Title: A Phase 1b, 4-Period Crossover, Placebo-Controlled, Randomized, Single Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-925 in Sleep-Deprived Healthy Adults Utilizing Modafinil as an Active Comparator

NCT Number: NCT03522506

SAP Approve Date: 29 November 2018

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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-925-1002

A Phase 1b, 4-Period Crossover, Placebo-Controlled, Randomized, Single Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-925 in Sleep-Deprived Healthy Adults Utilizing Modafinil as an Active Comparator

PHASE 1

Version**:** Final

Date**:** 29 November 2018

Prepared by:

PPD

Based on:

Protocol Version: Amendment 01

Protocol Date: 08 May 2018

1.0 APPROVAL SIGNATURES

Study Title: A Phase 1b, 4-Period Crossover, Placebo-Controlled, Randomized, Single Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-925 in Sleep-Deprived Healthy Adults Utilizing Modafinil as an Active Comparator

Approvals:

2.0 TABLE OF CONTENTS

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LIST OF ABBREVIATIONS

%CV	percent coefficient of variation
ADaM	Analysis Data Model
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{∞}	area under the first moment 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
BMI	body mass index
BP	blood pressure
CCBT	Cambridge Cognition Computerized Battery of Tests
C_{eoi}	plasma concentration observed at the end of infusion
CI	confidence interval
CL	total clearance after intravenous administration
C_{max}	maximum observed plasma concentration
CPK	creatine phosphokinase
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
EEG	electroencephalogram
GGT	γ-glutamyl transferase
HD	high dose
HR	heart rate
ICH	International Conference on Harmonisation
IV	intravenous
KSS	Karolinska Sleepiness Scale
LD	low dose
LFT	liver function test
LLN	lower limit of normal
LS	least square
M-I, M-II	metabolites of TAK-925
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MWT	maintenance of wakefulness test
NPSG	nocturnal polysomnography
NT1	narcolepsy type 1
NT2	narcolepsy type 2

OX	orexin
OX1R	orexin receptor 1
OXR2	orexin receptor 2
PD	pharmacodynamic(s)
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PO	oral administration or orally
POMS	Profile of Mood States
PSG	polysomnography
PT	preferred term
PTE	pretreatment event
QTcF	QT interval with Frederica correction method
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SOC	system organ class
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
VAS	visual analog scale
V_{ss}	volume of distribution at steady state after intravenous administration
V_z	volume of distribution during the terminal disposition phase after intravenous administration
WBC	white blood cell

3.0 OBJECTIVES

Primary Objectives

1. To determine the effect of TAK-925 after a single IV dose (compared to placebo) on promoting wakefulness as measured by sleep latency on the MWT (performed at approximately 2, 4, 6, and 8 hours post-dosing starting at approximately 1:00 AM and then at approximate times of 3:00, 5:00, and 7:00 AM) in sleep-deprived healthy volunteers.

   Hypothesis: At least 1 of the tested doses of TAK-925 is superior to placebo for promoting wakefulness as measured by sleep latency on the MWT (a difference between TAK-925 and placebo of 9 minutes or greater is estimated).

Secondary Objectives

2. To assess the safety/tolerability and PK parameters of a single IV infusion of TAK-925 in sleep-deprived healthy volunteers.

   Hypothesis: TAK-925 is generally well tolerated when administered as a single IV infusion, including effects on BP. (Overall mean difference in time-matched BP increase following administration of safe, tolerable, and effective dose of TAK-925 is less than or equal to 10 mmHg over placebo.)

3. To determine the effect of a single dose of modafinil (300 mg) on promoting wakefulness as measured by sleep latency on the MWT in order to confirm assay sensitivity.

   Hypothesis: Modafinil (300 mg) is superior to placebo on promoting wakefulness as measured by sleep latency on the MWT (a difference between modafinil and placebo of 9 minutes is estimated [1].

4. To evaluate the effect of TAK-925, 44 mg (low dose [LD]) and 112 mg (high dose [HD]), on a measure of sleepiness, as compared to placebo.

