosis Dates

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as earliest of: 01-MMM-YYYY, first dose date.
- If day and month are missing (UU-UUU-YYYY), impute as earliest of: 01-JAN-YYYY, first dose date.
- No imputation for a completely missing date (UU-UUU- UUUU)
- Additional adjustment(s) may be applied depending on Takeda's medical's review on the prior anti-cancer therapies data

Prior Anti-Cancer Therapies Dates

Start Date:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as earliest of: 01-MMM-YYYY, first dose date.
- If day and month are missing (UU-UUU-YYYY), impute as earliest of: 01-JAN-YYYY, first dose date.
- No imputation for a completely missing date (UU-UUU- UUUU)
- If an imputed prior treatment start date is before diagnosis date, re-impute as diagnosis date.

Stop Date:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as the earliest of
  - 30-MMM-YYYY if month is April, June, September or November, 28-MMM-YYYY if month is February, 31-MMM-YYY otherwise
  - First dose of study drug date
- If day and month are missing (UU-UUU-YYYY), impute as earliest of: 31-DEC-YYYY, first dose of study drug date.

If after applying above rules, any prior treatment stop dates are prior to corresponding prior treatment start date, impute as start date.

Duration of a selected prior anti-cancer therapy will be calculated using the following formula: duration = stop date – start date +1. Duration will be calculated with imputed dates when necessary. Total duration will be the sum of the individual durations.

Time since the stop date of a selected prior anti-cancer therapy to the first dose of study treatment will be calculated using the following formula: time since stop date = stop date – first dose date +1. Time since the stop date to the first dose date will be missing in the case of a completely missing stop date.

7.1.5.2 Analysis of Missing AE Dates

Imputation Rules for Missing Onset Date and Resolution Date of AEs

In general, the imputation will be conservative such that onset dates will be imputed to be as early as possible and resolution dates will be imputed to be as late as possible. Resolution date will be imputed first and then used to impute onset date.

Resolution Date:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as the earliest of:
  - Last day of the month (28, 29, 30 or 31 depending on in which month the adverse event resolved)
  - Data cutoff date
  - Death date
- If day and month are missing (UU-UUU-YYYY), impute as the earliest of:
  - December 31 (31-DEC-YYYY)
  - Data cutoff date
  - Death date
- If date is completely missing (e.g., AE is ongoing), impute as earliest of:
  - Data cutoff date
  - Treatment discontinuation date + 30 days
  - Death date

Onset Date:

- If day is missing but month and year are non-missing (UU-MMM-YYYY), impute as follows:
  - If year and month are the same as year and month of first dose date:
    - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
    - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of first day of the month or informed consent date
  - If year is the same as year of first dose date and month is after month of first dose date, impute as first date of month
  - If year is the same as year of first dose date and month is before month of first dose date, impute as latest of first day of the month or informed consent date
  - If year is after year of first dose date, impute as first day of month
  - If year is before year of first dose date, impute as latest of first day of the month or informed consent date
- If day and month are missing and year is non-missing (UU-UUU-YYYY), impute as follows:
  - If year is the same as year of first dose date:
    - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
    - If resolution date (or imputed resolution date) is prior to first dose date, impute as latest of first day of the month or informed consent date
  - If year is after year of first dose date, impute as January 1 (01-JAN-YYYY)
  - If year is before year of first dose date, impute as latest of first day of the year (01-JAN-YYYY) or informed consent date
- If date is completely missing:
  - If resolution date (or imputed resolution date) is on or after first dose date, impute as first dose date
  - If resolution date (or imputed resolution date) is prior to first dose date, impute as informed consent date.

7.2 Randomization and Stratification

This is a single arm fixed-sequence design. No randomization is planned.

7.3 Unblinding

This is an open-label study.

7.4 Statistical Software

SAS version 9.4 (or higher) will be used for all analyses.

7.5 Analysis Sets

7.5.1 Pharmacokinetic (PK)-Evaluable Set

Patients will be considered PK-evaluable if they meet **all** of the following criteria during study Part A, Cycle 1:

1. Received the protocol-specified dosing regimen without dose reductions prior to Day 26.
2. Experienced no dose interruptions within 1 week prior to Day 24.
3. Experienced no more than 1 day of dose interruption within the first 14 days of TAK-788 treatment.
4. Did not receive any excluded concomitant medications through the completion of PK sampling (Day 26).

