Title: A Phase 1b Randomized, Double-Blind, Placebo-Controlled, Crossover Study of a Single Intravenous Infusion Dose of TAK-925 in Patients With Idiopathic Hypersomnia

NCT Number: NCT04091438

SAP Approve Date: 22 April 2020

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- 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: TAK-925-2002

A Phase 1b Randomized, Double-Blind, Placebo-Controlled, Crossover Study of a Single Intravenous Infusion Dose of TAK-925 in Patients With Idiopathic Hypersomnia

PHASE: 1b

Version: Final

Date: 22 April 2020

Prepared by:

PPD

Based on:

Protocol Version: Amendment 2

Protocol Date: 04 March 2020

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
AHI	apnea-hypopnea index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
BDI-II	Beck Depression Inventory II
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{eoi}	concentration at the end of the infusion
CPAP	continuous positive airway pressure
CRF	case report form
C-SSRS	Columbia - Suicide Severity Rating Scale
CV	coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EDS	excessive daytime somnolence
ESS	Epworth Sleepiness Scale
ET	early termination
FSH	follicle-stimulating hormone
HR	heart rate
ICH	International Conference on Harmonization
ICSD-3	International Classification of Sleep Disorders, 3rd edition
IH	idiopathic hypersomnia
IV	intravenous
CCI	[redacted]
LFT	liver function test
LS	least square
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MSLT	multiple sleep latency test
CCI	[redacted]
NPSG	nocturnal polysomnography
OSA	obstructive Sleep Apnea
CCI	[redacted]

PK	pharmacokinetic(s)
PLMAI	periodic limb movement arousal index
PSG	polysomnography
PTE	pretreatment event
CCI	[redacted]
QTcF	QT interval with Fridericia correction method
RT	reaction time
SAE	serious adverse event
SBP	Systolic blood pressure
SD	standard deviation
SE	standard error
SI	International System of Units
$t_{1/2z}$	terminal phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to evaluate the safety and tolerability of administering a single IV infusion of TAK-925 to adult subjects with IH.

4.2 Secondary Objectives

The secondary objective of this study is to investigate the PK of a single IV infusion of TAK-925 in adult subjects with IH.

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4.4 Study Design

This is a phase 1b, randomized, double-blind, placebo-controlled, 2-period, 2-treatment crossover study to evaluate the PK, CCI safety, and tolerability of a single IV infusion dose of TAK-925 in subjects with IH. Subjects will be males and females aged 18 through 75 years, inclusive, with IH diagnosed according to the ICSD-3 criteria as verified by a previous nocturnal polysomnography (nPSG) and multiple sleep latency test (MSLT) study performed within the last 10 years.

The treatment periods begin on Day 1 of Treatment Period 1 (Study Day 1) with Treatment Period 2 commencing on Study Day 3. In the morning of Day 1 of Treatment Period 1, eligible subjects will be randomized to 1 of 2 sequence groups as listed in Table 4.a. After randomization, the subject will be dosed in 2 treatment periods according to the order defined by the sequence group to which he/she is randomized. On Day 1 of each treatment period, TAK-925 (or placebo) will be administered as a single 9-hour IV infusion commencing at approximately 0800. CCI [redacted]

A summary of the treatment assignment and sequence is presented below:

Table 4.a Summary of Treatment Assignment for Each Sequence

Sequence	N	Treatment Period 1	Treatment Period 2
1	20	TAK-925 112 mg	Placebo
2	20	Placebo	TAK-925 112 mg