   Hypothesis: At least 1 dose of TAK-925 will be superior to placebo on the Karolinska Sleepiness Scale (KSS).

Additional Objectives

In sleep-deprived healthy volunteers:

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[redacted]

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4.0 STUDY DESIGN

This is a randomized, double-blind, double-dummy, placebo- and active-controlled, 4-period Williams design crossover study to evaluate the PK, PD, and safety of TAK-925 in sleep-deprived healthy volunteers. TAK-925 will be administered as an IV infusion over a 9-hour period based on the safety/tolerability and PK profiles established in healthy Japanese subjects in ongoing Study TAK-925-1001.

Healthy adult male subjects aged 18 to 40 years, inclusive, who satisfy inclusion and exclusion criteria will be enrolled in the trial. Approximately 20 subjects will be enrolled to ensure that at least 16 subjects complete the study.

On Day 1 of treatment period 1, eligible subjects will be equally randomized to 4 treatment sequence groups (Sequence 1 to 4) which define the order of the treatment administration (TAK-925 LD mg, TAK-925 HD mg [both delivered as a 9-hour IV infusion], modafinil 300 mg, and placebo).

A summary of the study drug assignment and sequence in presented in Table 4.a.

Table 4.a Summary of Study Drug Assignment and Sequence (Double Dummy for Placebo)

Sequence	N	Period 1	Period 2	Period 3	Period 4
1	5	TAK-925 LD mg	Placebo	TAK-925 HD mg	Modafinil 300 mg
2	5	TAK-925 HD mg	TAK-925 LD mg	Modafinil 300 mg	Placebo
3	5	Modafinil 300 mg	TAK-925 HD mg	Placebo	TAK-925 LD mg
4	5	Placebo	Modafinil 300 mg	TAK-925 LD mg	TAK-925 HD mg

During the day before dosing on Day 1, participants will be administered the KSS and CCBT at scheduled timepoints. A practice MWT session, as well as one practice CCBT, will be performed on Day 1 Treatment Period 1 (only once during the entire study) to familiarize subjects with the procedures. Study drug will be administered in the clinic in the evening on Day 1 of each treatment period. Subjects will undergo the MWT, KSS, and CCBT at specified timepoints after the start of the infusion. Subjects will be required to stay awake in between the MWT tests. Following completion of the IV infusion on Day 2, subjects will undergo an additional MWT test. When the final MWT test and cognitive testing have been completed, subjects will be allowed to sleep (recovery sleep) for approximately 6 hours. PSG recording will be collected during this time. Subjects may be discharged from the unit after completion on Day 2 with continuing actigraphy upon discharge (to begin on Day -6 before the next treatment period). The interval of each subsequent treatment period will be at least 7 days to assure that the subject's circadian rhythm has returned to a normal cycle. Subject's vital signs, including BP, will be continuously monitored during the dosing and testing period. Blood samples for determination of TAK-925 plasma concentrations will be collected at specified timepoints on Days 1 and 2 of each treatment period. Subjects will complete the C-SSRS during Screening, before study drug administration, and before discharge on Day 2 of each treatment period. Subjects will complete

the POMS before and post study drug administration, and undergo a drug-liking VAS following recovery sleep in each treatment period.

An overview of the dosing and sampling scheme is provided in Table 4.b.

Table 4.b Dosing and Sampling Scheme

		Treatment Period		
Screening Period	**Check-in and Baseline**	**Dose/Sample Collection**	**Sample Collection**	**Time Interval Between Subsequent Treatment Period**
Days -28 to -2	Day -1 NPSG/BP measurement [a]	Day 1 Sleep deprivation/study drug administration/study assessment	Day 2 Sleep deprivation/study drug continued infusion/study assessment/recovery sleep	Minimum of 7 days with actigraphy for 5 days
	X----------Confinement----------X			

Abbreviations: BP, blood pressure; NPSG, nocturnal polysomnography.
[a] NPSG and time-matched BP only on Day -1 of treatment period 1. For Periods 2, 3, and 4, subjects will be admitted to the unit and allowed to sleep normally without NPSG or time-matched BP measurement. The time interval from the end of 1 period to the start of the next period will be at least 7 days.

