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

Protocol Approve Date: 08 May 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.
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TAKEDA PHARMACEUTICALS

PROTOCOL

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

Study Identifier: TAK-925-1002

Compound: TAK-925

Date: 08 May 2018

Version/Amendment Number: 01

Date	Amendment Number	Region
08 March 2018	Initial Protocol	United States
08 May 2018	01	United States

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1.0 STUDY SUMMARY

Name of Sponsor:	**Compound:**
Takeda Pharmaceutical Company, Ltd 40 Landsdowne Street Cambridge MA 02139 USA	TAK-925
Study Identifier: TAK-925-1002	**Phase:** 1b

Protocol 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

Study Design:

Healthy adult male subjects aged 18 to 40 years, inclusive, who satisfy inclusion and exclusion criteria will be enrolled in the study. On Day 1 of treatment period 1, eligible participants will be equally randomized to 4 treatment sequence groups (sequence 1 to 4) which define the order of the treatment administration (TAK-925 44 mg [low dose, (LD)], TAK-925 112 mg [high dose (HD)] mg [both delivered as a 9-hour intravenous (IV) infusion], modafinil 300 mg, and placebo).

At the screening visit, subjects will complete medical examinations, an electrocardiogram (ECG), and clinical laboratory tests. After the screening visit, eligible participants will wear an actigraph from Day -6 until Day -1. After validation that actigraphy shows a normal sleep-wake cycle, and subjects have a negative drug screen, subjects will undergo an 8-hour nocturnal polysomnography to exclude any sleep disorders. Actigraphy results will also be collected for the 5-night period before Day-1 (Day -6 to Day -1) for every treatment period to ensure that sleep falls within normal nocturnal times (defined under Inclusion Criteria).

During the day before dosing on Day 1, subjects will be administered the Karolinska Sleepiness Scale (KSS) and Cambridge Cognition Computerized Battery of Tests (CCBT) at scheduled timepoints. A practice maintenance of wakefulness test (MWT) session, as well as a practice CCBT, will be performed on Day 1 of 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 time points 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 has been completed, subjects will be allowed to sleep (recovery sleep) for approximately 6 hours. Polysomnography (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 ensure that the subject's circadian rhythm has returned to a normal cycle. Subject's vital signs, including blood pressure (BP), will be continuously monitored during the dosing and testing periods. 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 Columbia–Suicide Severity Rating Scale (C-SSRS) during screening, before study drug administration, and before discharge on Day 2 of each treatment period. Subjects will complete the Profile of Mood States (POMS) before and post study drug administration, and undergo a drug-liking Visual Analog Scale (VAS) following recovery sleep in each treatment period.

Primary Objective:

To determine the effect of TAK-925 after a single IV infusion (compared to placebo) on promoting wakefulness as measured by sleep latency on the MWT (performed at approximately 2, 4, 6, and 8 hours postdosing 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.

Secondary Objectives:

1. To assess the safety/tolerability and pharmacokinetic (PK) parameters of a single IV infusion of TAK-925 in sleep-deprived healthy volunteers.
2. 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.
3. To evaluate the effect of TAK-925, LD and HD, on a measure of sleepiness, as compared to placebo.

Study Subject Population: Healthy male subjects, aged 18 to 40 years, inclusive.

Planned Number of Subjects:	**Planned Number of Sites:**
Approximately 20 subjects randomized	1 site in the US
Dose Levels: Study Drug TAK-925 112 mg (HD) TAK-925 44 mg (LD) Matching placebo Modafinil 300 mg Matching placebo	**Route of Administration:** Study Drug IV infusion Modafinil Oral (tablets)
Duration of Treatment: 1 dose of modafinil 300 mg or placebo followed by a continuous 9-hour IV infusion of study drug (TAK-925 HD mg, TAK-925 LD mg, or placebo) beginning in the evening on Day 1 of each of 4 treatment periods	**Planned Study Duration:** Up to approximately 12 weeks.

Main Criteria for Inclusion:

To be eligible for study participation, subjects must:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be a healthy male, aged 18 to 40 years, inclusive, at the screening visit.
4. Have a body mass index $\geq$18.5 and $\leq$30.0 (kg/m^2) at the screening visit.
5. Be a nonsmoker or have not used tobacco- or nicotine-containing products (eg, nicotine patch) for at least 6 months before study drug administration of the initial dose of study drug.
6. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug/invasive procedure.
7. Meet the specified birth control requirements.
8. Is a male subject who agrees to not donate sperm from trial drug administration on the first day of the first dose until 5 half-lives plus 90 days after the last dose of study drug administration.
9. Have regular sleep-wake habits (eg, routinely spending 6.5 to 8 hours sleeping nightly, not oversleeping by more than 3 hours on weekends, ie, total sleep not more than 11 hours) as determined by investigator interviews and confirmed in 5-day actigraphy records and whom regularly fall asleep between 9:30 PM and 12:00 AM.
10. Be willing to have actigraphy monitoring during the week before randomization and in each interval.

Main Criteria for Exclusion:

The subject must be excluded from participating in the study if the subject:

1. Has a positive alcohol or drug screen.
2. Has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
3. Has excessive sleepiness defined by a self-reported Epworth Sleepiness Scale score at screening greater than 10; irregular work hours; or routine night-shift work within 1 month before randomization.
4. Currently experiencing or having a history of any known/suspected sleep disorder, any disorder associated with excessive daytime somnolence, or any diagnosis interfering with assessment of sleepiness.
5. Abnormal findings on the initial PSG conducted on Day -1 (check-in), as specified in the study manual.
6. Traveled across 2 or more time zones 2 weeks or less before screening;
7. Current or previous history of serious, severe, or unstable physical or psychiatric illness that may affect sleep or wakefulness; any medical disorder that may make the full completion of the study unlikely.
8. Caffeine consumption of more than 400 mg/day for 2 weeks before screening (1 serving of coffee is approximately equivalent to 120 mg of caffeine).
9. Hypertension or history of hypertension. Systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg is excluded.
10. Other significant cardiovascular risk factors including abnormal ECG QT interval findings and heart rate (HR).
11. Screening ECG reveals a QT interval with Frederica correction method >450 milliseconds.

Main Criteria for Evaluation and Analyses:

The primary endpoint of the study is:

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.

The secondary endpoints will be assessed through evaluation of 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.
   - Area under the first moment plasma concentration-time curve from time 0 to infinity.
   - Maximum observed plasma concentration.
   - Plasma concentration observed at the end of infusion.
   - Time of first occurrence of C_{max}.
   - Terminal disposition phase half-life.
   - Total clearance after intravenous administration (TAK-925 only).
   - Volume of distribution during the terminal disposition phase after intravenous administration (TAK-925 only).
   - Volume of distribution at steady state after intravenous administration.

2. Sleepiness on the KSS.

Safety will be assessed through the following parameters:

1. Treatment-emergent adverse events. Subjects will be monitored closely throughout the study for any adverse events.
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 VAS.
7. POMS.
8. Continuous monitoring of BP, HR (eg, Bodyconnect) at time points specified in the protocol, and sleep cycle from Day -5 to -1 by actigraphy with digital technology.
9. C-SSRS.