At the screening visit, eligible subjects who have an ESS score of ≥11 will complete medical histories and physical examinations, semi-recumbent vital signs assessment, a 12-lead ECG, Beck Depression Inventory II (BDI-II), Columbia Suicide Severity Rating Scale (C-SSRS), and clinical safety laboratory tests. Subjects with an ESS score of <11 who are taking stimulants at screening may continue the screening process and repeat the ESS at Study Day -2 following washout. A total of 40 subjects will be randomized so that at least 36 subjects will complete the study. To avoid enrollment of short sleepers with chronic sleep deprivation, prospective participants will complete approximately 7 consecutive days of actigraphy supported by a sleep diary beginning on Study Day -9 and ending on Study Day -3 (ie, the day before their Study Day -2 admission to the clinical unit), to ensure an average nightly sleep duration of ≥420 minutes (7 hours) during the subject's normal nocturnal sleep period, and, if the subject's average nightly sleep duration is ≤480 minutes (8 hours), that the subject does not have insufficient sleep syndrome (sleeping >2 hours/night more on "off days" than on "work days"). During screening, eligible subjects must discontinue their stimulant medications used for treatment of IH. Medications must be discontinued for a minimum of 7 days or at least 5 half-lives of each medication, whichever is longer, before the first day of dosing (Day 1 of Treatment Period 1). Sodium oxybate must be discontinued at least 4 weeks before screening.

The screening period is up to 28 days. Following screening, subjects who meet all screening entry criteria will be admitted to the clinical unit (Study Day -2). Semi-recumbent vital signs will be obtained following admission, and the ESS will be recorded in the late afternoon. An overnight 8-hour nPSG will be performed commencing at approximately the subject's normal bedtime (eg, between 2200 and 2300) to confirm that the subject does not have other comorbid sleep disorders or clinically significant nocturnal hypoxemia (O_2 saturation ≤80% for ≥5% of total sleep time), and to confirm the apnea hypopnea index (AHI) is ≤10/hour and the periodic limb movement index associated with arousals (PLMAI) is ≤15/hour.

Study Day -1 is the designated baseline assessment day and is also intended for accommodation to sleeping in the clinical unit. CCI [redacted] afety assessments including BP, pulse, respiration rate, and ECG will be collected per the Schedule of Study Procedures.

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There will be a minimum 24-hour washout interval between the end of TAK-925 infusion and the commencement of treatment in the subsequent treatment period to allow for complete elimination of the preceding treatment effect. Study Days 2 and 4 are washout days. CCI [redacted] Blood samples for determination of TAK-925 plasma concentrations will be collected predose and at specified time points postdose, CCI [redacted]. Safety assessments including AEs, vital signs, and ECGs will be recorded. During the study, AEs will be recorded, and clinical labs, vital signs, and safety ECGs will be obtained. Subjects will be discharged from the unit following completion of study exit procedures in the afternoon of Study Day 4 (Day 2 of Treatment Period 2).

Subjects will return to the study site or be contacted by telephone approximately 7 days (±2 days) following unit discharge for a safety check and all women of childbearing potential must return to the study site to complete a urine pregnancy test at the end-of-study visit

An overview of inpatient unit study schedule is presented below:

Table 4.b Overview of the Inpatient Unit Study Schedule

Screening Period	**Check-in and Baseline**	**Treatment Periods 1 and 2**		**End-of-Study Visit**
		Dosing	**Washout**	
Study Days -28 to -3	Study Days -2 (nPSG [a]) and -1 (Baseline)	**Study Days 1 and 3** Study drug administration/C CI, PK, and safety assessments	**Study Days 2 and 4** [b] PK and safety assessments	Study Day 11 (±2 days) Follow-up (in clinic or by phone call)
	← Confinement Study Day -2 to Study Day 4 →			

nPSG: nocturnal polysomnography; CCI [redacted]; PK: pharmacokinetic.
[a] nPSG only on Study Day -2.
[b] Discharge from unit on Study Day 4.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- Percentage of subjects who experience at least 1 TEAE.
- Percentage of subjects who meet the markedly abnormal criteria for clinical safety laboratory tests at least once post a regimen.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post a regimen.
- Percentage of subjects who meet the markedly abnormal criteria for 12-lead safety electrocardiogram (ECG) parameters at least once post a regimen.

5.2 Secondary Endpoints

- TAK-925 PK parameters:
  - Observed plasma concentration at the end of infusion (C_{eoi}).
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).