5.0 ANALYSIS ENDPOINTS

Primary Endpoint

1. Latency for each MWT, defined as time to sleep onset.
    - Sleep onset is defined as the first epoch of greater than 15 seconds of cumulative sleep in a 30-second epoch. Trials are ended after 40 minutes if no sleep occurs, or after unequivocal sleep, defined as 3 consecutive epochs of stage 1 sleep, or 1 epoch of any other stage of sleep. If no sleep has been observed according to these rules, then the latency is defined as 40 minutes.

Secondary Endpoints

Secondary endpoints will be assessed through the following parameters:

1. The following PK parameters calculated from plasma concentrations of TAK-925 and its metabolites M-I and M-II:
    - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
    - Area under the first moment plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
    - Maximum observed plasma concentration (C_{max}).
    - Plasma concentration observed at the end of infusion (C_{eoi}).
    - Time of first occurrence of C_{max} (t_{max}).
    - Terminal disposition phase half-life ($t_{1/2z}$).
    - Total clearance after intravenous administration (CL) (TAK-925 only).
    - Volume of distribution during the terminal disposition phase after intravenous administration (V_z) (TAK-925 only).
    - Volume of distribution at steady state after intravenous administration (V_{ss}).
2. Sleepiness on the KSS.

Safety Endpoints

Safety will be assessed through the following parameters:

1. TEAEs. Subjects will be monitored closely throughout the study for any AEs.
2. Physical examinations.
3. Vital signs, including time-matched BP measurement and PK-BP relationships.
4. 12-lead ECGs.

5. Clinical laboratory safety evaluations (hematology, blood chemistry, and urinalysis).
6. Drug-liking visual analog scale (VAS).
7. Profile of Mood States (POMS).
8. Continuous monitoring of BP and heart rate (HR), eg, Bodyconnect, at time points specified in the protocol, and sleep cycle from Day -5 to -1 by actigraphy with digital technology.
9. Columbia-Suicide Severity Rating Scale (C-SSRS).

Exploratory Endpoints

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[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The sample size justification is based on a similar study to assess the alertness-promoting effects of MK-0249, a histamine subtype-3 receptor inverse agonist, and modafinil 200 mg, in healthy sleep-deprived males [2]. In that study, investigators observed a mean increase in sleep latency in the MWT of CCI with modafinil 200 mg compared with placebo at 6 hours postdose and a within-subject standard deviation of approximately CCI. With similar variability, 16 completers will provide approximately CCI power for detecting a difference in sleep latency in the MWT between TAK-925 and placebo if the true increase over placebo is CCI. This result is based on a 2-sided test with a CCI rate.

To account for dropouts, approximately 20 subjects will be enrolled. If a subject discontinues from the study, a replacement subject may be enrolled, if deemed appropriate by the investigator and sponsor. The study site should contact the sponsor for the replacement of subject's treatment assignment and allocation number.

Sixteen completers will also provide adequate precision for the estimation of changes in BP. Assuming a standard deviation for the difference between periods in the change from baseline SBP of CCI 3], a 95% CI for the true mean change in SBP between 1 dose level of TAK-925 and placebo will extend no more than CCI from the observed difference. For example, if the observed difference between TAK-925 and placebo is CCI, then the CI for the true difference will extend from CCI, and this is considered to represent adequate precision for the estimated treatment difference.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This Statistical Analysis Plan (SAP) was developed based on International Conference on Harmonization E3 [5] and E9 [6] Guidelines. This SAP should be read in conjunction with the study protocol and electronic case report forms (eCRFs). This version of the SAP was developed using the information provided in Protocol Amendment 01 TAK-925-1002, dated 26 April 2018 [4].

All study-related raw data, including derived data, will be presented in data listings. Continuous data will be summarized using: number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum, where appropriate. Where indicated, %CV (arithmetic and/or geometric) and geometric mean will also be included in the summary of continuous data. Categorical data will be summarized using the number and percentage of subjects for each category where appropriate.