Statistical Considerations:

The effect of TAK-925 on sleep latency on the MWT will be evaluated with a mixed effects model appropriate for a 4-period crossover study. The response variable in the model will be the observed value of sleep latency. The model will contain fixed effects for sequence, period, treatment (TAK-925 LD, TAK-925 HD, modafinil, and placebo), time (as a categorical variable), and the treatment-by-time interaction, and a random effect for subject.

The estimated mean sleep latency for each treatment and the associated standard error and 95% CI will be extracted from the model at each time, along with all treatment differences and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over all timepoints at which an MWT is performed, will also be extracted from the model using an appropriate contrast. The study objectives will be addressed using the results of the average treatment difference across all time points.

The change from time-matched baseline in HR and BP will be analyzed using a statistical model of the same form as for the primary endpoint. The estimated 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 all treatment differences and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over all postdose timepoints, will also be extracted from the model using an appropriate contrast.

Sample Size Justification:

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 [1]. In that study, investigators observed a mean increase in sleep latency in the MWT of CCI [redacted] with modafinil 200 mg compared with placebo at 6 hours postdose and a within-subject standard deviation of approximately 6.74 minutes. With similar variability, 16 completers will provide approximately 90% power for detecting a difference in sleep latency in the MWT between TAK-925 and placebo if the true increase over placebo is CCI [redacted]. This result is based on a 2-sided test with a CCI [redacted].

To account for dropouts, approximately 20 subjects will be enrolled.

1.1 Protocol Amendment 01 Summary of Changes

Rationale for Amendment 01

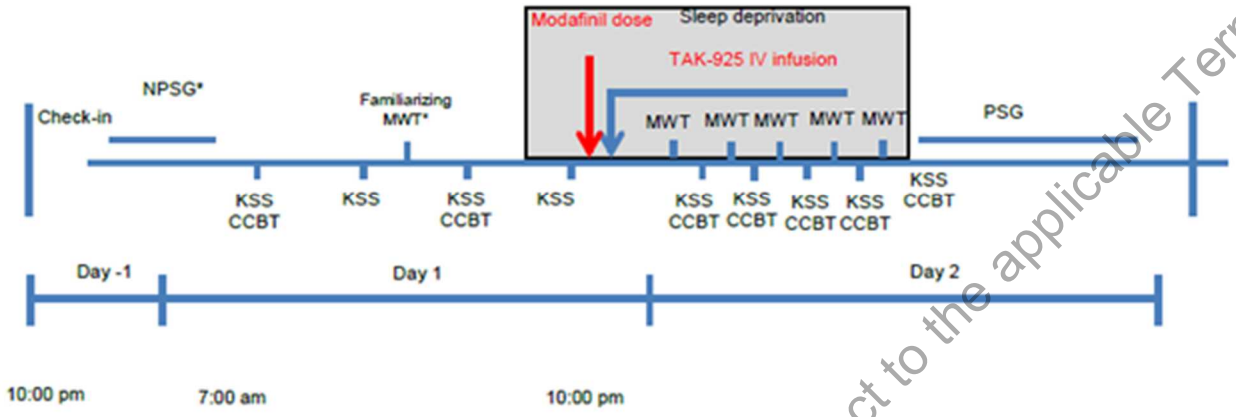
This document describes the changes in reference to the protocol incorporating Amendment No. 01. The primary reason for Protocol Amendment No. 1 is to update cognition rating scales and revise protocol text to align with the Inclusion/Exclusion Criteria. Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix E.

Changes in Amendment 01:

1. Removed Sustained Attention to Response Task (SART) assessment throughout protocol and updated study schematic accordingly.
2. Replaced Cogstate Cognitive Computerized Battery of Tests with Cambridge Cognition Computerized Battery of Tests (CCBT).
3. Updated alcohol consumption restrictions.
4. Updated caffeine consumption restrictions.
5. Updated smoking restrictions.
6. Added dose levels selected for the low dose (LD) and high dose (HD).

2.0 STUDY SCHEMATIC



Abbreviations: CCBT, Cambridge Cognition Computerized Battery of Tests; IV, intravenous; KSS, Karolinska Sleepiness Scale; MWT, maintenance of wakefulness test; NPSG, nocturnal polysomnography; PSG, polysomnogram.
*Performed once during the entire study.

3.0 SCHEDULE OF STUDY PROCEDURES

	Day	Each Treatment Period																				Day
		Day	Scheduled Time (Day 1 and 2)																		Day	
	-28 to -2	-1	Hours																		2 After Recovery Sleep	7
	Screen-ing [d]	Check -in	Pre dose	After Start of Infusion									After End of Infusion								Post dose/ Early Termina-tion	Follow -up Visit [a]
				1	2	3	4	5	6	7	8	9	0.17	0.5	1	2	3	4	6	9		
Administrative Procedures																						
Informed consent	X																					
Inclusion/exclusion criteria	X		X																			
Medical history	X	X																				
Concomitant medication review	X----------Continuous----------X																					
Clinic Procedures/Assessments																						
Full physical examination	X		X [b]																		X	X
Height	X																					
Weight	X	X																			X	X
Body mass index	X																					
Vital signs (BP, HR) [c]	X	X	X	X	X		X		X			X			X	X		X			X	X
Continuous monitoring with digital technology (BP, HR) [d]		X	X----------Continuous----------X																			
Vital signs (respiratory rate, oral/tympanic temperature) [e]			X						X												X	
12-lead ECG [e]	X		X						X												X	
Study drug administration [f]				9-hour continuous IV infusion																		

	Day	Each Treatment Period																			Day	Day
		Day	Scheduled Time (Day 1 and 2)																		Day	Day
	-28 to -2	-1	Hours																		2 After Recovery Sleep	7
	Screen-ing [d]	Check -in	Pre dose	After Start of Infusion									After End of Infusion								Post dose/ Early Termina-tion	Follow -up Visit [a]
				1	2	3	4	5	6	7	8	9	0.17	0.5	1	2	3	4	6	9		
C-SSRS	X	X																			X	
Drug-liking VAS																					X	
Actigraphy [g]	X																					
Sleep deprivation			X	X---------- X																		
Adverse events monitoring	X----------Continuous----------X																					
Pharmacodynamic Evaluations																						
Screening polysomnography (PSG)		X [h]																				
Maintenance Wakefulness Test (MWT), power spectrum EEG [i]			X		X		X		X		X				X							
Karolinska Sleepiness Scale (KSS) [j]			X			X		X		X		X			X							
CCBT [J]			X			X		X		X		X			X							
POMS [k]			X									X										
Recovery sleep PSG																X-----Continuous-----X						
Laboratory Procedures/Assessments																						
Hematology	X	X																			X	X
Urinalysis	X	X																			X	X