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6.0 DETERMINATION OF SAMPLE SIZE

Up to 40 subjects are planned to be randomized equally to each treatment sequence to ensure 36 subjects complete the study. This number of subjects is typical for phase 1 crossover study designs and is considered sufficient for assessment of safety. CCI [redacted] n addition, when the true difference between TAK-925 and placebo is minimal, the chance to observe the same event is no more than 10%. Non-informative prior distributions were used in the above probability calculation. Allowing for 4 dropouts (10%), 40 subjects are planned to be randomized.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

Randomized subjects are the subjects who are enrolled and received a randomization number.

Continuous data will be summarized using the following descriptive statistics: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, the coefficient of variation (%CV) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percent of subjects for each category, where appropriate.

Except when noted as otherwise, all confidence intervals (CIs), statistical tests, and resulting p-values will be reported as nominal 2-sided and will be assessed at the 5% significance level. No adjustments will be made for multiplicity. P-values will be reported to 3 decimal places. Posterior probabilities will be multiplied by 100 and rounded to one decimal point.

Unless otherwise noted, baseline for the study will be defined as the last non-missing measurement prior to first dose of study drug in the entire study

Unless specified, for continuous variables, minimum and maximum values will be reported in the same precision as that for the individual values; means, medians, LS-means and posterior means will be reported after rounding the original reported value to one decimal place; SD, SE and confidence intervals will be calculated using the original reported values and rounded to the second decimal place. Percentages and %CV will be reported after rounding to one decimal place.

All data analyses and figures will be generated using SAS System® Version 9.4 or higher.

7.1.1 Definition of Study Days

Study day prior to the first dose of study drug will be calculated as: date of assessment/event – date of first dose of study drug; study day on or after the date of first dose of study drug will be calculated as: date of assessment/event – date of first dose of study drug + 1.

Day prior to the first dose of study drug (up to Day -2) in a period will also be derived as: date of assessment/event – date of first dose of study drug in a period; Day on or after the date of first dose of study drug in a period (up to the last post dose procedure for that period) will be calculated as: date of assessment/event – date of first dose of study drug in that period + 1.

7.1.2 Definition of Study Visit Windows

There will be no visit windows.

7.1.3 Conventions for Missing Adverse Event Dates

7.1.3.1 Imputation of missing or partial dates of AE start dates

The following methods will be used to impute missing or partial dates of AE start dates.

- Month/year available and day missing:
  - If the month and year are the same as those in the first dose date, the first dose date is to be used to impute the AE start date.
  - If the month and year are different from those in the first dose date, the first day of the month will be used for the start date.
- Year available and month/day missing:
  - If the year is the same as the year of the first dose, the first dose date is to be used to impute the AE start date.
  - If the year is not the same as the year of the first dose date, set the start date as January 1.
- Year/month/day all missing:
  - The first dose date is to be used to impute the AE start date.

7.1.3.2 Imputation of missing or partial dates of AE end dates

The following methods will be used to impute missing or partial dates of AE end dates:

If the event is indicated as ongoing at the end of the study, no imputation is needed.

If the event is not indicated as ongoing:

- Month/year available and day missing:
  - Use the last day of the month to impute the AE end date. If the imputed end date is before the AE start date, use the start date as the end date. If the subject died, use the date of death to impute the end date.
- Year available and month/day missing:
  - If the year is the same as or before the year of the last dose, set the end date as December 31.

- If the year is after the year of the last dose, set the end date as January 1 or the last day of contact, whichever is later.

- Year/month/day all missing:
  - Impute the end date as December 31 of the last dose year. If the imputed end date is before the AE start date, keep the end date same as the start date. If the subject died, use the date of death to impute the end date.

7.1.4 Conventions for Missing Concomitant Medication Dates

There will be no imputation of incomplete or missing concomitant medication dates.

7.1.5 Conventions for Missing PK Data

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summarization of concentration values and derivation of PK parameters. These values will be flagged in the data listings and deviations from this convention may be considered on a case-by-case basis as deemed appropriate.