In the following, treatment (or study drug) refers to TAK-925 44 mg, TAK-925 112 mg, modafinil 300 mg, and placebo.

Statistical analysis will be performed using the SAS System®, Version 9.4 or higher, on a Windows platform.

7.1.1 Study Definitions

7.1.2 Definition of Study Days and Baseline

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 -7) 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.

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. Baseline for a specific period will be defined as the last non-missing measurement prior to the first dose of study drug in the respective treatment period.

7.1.3 Definition of Study Visit Windows

Not applicable.

7.1.4 Conventions for Missing Adverse Event Dates

7.1.4.1 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 and the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date.
  - If the month and year are the same as those in the first dose date and the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE start date. If the date prior to the first dose date is in previous month/year, set the start month/year to the previous month/year.
  - 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 and the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date.
  - If the year is the same as the year of the first dose date and the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE start date. If the date prior to the first dose date is in previous month/year, set the start month/year to the previous month/year.
  - 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:
  - If the event is not indicated as a pre-treatment event, the first dose date is to be used to impute the AE start date.
  - If the event is indicated as a pre-treatment event, the date prior to the first dose date is to be used to impute the AE start date.

7.1.4.2 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, keep the end date same as the start 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.
- 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.

7.1.5 Conventions for Missing Concomitant Medication Dates

Missing concomitant medication dates will not be imputed.

7.2 Analysis Sets

Safety Analysis Set — The safety analysis set will consist of all subjects who are enrolled and received at least 1 dose of study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

PK Analysis Set — The PK set will consist of all subjects who receive at least 1 dose of study drug and have at least 1 measurable plasma concentration.

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[redacted]

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 number and percentage of subjects will be summarized for reasons of study discontinuation for each sequence and overall. Subjects' study completion data, including the dates of the first and last dose, and reasons for premature termination, will be listed. The number and percentage of subjects comprising each analysis set will be summarized for each sequence and overall.

7.4 Demographic and Other Baseline Characteristics

For randomized subjects, descriptive statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous demographic variables and baseline characteristics variables (age, height, weight, BMI, etc.) by treatment sequence and overall. The number and percentage of subjects in each class of the categorical demographic variables and baseline characteristics variables (sex, ethnicity, race, etc.) 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 and baseline BMI, and other demographic and baseline information collected in the eCRF.

7.5 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions that stopped at or prior to signing of informed consent. Concurrent medical conditions are those significant ongoing conditions that are present at signing of informed consent.

Medical history and concurrent medical condition verbatim reported terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). No summary statistics for medical history and concurrent medical conditions will be provided. All medical history and concurrent medical conditions will be listed.

7.6 Medication History and Concomitant Medications

Medication history information obtained includes any medication stopped at or within 28 days prior to signing of informed consent. Medications used from signing of informed consent through the end of study will be considered as concomitant medications.

Medication history and concomitant medications will be coded using World Health Organization Drug Dictionary (WHO Drug). No summary statistics for medication history and concomitant medications will be provided. 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.

7.8 Efficacy Analysis

All efficacy measures will be analyzed using the PD analysis set and will be presented in data listings.

7.8.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint, sleep latency on the MWT, will be summarized (N, mean, SD, median, minimum, and maximum) by treatment and scheduled time point.

The effect of TAK-925 will be evaluated with a linear mixed effects model appropriate for a 4-period crossover study. The response variable in the model will be the observed post-infusion start value of sleep latency. The model will contain fixed effects for sequence, period, treatment, time (as a categorical variable), and the treatment-by-time interaction, and a random effect for subject. CCI [redacted]

The LS mean sleep latency for each treatment and the associated standard error and 95% CI will be estimated from the model at each time, along with differences between active treatments and placebo, and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over the 4 timepoints during the infusion (2, 4, 6, and 8 hours post-infusion start), will be extracted from the model using an appropriate contrast. CCI [redacted]

In addition, an ANOVA model will be used to evaluate the 1 hour post the end of infusion MWT. The response variable in the model will be the observed 1 hour post the end of the infusion start value of sleep latency. The model will contain fixed effects for sequence, subject within sequence, period, treatment. The error term for the sequence effect will be subjects within Sequence. The LS mean sleep latency for each treatment and the associated standard error and 95% CI will be estimated from the model, along with the differences between active treatments and placebo, and associated standard errors, 95% CIs, and p-values.