The PK-evaluable set will be used for all PK analyses. Assessment of the PK-evaluable set will be conducted when dosing and safety (ie, vomiting) data become available and prior to study closure.

7.5.2 Safety Analysis Set

The safety set is defined as all patients who received at least 1 dose of any study drug (TAK-788 or midazolam). The patients in this safety analysis set will be analyzed according to the study drug they actually received. The safety population will be used for all safety analyses.

7.6 Disposition of Subjects

7.6.1 Subject Disposition

Patient disposition will be summarized including the number of patients in the following categories: patients treated, patients in the PK-evaluable population, patients who have completed Part A treatment, patients ongoing on treatment, patients ongoing on study, patients discontinued from treatment and patients discontinued from study.

Primary reason leading to study treatment discontinuation and study discontinuation will also be tabulated. Reasons for study treatment discontinuation include AE, protocol deviation, lost to follow-up, withdrawal by patient, pregnancy, progressive disease, symptomatic deterioration, initiation of new anti-cancer therapy, study termination by sponsor and other. Reasons for study discontinuation include: death, lost to follow-up, withdrawal by patient, progressive disease, initiation of new anti-cancer therapy, study termination by sponsor, and other. Percentages will be based on the number of patients in the safety populations unless otherwise indicated. Follow-up time in months will be defined as follows: (Last Contact Date – First Dose Date + 1)/30.4375.

Patient disposition date will also be presented in a by-patient listing.

7.7 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Mean, SD, minimum, median and maximum will be calculated for continuous variables. Frequency and percentages will be calculated for categorical variables.

Continuous variables include age, time since initial diagnosis, time since diagnosis of locally advanced or metastatic disease, number of organs involved at study entry, weight, height, BMI, and sum of target lesion diameter.

Categorical variables include age, gender, race, ethnicity, stage at diagnosis, stage at study entry, histopathological classification at study entry, lung involvement at study entry, metastatic sites at study entry, number of organs involved at study entry, cigarette smoking history, cigarette smoking amount among current smokers, cigarette smoking amount among former smokers, Eastern Cooperative Oncology Group (ECOG) Performance Status, geographic region, epidermal growth factor receptor (EGFR) abnormality detected, EGFR mutation method of assessment, EGFR mutation type, EGFR EXON20 insertion detected, EXON20 insertion type, human epidermal growth factor 2 (HER2) abnormality detected and other mutations, prior anticancer therapies, number of prior systemic anticancer therapies/regimens (0, 1, 2, 3+), received chemotherapy received TKI, received immuno-oncology therapy, any prior radiotherapy, prior radiotherapy in the brain, and time since last radiotherapy in the brain.

7.7.1 Inclusion/Exclusion Criteria

All inclusion/exclusion information on enrolled patients will be included in by-patient listings. These listings will include whether all criteria were satisfied. For patients who did not satisfy the criteria, the criteria number will be listed with the deviation.

7.7.2 Medical History

Patients with a medical (and/or surgical) history will be presented in a by-patient listing, including the medical history and concurrent medical condition, date of onset and the outcome status (whether it is resolved or ongoing).

7.7.3 Concomitant Medications

All concomitant medications will be mapped to generic terms according to the World Health Organization (WHO) drug dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term, presented for the safety population. Patients are counted once for each WHO drug generic term. Concomitant procedures will not be coded.

Concomitant medication is defined as any medication that occurs after administration of the first dose of study treatment during through 30 days after the last dose of study drug.

Concomitant medications with start or end dates that are completely or partially missing will be analyzed using the same imputation rules as AEs.

Concomitant medications and procedures will be presented in by-patient listings.