7.2 Analysis Sets

Safety analysis set

The safety analysis set will include all subjects who were randomized and received at least 1 dose of the study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK analysis set

The PK analysis set will consist of subjects who receive at least 1 dose of study drug and who have at least 1 measurable plasma concentration of TAK-925 CCI).

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7.3 Disposition of Subjects

The number and percentage of randomized subjects who complete the study and those who prematurely discontinue the study will be summarized for each treatment sequence and overall. In addition, the reason of study discontinuation will be summarized for each sequence and overall.

A summary of demographics (age, gender, ethnicity, and race) for screen failures and the primary reason for failure will also be provided.

Subjects' study completion data, including the dates of the first and last dose, and reasons for premature termination, will be listed.

7.4 Demographic and Other Baseline Characteristics

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic and baseline characteristics variables (including but not limited to age, height, weight, BMI, O_2 saturation index, BDI-II total score (screening), Epworth Sleepiness Scale (ESS) total score, Day -1 mean sleep latency, CCI and overall using the Safety Analysis Set. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (sex, ethnicity, race, substance use) will be tabulated by treatment sequence and overall.

All individual demographic and baseline characteristics will be listed by treatment sequence and subject number. The demographic data listing will include subject identifier, treatment sequence, date of informed consent, date of birth, age at date of informed consent, gender, ethnicity, race, height, baseline weight, baseline BMI.

7.5 Medical History and Concurrent Medical Conditions

All medical history and concurrent medical conditions will be listed.

7.6 Medication History and Concomitant Medications

All medication history and concomitant medications data will be listed.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing. Listings and summary statistics for TAK-925 plasma concentrations and pharmacokinetic parameters will be provided. No other summary statistics for the extent of exposure to study drug or compliance calculations will be performed for this study.

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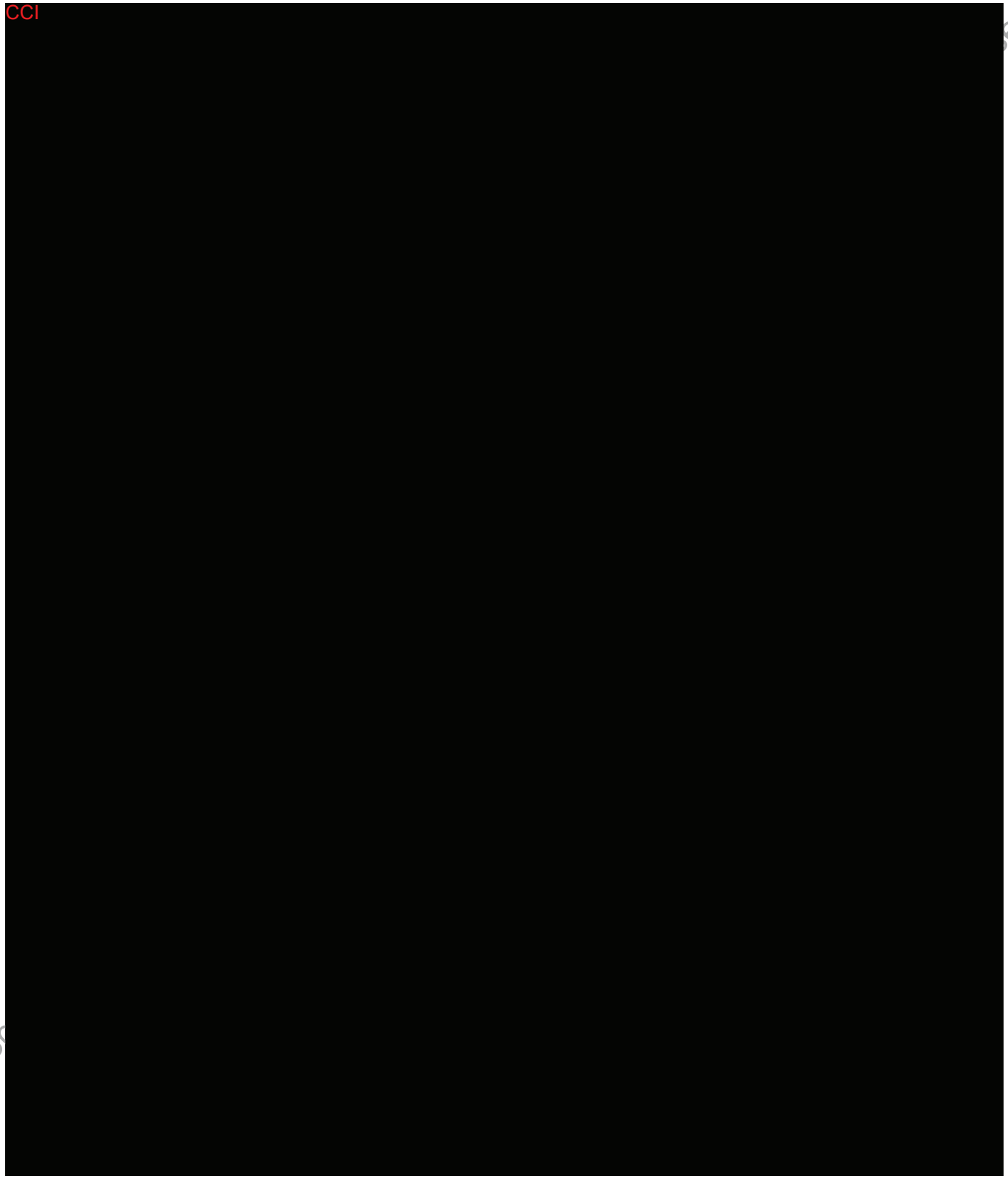