	Day	Each Treatment Period																			Day	Day
	Day	Day	Scheduled Time (Day 1 and 2)																		Day	Day
	-28 to -2	-1	Hours																		2 After Recovery Sleep	7
	Screen-ing [d]	Check -in	Pre dose	After Start of Infusion									After End of Infusion								Post dose/ Early Termina-tion	Follow -up Visit [a]
				1	2	3	4	5	6	7	8	9	0.17	0.5	1	2	3	4	6	9		
Chemistry	X	X																			X	X
Urine drug screen [l]	X																					
Hepatitis screen	X																					
HIV	X																					
Blood for retained samples and pharmacogenomics [h]		X																				
Pharmacokinetics Evaluations																						
Blood for plasma PK TAK-925 and metabolites assay [m]			X	X	X		X		X			X	X	X	X	X	X	X	X	X	X	
Other																						
Confinement		X----------Continuous----------X																				

Abbreviations: BP, blood pressure; CCBT, Cambridge Cognition Computerized Battery of Tests; C-SSRS, Columbia–Suicide Severity Rating Scale; EEG, electroencephalogram; HIV, human immunodeficiency virus; HR, heart rate; IV, intravenous; KSS, Karolinska Sleepiness Scale; MWT, Maintenance of Wakefulness; POMS, Profile of Mood States; PSG, polysomnography; PK, pharmacokinetics; VAS, visual analog scale.

[a] Follow-up visit will occur Day 7 (±2) after the last dose of study drugs.

[b] Can be performed within approximately 24 hours before study drug dosing.

[c] Vital signs (HR, BP) will be obtained as follows:

Day -1: will be obtained time matched with Day 1. Day -1 vital signs are to mirror the planned scheduled vital signs for Day 1 as it relates to predose and postdosing scheduled vital signs. Predose and postdose vital signs at the identical times allows for a time-matched comparison.

Day 1: predose, 1, 2, 4, 6, 9, 10, 11, 13 hours post IV dose

Follow-up visit

BP will be checked with the subject lying in a bed with the head of the bed at 30 degrees. See Section 6.2.4 for order of assessments.

[d] BP and HR will be continuously monitored during the confinement period, starting in the evening on Day -1.

[e] Vital signs (other than HR and BP) and 12-lead ECG will be performed within approximately 1 hour predose and 6 hour after start of infusion on Day 1 and at discharge on Day 2.

[f] Modafinil or matching placebo capsule will be administered at approximately an hour before start of IV dosing on Day 1. TAK-925 or matching placebo will be started infusing approximately at 11:00 PM on Day 1.

[g] Subjects will be monitored with actigraphy from Day -6 through Day -1.

[h] Will be performed only once in each subject before treatment period 1.

[i] MWT will be performed as following; approximately 2, 4, 6, 8, 10 hours after start of IV infusion. The MWT done at approximately 10 hours will be approximately 1 hour and 20 minutes after the end of the drug infusion. A practice MWT session will be performed on Day 1 of treatment period 1 (only once during the entire study) to familiarize subjects with the procedure.

CCI [redacted]

[k] The POMS will be done predose to modafinil/placebo or IV drug administration and after the last MWT and KSS, and CCBT have been completed.

[l] Urine drug screen will be done at first period only, and not subsequent periods.

[m] Blood for TAK-925 PK will be collected: Pre, 1, 2, 4, 6, and 9 hours after start of infusion; 0.17, 0.5, 1, 2, 3, 4, 6, 9 hours after end of infusion; and at discharge.

4.0 INTRODUCTION

4.1 Background

Orexin (OX) is a neuropeptide that was discovered independently by research groups in Japan and the United States. The orexinergic system is a major wake-promoting system of the brain. OX-producing neurons are localized in a specific region of the lateral hypothalamus and have excitatory projections to wide areas of the neuraxis, including the cerebral cortex and other wake-promoting nuclei (cholinergic neurons of the basal forebrain, tuberomammillary nucleus, locus coeruleus, ventral tegmental area and dorsal raphe nucleus). The orexinergic system is also involved in several other functions, such as feeding, reward, and sympathetic activity. Two orexinergic neuropeptides, orexin-A and orexin-B, have been identified to date. The orexins exert effects via 2 types of receptors; orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R). Orexin-A has a high affinity to OX1R and OX2R, and orexin-B has a high affinity to OX2R. The 2 OX receptors have a distinct distribution in the arousal network–the locus coeruleus contains only OX1R, the tuberomammillary nucleus only OX2R, whereas both receptor types occur in the dorsal raphe nucleus and ventral tegmental area. The 2 OX receptors make distinct contributions to the regulation of arousal. OX2R in the tuberomammillary nucleus are essential for the maintenance of wakefulness (MWT), whereas both receptor types are required for the inhibition of rapid eye movement (REM) sleep [2].

The pathological loss of orexinergic neurons is associated with the development of narcolepsy [3]. The symptoms of narcolepsy can be divided into 2 groups: (i) symptoms caused by the intrusion of non-REM sleep into wakefulness (excessive daytime somnolence [EDS], sleep attacks) and (ii) symptoms caused by the intrusion of REM sleep into wakefulness (cataplexy, hypnagogic or hypnopompic hallucinations, sleep paralysis) [2]. The REM–sleep-related symptoms reflect physiological accompaniments of REM sleep: loss of muscle tone (cataplexy, sleep paralysis) and dreaming (visual hallucinations).

Narcolepsy can also occur without cataplexy, termed narcolepsy type 2 (NT2); patients with this disorder may exhibit all clinical features of narcolepsy with the exception of cataplexy [4]. Narcolepsy with cataplexy, or narcolepsy type 1 (NT1), has been defined by International Classification of Sleep Disorders, 3rd edition (ICSD-3) criteria as having low levels of OX in cerebrospinal fluid (CSF) (<110 pg/mL; <30% of normal levels) and narcolepsy without cataplexy (NT2) with CSF OX levels >110 pg/mL (at least 30% of normal).

The pathophysiology of NT1 has a presumed, though unproven, autoimmune basis in individuals with a specific genetic predisposition, the most common of which is the HLA DQB1*0602 (HLA DQB1 [major histocompatibility complex, class II, DQ beta 1]) [5,6]. The proposed etiology involves T-cell mediated destruction of OX-producing neurons in the hypothalamus [6-8]. Loss of OX-producing neurons are reflected by low CSF OX levels [9].

The presumed pathophysiology of NT2 is unclear. However, there are examples of patients initially classified as having NT2 who later develop cataplexy. In a few patients, CSF levels of OX have been demonstrated to decrease over time [10]. The dichotomy of the ICSD-3 criteria have also been subject to some criticism since measurement of OX in CSF is only performed as a

research tool and is not clinically available, and the symptoms of cataplexy may be quite subtle and unrecognized. As many as 30% of patients with NT2 are found to have CSF OX levels that are lower than normal [11]. African Americans are more likely to have low OX levels, even if cataplexy is absent [12]. It may be that there is a spectrum of narcolepsy such that some OX loss results in EDS without cataplexy, whereas greater loss results in cataplexy. This concept of a narcolepsy spectrum is supported by murine models of narcolepsy that show greater hypocretin loss in animals exhibiting cataplexy than in those exhibiting only sleep fragmentation/wakefulness [11].