7.8 Study Drug Exposure and Compliance

Exposure and compliance to study treatment will be summarized separately by study drug and study part using the following measures:

Exposure

- Time on study treatment (days for Part A continuous; months for Part B continuous and categorical in increments of <1, 1-< 3, 3-<6, 6-<12, and >=12 months)
- Number of days dosed
- Total cumulative dose administered
- Dose intensity (mg/day)
- Relative dose intensity (%)

Compliance

- Dose interruption
    - Number of patients with at least one occurrence (%)
    - Total duration (days) of time off study drug prior to treatment discontinuation
- Number of patients with at least one dose reduction (%)
    - Number of patients with at least one occurrence (%)
    - Returned to dosing after dose reduction (%)
    - Returned to target dose after dose reduction (%)
- Number of patients with at least one dose modification (%)

Time on study treatment for TAK-788 will be defined as the time interval from the first dose date to the last dosing date and computed with the following formula:

Time (days) on treatment= last non-zero dose date – first dose date + 1

Dose intensity will be calculated with the following formula:

Dose intensity = Total cumulative dose/ Time (days) on study treatment

Relative dose intensity will be defined as the proportion of the planned dose received by patients and will be defined as follows:

Relative dose intensity = Total cumulative dose administered / Total dose planned x 100%, where the total dose planned does not consider intra-patient dose escalation.

Total person years for a treated patient will be calculated using the following formula:

Total person years = Time (days) on study treatment / 365.25. The total person years in an analysis population will be the sum of the total person years of all the patients in this population.

7.9 Efficacy Analysis

There will be no efficacy analysis in the Part A primary analyses. Details of the efficacy analysis in the safety and efficacy update are included in Section 7.15.

7.10 Pharmacokinetic Analysis

In Part A (Cycle 1: PK Cycle), individual and mean plasma concentration data for midazolam and its metabolite 1-hydroxymidazolam after oral dosing of midazolam on Days 1 and 24 and IV dosing of midazolam on Days 2 and 25 will be plotted over time and listed by patient in the absence and presence of TAK-788. Plasma PK parameters of midazolam and 1-hydroxymidazolam for individual patients after oral and IV dosing of midazolam in the absence and presence of TAK-788 will be derived using noncompartmental analysis methods. Plasma concentrations and PK parameters (including but not limited to AUC_{∞}, C_{max}, and t_{max}) of midazolam and 1-hydroxymidazolam in the presence and absence of TAK-788 will be summarized using descriptive statistics.

For the estimation of the effect of TAK-788 on the PK of oral- and IV-dose midazolam, the ratios of geometric mean midazolam AUC_{∞} (or area under the plasma concentration-time curve from time 0 to last time [$_{AUClast}$] if AUC_{∞} cannot be estimated accurately) and C_{max} (in the absence and presence of TAK-788) and the associated 2-sided 90% CIs will be calculated on the basis of the within-patient variance using a mixed-effects analysis of variance (ANOVA) model fitting terms for treatment (midazolam in the absence and presence of TAK-788). The patient will be treated as a random effect in the model. After log transformation, AUC_{∞} (or AUC_{last} if AUC_{∞} cannot be estimated accurately) and C_{max} will be separately analyzed. Point estimates and adjusted 90% CIs for the difference in treatment will be calculated and then exponentially back transformed to provide point and CI estimates for the ratios of interest.

The oral bioavailability of midazolam and the 1-hydroxymidazolam to midazolam AUC ratios following IV and oral midazolam dosing will be descriptively summarized, in the absence and presence of TAK-788.

Plasma concentrations of TAK-788 and its active metabolites AP32960 and AP32914 will be listed by patient and summarized using descriptive statistics. Individual and mean plasma concentrations of TAK-788, AP32960, and AP32914 will be plotted over time. Plasma PK parameters for TAK-788, AP32960, and AP32914 for individual patients will be derived using noncompartmental analysis methods and listed by patient and summarized using descriptive statistics.

7.11 Pharmacodynamic Analysis

Change of the ratio of 4β-hydroxycholesterol versus cholesterol on Day 24 of Part A from the baseline will be evaluated and summarized with descriptive statistics.

7.12 Safety Analysis

7.12.1 Adverse Events

A treatment-emergent AE (TEAE) is defined as any AE with an onset date on or after the first dose date and within 30 days after the last dose of study drug. In the case of missing onset date, impute using the rules defined in section 7.1.5.2 of this SAP.