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7.10 Pharmacokinetic Analysis

7.10.1 Pharmacokinetic Analysis

The following PK parameters of TAK-925 CCI will be determined from plasma concentrations from all evaluable subjects using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

AUC_{∞}	$t_{1/2z}$
AUC_{last}	V_{ss} (TAK-925 only)
C_{max}	V_z (TAK-925 only)
C_{eoi}	CL (TAK-925 only)
t_{max}	CCI

Additional PK parameters may be calculated as appropriate. A detailed PK analysis plan will be prepared before PK parameter computation.

Individual plasma concentrations and PK parameter estimates of TAK-925 CCI will be listed for each subject. Plasma concentrations will be summarized using descriptive statistics (N, mean, SD, %CV, median, minimum, and maximum) at each nominal time point. PK parameters will be summarized for TAK-925 112 mg. Geometric means will also be computed for C_{eoi}, C_{max}, AUC_{last}, and AUC_{∞}. Mean ($\pm$SD) concentration-time profiles will be plotted for TAK-925 CCI. Individual concentration-time profiles will be presented in spaghetti plots for TAK-925 112 mg.

7.10.2 PK CCI Safety Analysis

The relationships between TAK-925 plasma concentrations and selected CCI safety measures will be explored graphically as data permit.

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[redacted]

Similar scatterplots will be produced for time-matched differences in HR, SBP, and DBP between TAK-925 and placebo. TAK-925 plasma concentration will be plotted on the x-axis; the difference in time-matched TAK-925 and placebo pairs in HR and BP (separately for SBP and DBP) will be plotted on the y-axis.

In addition, mean profile plots of TAK-925 plasma concentration and the difference from time-matched TAK-925/placebo pairs in HR, SBP, and DBP will be produced. The scheduled time point will be the x-axis, mean (± SD) TAK-925 plasma concentration will be on the left y-axis, and difference in the LS means (± SE) of time-matched TAK-925/placebo in HR, SBP or DBP will be on the right y-axis. Both dose levels of TAK-925 will be presented on the same plot.

7.11 Safety Analysis

Safety measures include AEs, clinical laboratory parameters, vital sign parameters, 12-lead ECG results, and other safety parameters. The Safety analysis set will be used for all summaries for safety data.

7.11.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA.