Mild to moderate loss of OX neurons has also been shown to occur in several neurodegenerative diseases (60% in Parkinson's disease, 40% in Alzheimer's disease, and 30% in Huntington's disease, in contrast to 90% in narcolepsy) and this may contribute to the EDS observed in some patients with these diseases.

Currently available medications for EDS include modafinil, methylphenidate hydrochloride, dextroamphetamine sulfate, and/or sodium oxybate. These drugs have limited effectiveness and/or undesirable side effects such as nausea, headache, and dizziness [13]. The adverse effects from amphetamines also include irritability, hyperactivity, tremor, and mood changes [14]. Based on the data described above demonstrating that partial or complete OX deficiency plays an important role in the development of EDS, OX replacement therapy is expected to improve EDS through the pathophysiology-directed mechanism of action (MOA). A novel drug that acts to help address the deficiency of OX may address the spectrum of narcolepsy symptoms, and may have greater efficacy than currently approved drugs for treatment of EDS.

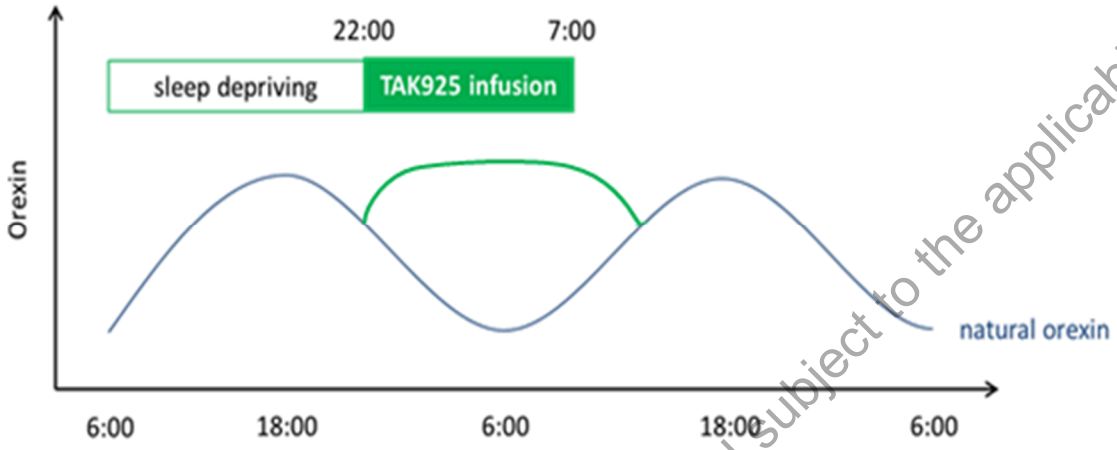
TAK-925 is a highly selective OX2R agonist being developed by Takeda for the treatment of narcolepsy. The OX receptor is a G protein-coupled receptor that has 2 subtypes, OX1R and OX2R. Upon activation, OX1R and OX2R couple with Gq protein to increase intracellular calcium (Ca^{2+}) concentration. In Chinese hamster ovary K1 cells expressing recombinant human OX2R, TAK-925 increased intracellular Ca^{2+} levels in a concentration dependent manner. In vivo pharmacology studies have demonstrated that TAK 925 increased wakefulness and decreased cataplexy-like events in the OX/ataxin-3 mouse model of NT1. TAK-925 significantly and dose-dependently enhanced wakefulness in wild type (WT) mice, common marmosets, and cynomolgus monkeys. Please refer to the TAK-925 Investigator's Brochure for complete information on the investigational product.

4.2 Rationale for the Proposed Study

TAK-925 showed arousal effects in WT mice and monkeys as well as in OX/ataxin-3 mice, a narcolepsy mouse model with a loss of OX-producing neurons. This strongly suggests that TAK-925 can stimulate the OX wake promoting system, even if it is not deficient. It is important to note that the effects in the WT animals were found during their "sleep phase". OX levels vary across the diurnal cycle [15,16], lowering midnight to early morning in the squirrel monkey, which has a pattern of wakefulness similar to that of humans [15]. As rigorous translation of animal models to the human condition is critical to our understanding of drug mechanisms in this study,

TAK-925 will be administered to sleep-deprived healthy subjects during nighttime to evaluate effects on wakefulness in sleep phase (see Figure 4.a) [15].

Figure 4.a Model of Diurnal Intrinsic OX Level in Brain Over Time



4.3 Benefit/Risk Profile

As this study will be conducted in healthy subjects, there is no expected clinical benefit to study participants other than receiving medical examinations and information about their overall health conditions. It is possible that the information obtained in the present study will become beneficial to patients with narcolepsy in the future.

This phase 1 study has been designed to mitigate the potential risks based on nonclinical findings. In addition, there is minimal risk associated with study noninvasive procedures including vital sign assessments and electrocardiograms (ECGs).

The principal mitigation for these risks includes appropriate selection of the study population, the clinical research unit setting, which permits close monitoring and rapid institution of appropriate care as needed, appropriate specified monitoring procedures, and utilization of experienced staff trained in study procedures. Overall, the risk:benefit profile is considered appropriate for this study.

4.3.1 TAK-925

TAK-925 safety information is derived from the data obtained from nonclinical studies and preliminary data from the ongoing first-in-human (FIH) study TAK-925-1001 in Japanese subjects.

Risks observed during the nonclinical studies included convulsions, vomiting, and blood pressure (BP) increase. Convulsions were observed in a single-dose intravenous (IV) escalating administration toxicity study in monkeys at a high infusion rate, but were not observed in 2-week Good Laboratory Practice toxicology studies with a slower infusion rate. Vomiting was seen in 2-week toxicology studies in animals given higher doses. Nausea and vomiting are readily

monitored in subjects and managed as appropriate, including potentially stopping the study drug infusion. A mean systolic blood pressure (SBP) increase up to 19 mmHg was also noted in a monkey safety pharmacology study, and based on published literature this is considered a potential mechanism-based risk for OX2R agonists [17]. Therefore, frequent BP measurements will be obtained throughout the study. Detailed plans for management of BP increase are in Section 7.6. As the drug is expected to have a short half-life, stopping the infusion should result in rapid BP lowering if toleration does not develop with continued study drug infusion.

The FIH phase 1 study of TAK-925, TAK-925-1001 is currently being conducted in Japan. It is assessing the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a single 9-hour IV dose of TAK-925 when administered to healthy adult and elderly adult volunteers and patients with narcolepsy. This study consists of 2 parts: Part 1 and Part 2.

Part 1 is an alternating panel, randomized, double-blind, placebo-controlled, dose-escalation, crossover study to assess the safety, tolerability and PK of TAK-925 when administered as a single-dose to healthy adult and elderly adult volunteers. In Part 1, the safety, tolerability and the PK including the concentration of TAK-925 in the CSF when administered as a single dose to healthy adult volunteers will also be evaluated in a unblinded fashion.

Part 2 is a sequential panel, randomized, double-blind (sponsor unblinded), placebo-controlled, 2-period crossover study to assess the safety, tolerability, PK, and PD of 1 or more doses of TAK-925 versus placebo in patients with NT1.