A mean profile plot of sleep latency over time will be produced. The scheduled time point (2, 4, 6, 8 hours post the start of the infusion and 1 hour post the end of the infusion) will be the x-axis; the LS mean (± SE) sleep latency (estimated from above two models) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

7.8.2 Secondary Efficacy Endpoint(s)

Similar analysis described for the MWT will be performed for sleepiness as assessed by the KSS. A linear mixed effect models will be performed for all observed KSS parameters at scheduled time points. The response in the model will be the observed KSS value. The model will contain fixed effects for sequence, period, treatment, time (9 scheduled timepoints including the 1 hour post the end of infusion, as a categorical variable), and the treatment-by-time interaction, and a random effect for subject. CCI [redacted]

The LS mean sleepless scale for each treatment and the associated standard error and 95% CI will be estimated from the model at each time point, along with the differences between active treatments and placebo, and associated standard errors, 95% CIs, and p-values. CCI [redacted]

CCI . The difference between the average of the 4 time points after and before the start of the infusion (delta: after – before) will be calculated for each regimen, along with the associated standard errors and 95% CI. In addition, the differences between the active regimens and placebo in the "deltas" (double delta), associated standard error and 95% CI, will be derived.

A mean profile plot of KSS over time will be produced. The scheduled time point will be the x-axis; the LS mean (± SE) sleep latency will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

7.8.3 Additional Efficacy Endpoint(s)

CCI

7.9 Pharmacokinetic/Pharmacodynamic Analysis

The relationship between TAK-925 exposure and efficacy will be explored graphically. A scatterplot of TAK-925 plasma concentration (x-axis) versus the observed post-infusion start measurement of sleep latency on the MWT (y-axis) will be produced. TAK-925 plasma concentrations for placebo data will be included in the plot with a concentration of 0. A

horizontal reference line will be drawn at the mean post-infusion start sleep latency. Only measurements from time points common to both assessments (MWT and PK) will be used. Data from the low dose and high dose of TAK-925 will be displayed together in the plot with different symbols.

Similar scatterplots will be produced for changes in HR, SBP, and DBP. TAK-925 plasma concentration will be plotted on the x-axis; the change from time-matched baseline 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 change from time-matched baseline 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 LS mean (± SE) change from time-matched baseline in HR (separately for SBP and DBP) will be on the right y-axis. Both dose levels of TAK-925 will be presented on the same plot with different symbols.

7.9.1 Pharmacokinetic Analysis

Plasma concentrations of TAK-925 and its metabolites M-I and M-II and the PK parameter estimates described in Section 5.0 will be listed for each subject and summarized using descriptive statistics (N, mean, SD, %CV, median, minimum, and maximum) by each time point for each treatment. Geometric means, in addition, will be computed for C_{max}, AUC_{last}, and AUC_{∞}. Mean (± SD) concentration-time profiles will be produced for TAK-925 and the metabolites M-I and M-II.

7.9.2 Other Pharmacodynamic Analysis

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[redacted]

7.10 Safety Analysis

7.10.1 Adverse Events

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

The 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 TEAEs will also be

summarized for all subjects in the overview assessment. The following is a list of TEAE summary tables to be generated:

- Overview of TEAEs
- TEAEs by SOC and PT
- Subject Mappings for TEAEs
- TEAEs by PT
- Drug-Related TEAEs by SOC and PT
- Relationship of TEAEs to Study Drug by SOC and PT (related vs not related)
- Intensity of TEAEs by SOC and PT
- Intensity of Drug-Related TEAEs by SOC and PT.

Additional AE summary tables may be added as appropriate.