The Treatment-Emergent Adverse Events (TEAE) summary tables will include numbers and percentages of subjects experiencing at least one TEAE by SOC and PT and will be tabulated by treatment. The following is a list of TEAE summary tables to be generated:

- Overview of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events by Preferred Term
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Most Frequent (>=2 subjects in any treatment) Treatment-Emergent Adverse Events by Preferred Term
- Most Frequent (> 5% subjects in any treatment) Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Relationship of Treatment-Emergent Adverse Events to Study Drug by System Organ Class and Preferred Term
- Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Drug-Related Treatment-Emergent Adverse Events by Preferred Term

- Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

A treatment-emergent adverse event (TEAE) is defined as an AE whose date/time of onset occurs on or after the first dose of study drug. TEAEs are assigned to the treatment received within a period: AEs with the start date on or after the first dose within the treatment period and before the first dose of study drug within the next period.

In addition, subject mappings for the TEAEs by SOC and PT will be generated.

Data listings will be provided for all AEs including pre-treatment events (PTE), TEAEs, and AEs leading to death, AEs leading to study drug or study visit discontinuation, and SAEs

7.11.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis. They are measured at Study Day -2 and Study Day 4 prior to discharge or at early termination (ET).

Descriptive statistics (N, mean, SD, median, minimum and maximum) of continuous clinical laboratory variables will be summarized for baseline, post-dose (at discharge or ET), and change from baseline to post-dose overall by treatment sequence. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

Individual results for clinical laboratory tests will be evaluated against the Takeda predefined laboratory markedly abnormal values (MAV) criteria (Appendix A). All subjects with at least 1 post-dose laboratory result that meets the MAV criteria will be presented in a data listing.

The number and percentage of subjects with at least 1 post-dose markedly abnormal laboratory test result will be summarized overall for each laboratory parameter. The evaluation of clinical lab MAV will include scheduled and unscheduled results.

All clinical laboratory data will be presented in SI units in data listings.

7.11.3 Vital Signs

Vital sign measurements include blood pressure (SBP and DBP), HR, respiratory rate, and body temperature.

Heart rate, SBP, and DBP will be summarized (N, mean, SD, median, minimum and maximum) by treatment and time (before infusion and at the post dose timepoints). Only the scheduled measurements will be included in the summary. As there are time-matched baseline measures collected on Day -1, the time-matched baseline will be summarized by time-point for Day -1.

Respiratory rate and temperature will be summarized at baseline, post dose time points and change from baseline by treatment. Measures at pre-dose on Day 1 of each period will be defined as the baseline for the period.

In addition, observed heart rate, SBP, and DBP at pre- and post-infusion start time points (0, 1, 3, 5, 7, 9, 10, 13 and 24 hours) in each period will be analyzed using a linear mixed effect model for repeated measures. The model will include sequence, period, treatment, time (as a categorical variable), and treatment by time point interaction as fixed effects and a random effect for subject within sequence. The least square (LS) mean HR, SBP and DBP for each treatment and the associated SE and 95% CI will be extracted from the model at each time point, along with all pairwise differences from placebo and associated SEs, 95% CIs, and p-values. The same quantities will be estimated from the model with the appropriate contrasts for the average over the time points during the infusion (0, 1, 3, 5, 7 hours post-infusion start) and the average over the time points after the end of the infusion (9, 10, 13, and 24 hours post-infusion start).

The LS- mean HR, SBP and DBP over time will be plotted. The scheduled time points will be on the x-axis; the least-square mean (± SE) (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols. The LS mean differences from placebo will also be plotted.

Individual plots of the HR, SBP, and DBP over time will be plotted. The scheduled time points will be on the x-axis; the observed values will be on the y-axis. All treatments and the time-matched values from Day -1 will be displayed on the same plot and differentiated by different symbols.

Functional mixed-effect models may be performed for HR, SBP and DBP to take into account periodic (circadian) component of the signal and would allow to identify the parameters of the variation such as amplitude, phase, and intercept. Each parameter will have fixed and random components, while time dependence will be described by periodic function of time within each period. Fixed effects will include sequence, period, treatment and random effects will be specified for each subject within sequence as random intercept. The least square means and associated SE 95% CI for each parameter will be estimated from the model, along with the pairwise contrasts between treatment levels and corresponding SE, 95% CI, and p-values.