In Part 1, In the ongoing FIH study TAK-925-1001, single doses of TAK-925 or matching placebo given IV for 9 hours have been administered in Part 1 to 16 subjects (12 active and 4 placebo) in 2 cohorts in an alternating panel design. Cohort 1 received 7, 28, and 112 mg TAK-925/placebo as single doses and Cohort 2 received 14, 56, and 134.4 mg TAK-925/placebo as single doses in 2 treatment periods, with a washout period of at least 7 days. Following review of the safety, tolerability, and PK in these cohorts, 6 healthy elderly adult subjects received a single IV dose of 112 mg TAK-925 and 2 subjects received placebo. Cohort 4 will assess the safety and tolerability, and PK of TAK-925 including the concentration of TAK-925 in the CSF in 4 healthy adults.

TAK-925 was safe and tolerable in dose range tested between 7 mg and 134.4 mg (as of 19 February 2018). PK parameters showed dose proportional increases with a relatively longer half-life (approximately 3 to 5 hours) in man than in animals.

A total of 16 subjects were initially dosed; however, in the first cohort (7 mg/placebo), 1 subject experienced a headache, and withdrew from the study. This subject was later diagnosed with influenza (headache included under symptom term). Subsequent cohorts that included that panel had 7 rather than 8 subjects. No other subject withdrawals have occurred. There have been no serious adverse events (SAEs) or severe adverse events (AEs).

All AEs except influenza (considered as moderate) were mild in severity. All cardiovascular effects related AEs (BP increased, pulse rate increased) were considered as mild.

A summary of blinded treatment-emergent adverse event (TEAE) data (verbatim terms) reported in Cohorts 1 and 2 (healthy adult subjects) and Cohort 3 (healthy elderly adult subjects) in Study TAK-925-1001 is provided in Table 4.a and Table 4.b, respectively.

Table 4.a Summary of Blinded TEAE Data From Study TAK-925-1001 (Cohorts 1 and 2, Healthy Adult Subjects [a])

	Number of Events					
	Part 1 SRD Cohorts 1-2 TAK-925 or Placebo (Healthy Adults [a])					
Verbatim Term	7 mg n=8	14 mg n=8	28 mg n=7	56 mg n=8	112 mg n=7	134.4 mg n=8
Any TEAE	**2**	**0**	**1**	**3**	**1**	**7**
Orthostatic hypotension	1	0	0	0	0	0
Influenza	1	0	0	0	0	0
Electrocardiogram PR prolongation	0	0	1	0	1	0
Pharyngodynia	0	0	0	1 [b]	0	0
White blood cell count increased	0	0	0	1	0	0
Triglyceride increased	0	0	0	1	0	0
Pulse rate increased	0	0	0	0	0	3
Blood pressure increased	0	0	0	0	0	2
Nausea	0	0	0	0	0	1
Feeling drunk	0	0	0	0	0	1

Abbreviations: SRD, single rising dose; TEAE, treatment-emergent adverse event.
[a.] Aged 20 to 55 years, inclusive.
[b] Predose.

Table 4.b Summary of Blinded TEAE Data From Study TAK-925-1001 (Cohort 3, Healthy Elderly Adult Subjects [a])

	Number of Events
	Part 1 SRD Cohort 3 TAK-925 or Placebo
Verbatim Term	112 mg (Healthy Elderly Adults [a]) n=8
Any TEAE	**4**
Blood pressure increased	4

[a.] Aged 65 to 80 years, inclusive.

Please refer to the TAK-925 Investigator's Brochure for available clinical information on the investigational product.

4.3.2 Modafinil

Modafinil is approved in the United States as Provigil and name brand drug will be supplied for this study. The most serious risks noted in the prescribing information are noted below.

There is a very low risk of serious rash, which may require hospitalization and discontinuation of treatment in adults in association with the use of modafinil. The risk is even lower with only 1 dose of the drug. The full prescribing information notes that no serious skin rashes have been reported in adult clinical studies (0 per 4264) of modafinil. Rare cases of serious or life-threatening rash, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms have been reported in adults and children in worldwide postmarketing experience. The reporting rate of toxic epidermal necrolysis and Stevens-Johnson syndrome associated with modafinil use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate.

There are no factors that are known to predict the risk of occurrence or the severity of rash associated with modafinil. Nearly all cases of serious rash associated with modafinil occurred within 1 to 5 weeks after treatment initiation. Although benign rashes also occur with modafinil, it is not possible to reliably predict which rashes will prove to be serious. Accordingly, modafinil should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug-related. Discontinuation of treatment may not prevent a rash from becoming life-threatening or permanently disabling or disfiguring.

One serious case of angioedema and 1 case of hypersensitivity (with rash, dysphagia, and bronchospasm), were observed among 1595 patients treated with armodafinil, the *R*-enantiomer of modafinil (which is the racemic mixture). No such cases were observed in modafinil clinical studies. However, angioedema has been reported in postmarketing experience with modafinil.

Multi-organ hypersensitivity reactions, including at least 1 fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days: range 4-33) to the initiation of modafinil. Although there have been a limited number of reports, multi-organ hypersensitivity reactions may result in hospitalization or be life-threatening. There are no factors that are known to predict the risk of occurrence or the severity of multi-organ hypersensitivity reactions associated with modafinil. If a multi-organ hypersensitivity reaction is suspected, Provigil should be discontinued.

In the adult modafinil controlled trials database, psychiatric symptoms resulting in treatment discontinuation (at a frequency >0.3%) and reported more often in patients treated with modafinil compared to those treated with placebo were anxiety (1%), nervousness (1%), insomnia (<1%), confusion (<1%), agitation (<1%), and depression (<1%). Caution should be exercised when Provigil is given to patients with a history of psychosis, depression, or mania.

BP monitoring in short-term (<3 months) controlled trials showed no clinically significant changes in mean SBP and diastolic blood pressure (DBP) in patients receiving Provigil as compared to placebo.

Please refer to the current package labeling for modafinil for detailed information regarding the safety risks and risk mitigation measures for modafinil.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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).

5.1.2 Secondary Objectives

1. 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.)

2. 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 [18].

3. 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).

5.1.3 Exploratory Objectives

In sleep-deprived healthy volunteers:

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5.2 Endpoints

5.2.1 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.

5.2.2 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.

5.2.3 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).

5.2.4 Exploratory Endpoints

Exploratory endpoints will be assessed through the following parameters:

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6.0 STUDY DESIGN AND DESCRIPTION

6.1 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 6.a.

Table 6.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

Abbreviations: HD, high dose; LD, low dose.

At the screening visit, subjects will complete medical examinations, an electrocardiogram (ECG), and clinical laboratory tests. After the screening visit, eligible participants will wear an actigraph from Day -6 until Day -1. After validation that actigraphy a normal sleep-wake cycle, and subjects have a negative drug screen, subjects will undergo an 8-hour nocturnal polysomography (NPSG) to exclude any sleep disorders. Actigraphy results will also be collected for the 5-night period before Day-1 (Day -6 to Day -1) for every treatment period to ensure that sleep falls within normal nocturnal times (defined under Inclusion Criteria).