AEs will be evaluated based on CTCAE version 5.0 and will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 22 or higher.

In the summary tables, MedDRA Preferred Terms (PTs) will be sorted in a descending order of incidence rate first then alphabetically in case of tied incidence rates. In the tables of treatment emergent AEs grouped by MedDRA System Organ Class (SOC) and PT, SOCs will first be sorted by the international sort order with PTs sorted in a descending order of incidence rate first then alphabetically in case of tied incidence rates. All sorting will be based on the total column.

TEAEs will be tabulated by preferred term (PT). Summary tabulations include the following subsets:

- TEAEs
- Drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher drug related TEAEs
- TEAEs resulting in study drug discontinuation
- TEAEs resulting in study drug reduction
- TEAEs resulting in study drug interruption
- TEAEs resulting in study drug modification
- Serious Adverse Events (SAEs)

AEs will also be tabulated by system organ class (SOC), and PT. Summary tabulations include the following subsets:

- TEAEs
- Drug-related TEAEs
- Grade 3 or higher drug related TEAEs
- Most commonly reported TEAEs (ie, those events occurring in ≥10% of all patients).

By patient listings will be presented for all TEAEs, all SAEs, TEAE's resulting in study drug discontinuation, and TEAE's resulting in death.

7.12.1.1 Adverse Events of Clinical Interest

The sponsor has designated some AEs as being of clinical interest. These are not based upon a safety signal in the review of the clinical data but rather are being considered of clinical interest due to other factors which include, but are not limited to those:

1) identified by searches of the clinical database considering the context of the intended patient population;
2) adverse reactions for commercially available EGFR TKIs (e.g., gastrointestinal events, rash, …);
3) AEs common within the TAK-788 program (e.g., gastrointestinal events, rash…)

The AEs selected were pneumonitis/ ILD, pneumonia/ respiratory failure, GI toxicities (diarrhea, nausea, vomiting), cardiomyopathy (congestive heart failure, QTc prolongation, Supraventricular tachyarrhythmias, Myocardial infarction), amylase/lipase increase, rash, and stomatitis.

Analyses of TEAEs of clinical interest will be conducted using the safety analysis set. A summary table of patient incidence of all TEAEs of clinical interest will be provided.

7.12.2 Presentations of Laboratory Parameters

Hematology, serum chemistry, and serology assessments will be performed locally, with reference ranges provided in the electronic data capture (EDC) system. Clinical laboratory evaluations will be performed according to the schedule of events (SOE) throughout the study.

Hematology assessments will include hemoglobin, white blood count (WBC) with 5-part differential (lymphocytes, monocytes, neutrophils, eosinophils, basophils), and platelet count. Chemistry assessments will include the following: albumin , total protein, alkaline phosphatase (ALP), alanine transaminase (ALT/serum glutamic pyruvic transaminase [SGPT]), aspartate transaminase (AST/serum glutamic oxaloacetic transaminase [SGOT]), amylase, bilirubin (total and direct/indirect), blood urea nitrogen (BUN), calcium, creatinine, chloride, glucose, lipase, phosphorous, magnesium, potassium, sodium, bicarbonate or total carbon dioxide.

Laboratory data will be summarized as shift from baseline to highest on-study grade as defined by CTCAE 5.0. On-study grade will be defined using the minimum and/or maximum post-exposure result as appropriate. For example, glucose will be evaluated for hypoglycemia using the patient's minimum post-exposure value, and for hyperglycemia using the patient's maximum post-exposure value. For laboratory parameters that are not graded according to CTCAE 5.0, shifts below and above the normal range using the minimum and maximum on study values will be summarized.

Descriptive statistics summarizing the distribution in laboratory tests over time and the change from baseline by visit will be presented. Listings of laboratory test results will also be generated.

7.12.3 Vital Signs

Vital signs will be measured at each visit before dose administration of study drug(s) in Parts A and B, after 3 to 5 minutes in the supine position, and will include measurements of diastolic and systolic blood pressure, respiratory rate, heart rate, pulse oximetry, and body temperature.