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, SAEs, and signs and symptoms of AEs related to increased liver function tests.

7.10.2 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis.

Descriptive statistics (N, mean, SD, median, minimum and maximum) of clinical laboratory variables will be summarized for baseline, post-dose, and change from baseline to post-dose by treatment and time. 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) using the result and criteria in SI units. 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 also be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying laboratory result. All post-dose clinical lab MAV results, including scheduled and unscheduled measurements, will be included in the MAV summaries.

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

7.10.3 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) for baseline (defined, here, as all time-matched measurements on Day -1 and Day 1 prior to

dosing of each treatment period), post-dose, and change from time-matched baseline to post-dose by treatment and time. Only the scheduled measurements will be included in the summary.

In addition, the change from time-matched baseline will be analyzed using a statistical model of the same form as for sleep latency on the MWT. The LS mean change from time-matched baseline for each treatment and the associated standard error and 95% CI will be extracted from the model at each time, along with differences to placebo and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over all post-dose timepoints, will be extracted from the model using an appropriate contrast. Only the scheduled measurements will be included in the analysis.

All other vital signs will be summarized for baseline (last non-missing value prior to dose), post-dose, and change from baseline by treatment and time. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

All individual vital signs 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. Subjects who meet the MAV criteria will be mapped to their respective qualifying vital sign result. All post-dose MAV vital signs, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

All vital signs data will be presented in both SI and conventional units in data listings.

7.10.4 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 ECG machine: heart rate, PR interval, QT interval, QRS interval, and QT interval with Fridericia correction method (QTcF).

Descriptive statistics of the continuous ECG parameters will be summarized for baseline, post-dose, and change from baseline at each post-dose time point by treatment and time. 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.

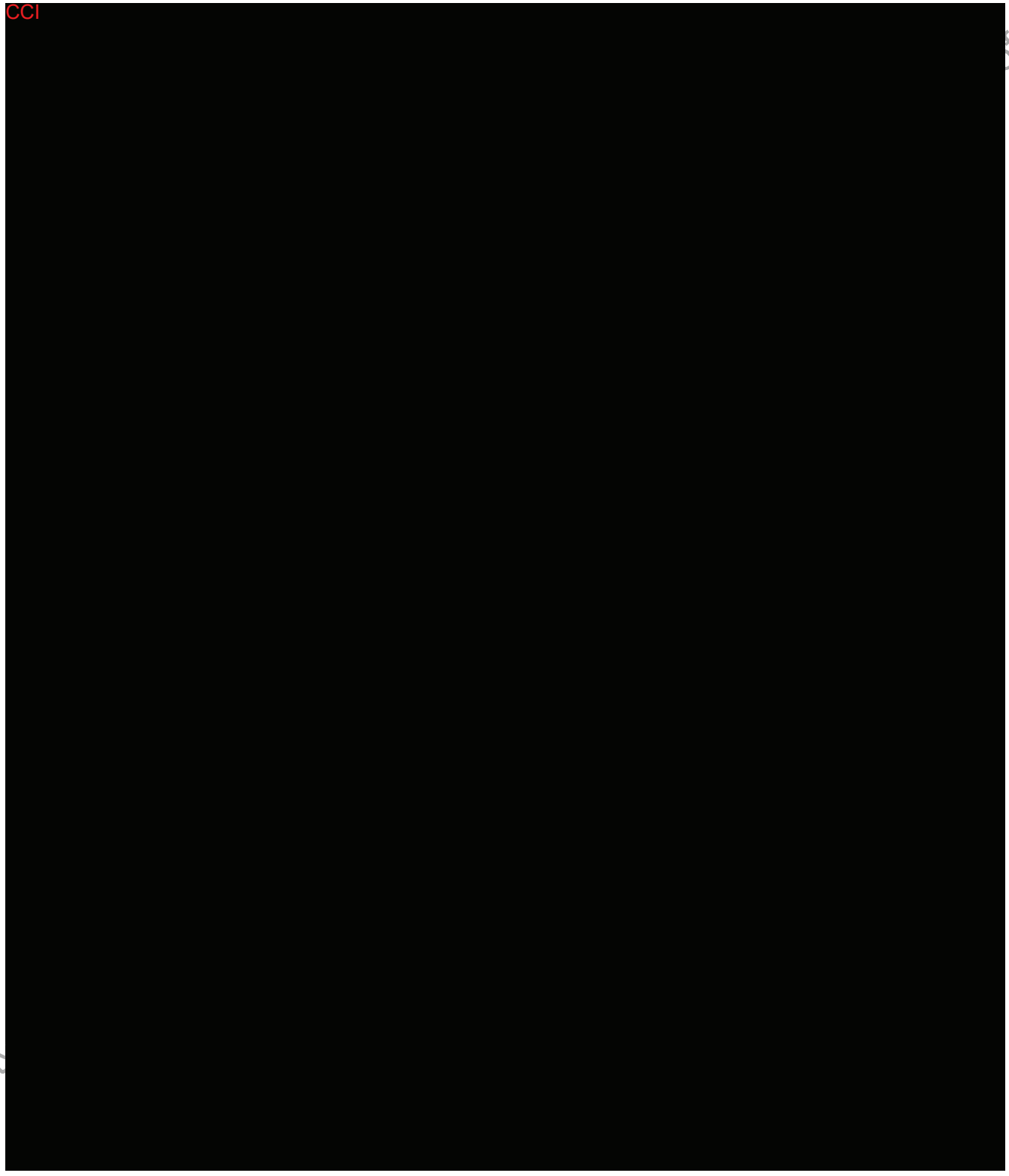
All individual ECGs that meet Takeda's predefined criteria for MAVs (Appendix C) will be listed. The number and percentage of subjects with at least 1 post-dose markedly abnormal ECG measurement will be summarized by treatment. Subjects who meet the MAV criteria will be mapped to their respective qualifying ECG result. All post-dose MAV ECG parameters, including both scheduled and unscheduled measurements, will be included in the MAV summaries.