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 6.b.

Table 6.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.

6.2 Rationale for Study Design, Dose, and Endpoints

6.2.1 Rationale of Study Design

The study population chosen for this study consists of males aged 18 to 40 years who are generally in good health and normotensive (see inclusion/exclusion criteria for specifics). Healthy males only are being used in this study to minimize any inter- and intra-individual variability related to between gender effects of the sleep cycle, as well as potential effects of the menstrual cycle on sleep. The age range specified is to again to mitigate against any effects of older age on sleep, as well as the higher likelihood of sleep abnormalities that rises with increasing age. This cohort is similar to that in other investigational drug studies with sleep deprivation in healthy normal subjects.

This 4-period, Williams design crossover study is a design that has been previously used in other studies of drugs that have been evaluated for effects on wakefulness [18]. While there is a risk of dropouts during the study, a relatively short time between periods will aid in subject retention. A crossover design requires fewer subjects than a parallel group design, as treatment comparisons are based on intra-subject differences which are typically associated with smaller variability than between-subject differences. The study is directly translational from the data obtained in normal animals including 2 species of non-human primates.

Nighttime is considered the most appropriate time period to evaluate the efficacy of TAK-925 in this sleep-deprived model study since there is evidence that OX levels are relatively lower during the nighttime compared to daytime. Considering the MOA of TAK-925, it is a reasonable assumption that the sensitivity to detect the efficacy of TAK-925 in healthy normal persons should be greater during nighttime.

Modafinil 300 mg, a standard treatment for EDS, will be included as an active reference compound. Modafinil is one of the most commonly used stimulants for narcolepsy, hypersomnolence associated with obstructive sleep apnea and shift-work disorder. Modafinil has previously been evaluated in both narcolepsy studies [19] and in sleep deprivation studies in healthy volunteers [20]. The t_{max} of modafinil is approximately 3 hours and in sleep-deprived healthy volunteers, MWT or efficacy on cognitive tests has been detected at approximately t_{max} post administration. Compared with placebo, modafinil showed greater effects on wakefulness on the MWT sleep latency in both sleep-deprived healthy volunteers and in narcolepsy patients, with 9-minute and 6-minute increases in sleep latency, respectively [1,21]. Modafinil loses its PD effects at 10 hours post dosing, which is close to the same duration of the 9-hour TAK-925 infusion. The timing of the dose of modafinil will be given so that t_{max} is achieved at the time of the first MWT. Modafinil will be given 1 hour before the start of the IV infusion. The study is not powered for use of modafinil as an actual comparator compound.

A double-dummy design will be used. Subjects receiving modafinil will receive IV normal saline. Those receiving TAK-925 will be given an oral (PO) placebo capsule.

6.2.2 Rationale for Dose

Based on the currently available information, this study will evaluate 2 dose levels of TAK-925, a low dose of 44 mg (LD) and high dose of 112 mg (HD). The HD of 112 mg was selected based on the safety and tolerability results in adult subjects from the ongoing FIH TAK-925-1001 study. Doses up to and including 134.4 mg, the maximum dose tested so far in healthy volunteers, were safe and well tolerated with no severe AEs or SAEs. All subjects dosed with 112 mg TAK-925 had acceptable safety and tolerability during the 9-hour IV infusion. The 44 mg LD was selected to evaluate a dose that may result in effects on wakefulness (as assessed by the MWT) that are greater than those of placebo, based on nonclinical studies, but are associated with systemic exposures of TAK-925 that are pharmacologically different those expected at the HD of 112 mg. Based on

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CCI [redacted]. Thus, the potential difference in the pharmacological response to TAK-925 has also been taken into consideration when choosing the LD and HD in sleep-deprived healthy subjects.

6.2.3 Rationale for Endpoints

6.2.3.1 Primary Endpoint

Effect on wakefulness as measured by sleep latency on the MWT was selected as the primary endpoint. The MWT is a validated objective measure that has been often used as a primary efficacy endpoint to measure EDS in clinical studies. An approximate 9-minute increase over placebo is considered as a benchmark PD effect size of TAK-925 in this study, based on the efficacy of modafinil 200 mg in a similar study in a sleep-deprived healthy population [18]. Note that the dose of modafinil used in this study will be 300 mg, which has been selected to demonstrate assay sensitivity.

6.2.3.2 Secondary Endpoints

KSS

The KSS is helpful in assessing the changes in response to the effects of drugs and is a measure of situational sleepiness. It is sensitive to fluctuations. It has been used in studies of shift work, jetlag, for driving abilities, attention and performance, and in clinical settings. It is helpful in assessing the changes in response to environmental factors, circadian rhythm, and effects of drugs. In a study conducted by [22,23] the authors investigated the validity of the KSS and found that it was highly correlated to EEG and behavioral variables. The results show that KSS has a high validity.

CCBT

The CCBT has been used in studies on sleep deprivation and shift work-related cognitive impairment and the potential for detection of pharmacological remediation has also been evaluated (internal data, Cambridge Cognition). Reaction time related batteries in the CCBT have shown significant deterioration with sleep deprivation [24-26].

Wearable Devices

Wearable digital devices will be implemented in this study for monitoring biometric and physical activities associated with the sleep-wake cycle. An actigraphy device will capture data on the subject's activity level, including intensity of movement, rest, and sleep. The primary purpose of this data is to confirm that the subject has maintained normal sleep/wake life habits before study drug administration.

BP data will be collected using a wrist- or finger-based device for measurement of radial arterial pressure or digital arterial pressure. BP data will be collected during PSG monitoring and continuous drug infusion to provide ample data for evaluation of PK-PD relationships between TAK-925 and BP versus placebo and BP. Outcome of these PK-PD analyses will help to inform assessment of the effects of TAK-925 on BP.

6.2.3.3 Exploratory Endpoints

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6.2.3.4 Safety Endpoints

The safety endpoints of TEAEs, vital signs, 12-lead ECGs, and clinical laboratory evaluations (including hematology, chemistry, and urinalysis) are standard methods for assessing safety and tolerability of drugs in clinical studies.

The drug-liking VAS is a standard tool for assessing drug abuse potential. Many stimulant drugs are scheduled substances based on the potential for abuse. While TAK-925 is early in development, it is important to begin assessing the potential for abuse. An assessment of drug liking will be included. Since, TAK-925 has central nervous system (CNS) activity in animals and is expected to have CNS activity in humans, abuse potential will be assessed. TAK-925 is theorized to have a low potential for abuse probability based on its high selectivity for OX2R over OX1R [28]. Preliminary information relevant to the potential for abuse could be informative for further development of TAK-925.

The POMS is a well-validated self-report measure of mood states, and has high internal consistency as well as predictive and constructive validity. POMS is used in many clinical studies including research in narcolepsy populations [29].

Subjects will be monitored for any signs of suicidal ideation or behaviors using the C-SSRS.