No statistical testing or modeling will be performed for other vital signs (temperature).

All individual vital sign values that meet Takeda's predefined criteria for MAVs (Appendix B) will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal vital sign measurement will be summarized by treatment for each vital sign parameter. The evaluation of MAV for vital signs will include both scheduled and unscheduled measurements.

All vital signs data will be presented in data listings.

7.11.4 12-Lead ECGs

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will manually interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The following parameters will be calculated automatically by the third party vendor: heart rate, PR interval, QT interval, QRS interval, QT interval with Bazett's correction formula (QTcB) and QT interval with Fridericia's correction formula (QTcF).

Descriptive statistics of the continuous ECG parameters will be summarized including baseline, Day 1 post dose timepoint, and change from baseline by treatment. Measures at pre-dose on Day 1 of each period will be used as the baseline in these summaries. Only the ECGs collected at the scheduled visits or time points will be included in the summary. No statistical tests will be performed for the observed ECG parameters.

All individual ECG values that meet Takeda's predefined criteria for MAVs (Appendix C) will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal ECG measurement will be summarized by treatment for each ECG parameter. The evaluation of MAV will include both scheduled and unscheduled measurements.

Individual subject ECGs will be presented in a data listing.

7.11.5 Other Observations

None.

7.12 Interim Analysis

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Safety data, such as AEs, vital sign changes and MAV summaries, will also be used when determining whether continue the study in this case. If the study will continue, the sample size may be re-estimated.

7.13 Changes in the Statistical Analysis Plan from Protocol

None.

8.0 REFERENCES

1. Thomann, J., Baumann, C.R., Landolt, H.P. and Werth, E., 2014. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. *Journal of Clinical Sleep Medicine*, *10*(09), pp.1019-1024.

Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	Both	< 0.8 × LLN	> 1.2 × ULN
Hematocrit	Both	< 0.8 × LLN	> 1.2 × ULN
RBC count	Both	< 0.8 × LLN	> 1.2 × ULN
WBC count	Both	<0.5 x LLN	>1.5 x ULN
Platelet count	Conventional	<75 x 10^3/μL	>600 x 10^3/μL
	SI	<75 x 10^9/L	>600 x 10^9/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	Both	--	>3 x ULN
AST	Both	--	>3 x ULN
GGT	Both	--	>3 x ULN
Alkaline phosphatase	Both	--	>3 x ULN
Total bilirubin	Both	--	>1.5 x ULN
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2 x ULN
Creatinine	Both	--	>1.5 x ULN
Blood urea nitrogen	Conventional	--	>40 mg/dL
	SI	--	>10.7 mmol/L
Sodium	Conventional	<130 mEq/L	>150 mEq/L
	SI	<130 mmol/L	>150 mmol/L
Potassium	Conventional	<3.0 mEq/L	>5.3 mEq/L
	SI	<3.0 mmol/L	>5.3 mmol/L
Glucose	Conventional	< 50 mg/dL	>300 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L
Calcium	Conventional	<7.7 mg/dL	>11.1 mg/dL
	SI	<1.92 mmol/L	>2.77 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<40	>115
Systolic blood pressure	mm Hg	<90	≥ 160
Diastolic blood pressure	mm Hg	<50	≥100
Systolic blood pressure change from baseline*	mm Hg		>20
Diastolic blood pressure change from baseline*	mm Hg		>20
Body temperature	^{o}C		>38.5
Respiratory Rate	Breath/min		>21

* change in blood pressure from the pre-dose value in each treatment period

Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Lower Criteria	Upper Criteria
Heart rate	<40 beats per minute	>115 beats per minute
PR	≤80 milliseconds	≥200 milliseconds
QTcF Interval	≤300 milliseconds	>500 milliseconds OR ≥30 milliseconds change from baseline and >450 milliseconds
QRS	≤80 milliseconds	≥180 milliseconds

* change in blood pressure from the pre-dose value in each treatment period

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	23-Apr-2020 13:43 UTC