Individual subject ECGs will be presented in a data listing.

7.10.5 Other Observations Related to Safety

The C-SSRS, physical examinations, and cases of overdoses will be listed.

CCI



7.11 Interim Analysis

Not applicable.

7.12 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

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3. Dinges DF, Arora S, Darwish M, Niebler GE. Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. Curr Med Res Opin 2006;22(1):159-67.
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5. Guideline on Structure and Content of Clinical Study Reports, International Conference on Harmonisation, Section ICH E3, 1996.
6. Guideline on Statistical Principles for Clinical Trials, International Conference on Harmonisation, Section ICH E9, 1998.

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	--	>3x ULN
AST	Both	--	>3x ULN
GGT	Both	--	>3x ULN
Alkaline phosphatase	Both	--	>3x ULN
Total bilirubin	Conventional	--	>2.0 mg/dL
	SI	--	>34.2 μmol/L
Albumin	Conventional	<2.5 g/dL	--
	SI	<25 g/L	--
Total protein	Both	<0.8x LLN	>1.2x ULN
Creatinine	Conventional	--	>2.0 mg/dL
	SI		>177 μmol/L
Blood urea nitrogen	Conventional		>30 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	>6.0 mEq/L
	SI	<3.0 mmol/L	>6.0 mmol/L
CPK	Both	--	>5x ULN
Glucose	Conventional	< 50 mg/dL	>350 mg/dL
	SI	< 2.8 mmol/L	>19.4 mmol/L

ALT=alanine aminotransferase, AST=aspartate aminotransferase, CPK=creatine phosphokinase, 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	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	°C	< 35.6	>37.7

Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Lower Criteria	Upper Criteria
Heart rate	<50 beats per minute	>120 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	29-Nov-2018 22:40 UTC
	Clinical Pharmacology Approval	29-Nov-2018 22:48 UTC
	Pharmacovigilance Approval	30-Nov-2018 15:47 UTC
	Clinical VP Approval	02-Dec-2018 19:58 UTC
	Clinical Approval	03-Dec-2018 18:39 UTC