BP increase is an identified risk from nonclinical safety studies. In the FIH study (TAK-925-1001), mild BP increase or HR increase were reported in 2 healthy normal subjects out of 8 subjects at the 134.4 mg dose level during study drug infusion. Continuous BP measurements will be obtained in this study to further characterize PK-PD relationships with any BP increase that may be observed after administration of TAK-925.

6.2.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, the MWT is the critical procedure and should be performed as close to the scheduled time as possible.

- Blood samples for PK evaluations must be drawn as close as possible to the specified time.
- ECG and vital sign measurements should be completed before blood sampling if the timing of these assessments overlap.
- All other procedures should be performed as close as possible (either before or after) the scheduled times.
- The suggested order of the PD assessments of each treatment period is as follows:
  - MWT.
  - KSS.
  - CCBT.
  - POMS.
- The order of priority can be changed during the study with joint agreement of the investigator and the sponsor.
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study subjects.

Some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data.

The following may occur:

- Changes in the dose of the study drug administered may occur.
- The interval between doses may be lengthened if supported by safety, PD, and PK evidence.
- The PK/PD sampling scheme may be modified during the study based on newly available PK or PD data (eg, to obtain data closer to the t_{max}). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional PD markers.
- For PK blood draw, the timing of sampling collection may be changed without changing the total number of samples which will be taken based on TAK-925-1001 study PK data.

- Additional MWT, neuropsychological tests (CCBT), and KSS evaluations could be added to characterize PK-PD relationships of TAK-925 based on TAK-925-1001 study results.
- Up to an additional 50 mL of blood may be drawn for PK and/or PD analyses. This blood volume may include repeat samples or modified PK/PD time points based on emerging data. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire study.
- The timing of planned procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, PK, or PD/biomarker data (eg, to obtain data closer to the time of peak plasma concentrations). These changes will not increase the number of study procedures for a given subject during his/her participation in the entire study.
- Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (eg, adding creatine kinase to serum chemistry panel that was already drawn).

It is understood that the current study may employ some or none of the alterations described above. Any alterations described above made to this protocol to meet the study objectives must be detailed by the sponsor in a letter to the Trial Master File and forwarded to the investigator for retention. The letter will be forwarded to the institutional review board (IRB)/independent ethics committee (IEC) at the discretion of the investigator.

6.4 Study Beginning and End/Completion

6.4.1 Definition of Beginning of the Study

The overall study begins when the first subject signs the study informed consent form.

6.4.2 Definition of End of the Study

The overall study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the study, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.4.3 Definition of Study Discontinuation

Study discontinuation because of nonsafety reasons, such as the following:

- A finding (eg, PK, PD, efficacy, biologic targets) from another nonclinical or clinical study using the study treatment(s) results in the study being stopped for a nonsafety-related reason.
- Data from comparator(s), drug(s) of the same class, or methodology(ies) used in this study become available and results in the study being stopped for a nonsafety-related reason.
- The study is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.

Study discontinuation because of safety reasons:

- Early study termination because of unanticipated concerns of safety to the study subjects arising from clinical or nonclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

6.4.4 Criteria for Premature Termination or Suspension of the Study

6.4.4.1 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of Good Clinical Practice (GCP), protocol, or contractual agreement, or is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.4.4.2 Procedures for Premature Termination or Suspension of the Study or the Participation of the Study Sites

In the event that the sponsor, an IRB/IEC, or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Be willing and able to comply with all study procedures and restrictions.
3. Be a healthy male, aged 18 to 40 years, inclusive, at the screening visit.
4. Have a body mass index (BMI) ≥18.5 and ≤30.0 (kg/m^2) at the screening visit.
5. Be a nonsmoker or have not used tobacco- or nicotine-containing products (eg, nicotine patch, chew, e-cigarettes, etc.) for at least 6 months before study drug administration of the initial dose of study drug.
6. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the screening visit and before administration of the initial dose of study drug/invasive procedure.
7. Meet the following birth control requirements:
    - Is a male subject who is sterile or agrees to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly, from the first dose of study drug until <5 half-lives plus 90 days> after the last dose of study drug. No restrictions are required for a vasectomized male subject provided the subject is at least 1 year postbilateral vasectomy procedure before the first dose of study drug. A male subject whose vasectomy procedure was performed less than 1 year before the first dose of study drug must follow the same restrictions as a nonvasectomized man. Appropriate documentation of surgical procedure should be provided.
    - Is a male subject who agrees to not donate sperm from study drug administration on the first day of the first dose until 5 half-lives plus 90 days after the last dose of study drug administration.
8. Have regular sleep-wake habits (eg, routinely spending 6.5 to 8 hours sleeping nightly, not oversleeping by more than 3 hours, ie, total sleep not more than 11 hours) as determined by investigator interviews and confirmed in 5-day actigraphy records and whom regularly fall asleep between 9:30 PM and 12:00 AM.
9. Be willing to have actigraphy monitoring during the week before randomization and in each interval.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Has participated in another investigational study within 4 weeks (or based on local recommendations) before the pretrial (screening) visit. The 4-week window will be derived from the date of the last study procedure and/or AE related to the study procedure in the previous study to the screening visit of the current study.
2. Is an employee or immediate family member (eg, spouse, parent, child, sibling) of the clinical research unit or of the sponsor.
3. Has a history of cancer (malignancy).
4. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerability to prescription or nonprescription drugs or food.
5. Has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), or HIV antibody/antigen, at Screening. Note: Subjects with positive hepatitis B virus (HBV) or HCV serology may be enrolled if quantitative polymerase chain reaction for HBV or HCV viral RNA is negative.
6. Has a positive alcohol or drug screen at screening.
7. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the pretrial (screening) visit.
8. Is unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 7 days before administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), until the poststudy visit. Excluded food substances and medications are listed in Appendix 4.
9. Has a history of alcohol consumption exceeding 2 standard drinks per day on average (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce] per day).
10. Has excessive sleepiness defined by a self-reported Epworth Sleepiness Scale score at screening greater than 10; irregular work hours; or routine night-shift work within 1 month before randomization.
11. Currently experiencing or having a history of any known/suspected sleep disorder, any disorder associated with EDS, or any diagnosis interfering with assessment of sleepiness.
12. Abnormal findings on the initial PSG conducted on Day -1 (check-in), as specified in the study manual.
13. Traveled across 2 or more time zones 2 weeks or less before screening or any time during study participation.

14. Current or previous history of serious, severe, or unstable physical or psychiatric illness that may affect sleep or wakefulness; current or past history of epilepsy or convulsion; or any medical disorder that may make the full completion of the study unlikely.
15. Caffeine consumption of more than 400 mg/day for 2 weeks before screening (1 serving of coffee is approximately equivalent to 120 mg of caffeine).
16. Participants treated with medications with CNS effects within 14 days of check-in including sedating antihistamines, decongestant sympathomimetics, and/or monoamine oxidase inhibitors. Participants need to comply with conventional phase 1 pharmacology study prohibited/excluded medications specified in protocol.
17. Hypertension or history of hypertension. SBP ≥140 mmHg or DBP ≥90 mmHg is excluded.
18. Other significant cardiovascular risk factors including abnormal ECG QT interval findings and HR.
19. Screening ECG reveals a QT interval with Frederica correction method (QTcF) >450 milliseconds.