Systolic and diastolic blood pressure will be summarized as shift from baseline to highest on-study grade as defined by CTCAE 5.0. Hypertension will be evaluated using the patient's maximum post-exposure value SBP and DBP as follows:

- Grade 0: SBP < 120mm Hg and DBP < 80 mm Hg
- Grade 1: SBP 120-139 mm Hg or DBP 80-89 mm Hg
- Grade 2: SBP 140-159 mm Hg or DBP 90-99 mm Hg
- Grade 3: SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg

Vital sign values will also be presented in a by-patient listing.

7.12.4 Electrocardiogram

A 12-lead Electrocardiogram (ECG) will be performed prior to dosing per the Schedule of Events throughout the study. ECGs will be recorded electronically and will be evaluated centrally. For consistency, the Fridericia correction - QTcF - method must be used for all calculations of QTc intervals.

$$QT_{cF} = \frac{QT}{\sqrt[3]{\frac{RR}{1s}}}$$

Descriptive statistics of maximum QTcF and change from baseline will be calculated following the International Council for Harmonisation (ICH)-E14 guidelines: the proportion of treated patients with at least 1 on-drug QTcF value >450 ms, 480 ms, and 500 ms; and the proportion of treated patients with a maximum change in QTcF from baseline >30 ms and >60 ms. The Fridericia correction (QTcF) will be used throughout. ECG data will also be displayed in a by-subject listing.

7.12.5 Echocardiogram/MUGA Scan for Left Ventricular Ejection Fraction

Cardiac monitoring, including assessment of left ventricular ejection fraction (LVEF) at baseline, Cycle 3 Day 1, and at the EOT will be conducted. Echocardiogram results will be presented in a by-patient listing

7.12.6 Other Measures

On-study assessments not covered by other sections of this document will be presented in summary tables of observed values and/or changes from baseline.

7.13 Biomarker analysis

A separate analysis plan for biomarkers will be developed.

7.14 Interim Analysis

No interim analysis is planned.

7.15 Safety and Efficacy Update

At the end of the Part B of the study, analyses of subject disposition, TAK-788 drug exposure and compliance, safety, clinical laboratory results, vital signs and 12-Lead ECGs will be repeated after combining data from both Part A and Part B, following the same methods described in previous sections.

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7.16 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

• Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

9.0 APPENDICES

Appendix 1 Notes from RECIST v1.1

Measurable Disease vs. Non-measurable Disease

Measurable disease is defined by the presence of at least one lesion with a longest diameter ≥ 10 mm or a pathological lymph node with a short axis of ≥ 15 mm. Lesions with prior local treatment are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable disease is defined as small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) or lesions truly non-measurable by reproducible imaging techniques.

Target Lesions vs. Non-target Lesions vs. New Lesions

1. Target lesions
    a. A maximum of five total (and two per organ, maximum) of lesions or pathological lymph nodes will be identified at baseline to follow up to assess tumor burden in target lesions for response determination. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as baseline or on-study sum diameters.
    b. Measurement of target lesions:
        - "Too small to measure" - In case that target lesions become very faint on CT scan and are reported as 'too small to measure': if it is the opinion of the radiologist that a lesion has likely disappeared, the measurement should be recorded as 0mm; if a lesion or lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
        - Lesions that split or coalesce on treatment - When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.
    c. Response criteria for target lesions:
        - Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
        - Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
        - Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the unequivocal appearance of one or more new lesions is also considered progression).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2. Non-target lesions
   a. All other lesions or pathological lymph nodes (or sites of disease) after the target lesions are chosen will be identified as non-target lesions and should also be recorded at baseline.
   b. Measurements are not required and these lesions will be assessed only qualitatively as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').
   c. Response criteria for non-target lesions
      - Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
      - Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
      - Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
   d. Assessment of progression of non-target lesions
      - When the patient has measurable disease at baseline, the designation of overall progression solely based on change in non-target disease in the face of SD or PR of target disease is extremely rare. To achieve 'unequivocal progression' based on the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently and requires discontinuation of treatment.
      - When the patient has only non-measurable disease at baseline, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. An unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is substantial and comparable in magnitude to the increase that would be required to declare PD form measurable disease: e.g., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion).

3. New lesions
   a. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
CCI	Biostatistics Approval	02-Oct-2020 20:50 UTC