7.3 Excluded Medications, Supplements, Dietary Products

7.3.1 Concomitant Medications

The use of concomitant medications (see Section 9.1.3) 7 days before administration of the first dose of study drug, throughout the study (including the washout interval between treatment periods), and until the follow-up visit is not permitted. Subjects must be instructed not to take any medications without first consulting with the investigator. Any concomitant medication use must first be discussed with the sponsor, unless the investigator or designee considers immediate administration is necessitated.

The occasional use of acetaminophen (approximately <1 g/day) is allowed.

7.3.2 Fruit Juice

Subjects will refrain from consuming grapefruit juice, grapefruits, and products containing grapefruit beginning approximately 7 days before administration of the first dose of study drug, throughout the study (including the washout interval between treatment periods), and until the follow-up visit.

Subjects also will refrain from consuming all juices 12 hours before and after administration of each dose of study drug on PK sampling days (Days 1 and 2 of each treatment period). Consumption of all fruits other than grapefruit is allowed on all days of the study.

7.3.3 Alcohol

Alcohol consumption is not allowed during the entire study.

7.3.4 Caffeine

Subjects will refrain from consuming caffeinated beverages 24 hours before the screening visit and follow-up visit and from 24 hours before and until the last PK blood sample has been collected in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 400 mg/day.

7.3.5 Smoking

Smoking or use of nicotine or tobacco products is not allowed during the entire study.

7.4 Diet, Fluids, and Activity

7.4.1 Diet and Fluids

On Day 1, study drug will be administered beginning at approximately 9:45 PM for tablet (modafinil or placebo) and approximately 10:45 PM for IV infusion (TAK-925 or placebo) for each treatment period. The modafinil or matching placebo will be given with 240 mL of water for PO administration. Subjects will be NPO for 2 hours after the PO modafinil/placebo administration.

Since study drug administration does not begin until evening, subjects will have a standard breakfast, lunch, and dinner on Day 1. Snacks may be given up until approximately 8:30 PM on the day of dosing (Day 1). No other food will be consumed until breakfast on Day 2. Subjects will fast from all food and drink except water between meals and snacks. The caloric content and composition of meals will be the same for all subjects in each treatment period. On Day 2, breakfast will be provided after the fourth MWT, KSS, and cognitive testing have been completed. After the postdose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition, and timing.

Subjects will refrain from consuming mustard greens (ie, kale, broccoli, watercress, collard greens, kohlrabi, Brussel sprouts, and mustard) and charbroiled meat 7 days before administration of the first dose of study drug, throughout the study (including the washout interval between treatment periods), and until the follow-up visit.

7.4.2 Activity

Subjects will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc) from the screening visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods), and until the follow-up visit.

Starting at approximately 8:30 PM, the subject's activities will be restricted so that they are not overstimulated or upset. Cell phone use will be restricted from approximately 8:30 PM until after recovery sleep the next day. Activities permitted from approximately 8:30 PM on until the start of recovery sleep are board games, puzzles, adult coloring books, drawing, reading, listening to music (not on cell phones), watching television or non-violent movies, and walking and talking

with other participants/staff. Subjects may bring in small craft projects they are interested in or are working on.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

    - Liver Function Test (LFT) Abnormalities:

      Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.2.13.1), if the following circumstances occur at any time during the study drug treatment:

      – Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8x upper limit of normal (ULN), or

      – ALT or AST >5x ULN and persists for more than 2 weeks, or

      – ALT or AST >3x ULN in conjunction with elevated bilirubin >2x ULN or international normalized ratio (INR) >1.5 ULN, or

      – ALT or AST >3x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

    - Suicidality:

      – Study drug should be discontinued immediately for subjects at imminent risk of suicide per the C-SSRS (score of 5) or per the investigator's clinical judgment.

    - BP increase:

      – Sustained SBP >180 mmHg, sustained DBP >110 mmHg, or sustained increase in SBP >40 mmHg from baseline (measured just before the start of infusion).

2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary

underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Other. Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination visit.

If a BP reading meets 1 of the criteria outlined in Section 7.5, the BP will be repeated at 5 minutes to confirm the value. If the subject has no cardiac or neurological symptoms, BP will continue to be observed at 15-minute intervals. If there are cardiac or neurological symptoms, the drug should be discontinued immediately, and the subject treated to lower BP according to the best judgment of the investigator and in accordance with good medical practice, and further emergency medical evaluation sought. Elevation to >200 mmHg SBP or >120 mmHg DBP will result in immediate discontinuation of drug. Sustained BP elevation at values >180 mmHg and ≤ 200 mmHg SBP, >110 mmHg and ≤120 mmHg DBP, or a sustained increase of 40 mmHg SBP will result in the infusion being discontinued, with duration of increased BP tolerated being 1 hour or based on investigator judgment and in accordance with good medical practice. If the BP does not fall after drug discontinuation within 30 to 60 minutes, the subject should be treated according to the best judgment of the investigator and in accordance with good medical practice. If the drug is discontinued in any one subject due to a BP increase, the subject will not be rechallenged with TAK-925 infusion.

7.7 Subject Replacement

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.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Details regarding the composition and extemporaneous preparation of the active drug and placebo are found in the Pharmacy Manual. Clinical study drug will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the sponsor needs to be contacted before dosing.

8.1.1 Clinical Study Drug Labeling

Clinical study drug will be affixed with a clinical label in accordance with regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

Clinical study drug must be stored in a secure, limited-access location under the storage conditions specified on the label. Inventory (receipt and dispensing) of study drug must be recorded by an authorized unblinded person at the trial site.

8.1.3 Clinical Study Drug Blinding

This is a double-blind study; the investigator and subjects are blinded to treatment assignment. Study drug will be provided to an unblinded pharmacist or other qualified study site personnel who will blind the study supplies. Treatment identity (name and strength or potency) will be included on the study drug container label; randomization code/disclosure envelopes or lists will be provided.

8.1.4 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

The clinical study drug blind will be maintained through a randomization schedule held by the site unblinded pharmacist. The clinical study drug blind shall not be broken by the investigator unless information concerning the clinical study drug is necessary for the medical treatment of the subject. If possible, the medical monitor should be contacted before the study drug blind is broken. Unblinding will be performed per the standard operating procedures of the site contract research organization.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator is responsible for keeping accurate records of the clinical study drug received from the sponsor or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the end of the study. For all study sites, the local country sponsor personnel or designee will provide appropriate documentation that must be completed for clinical study drug accountability, return, and destruction.

9.0 STUDY PROCEDURES

The following sections describe the study procedures to be performed and data to be collected as indicated in the Schedule of Study Procedures (Section 3.0). For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Please note that it may become necessary to perform the following procedures at unscheduled time periods, per the discretion of the investigator.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

Informed consent must be obtained before the subject enters the study and before any protocol-directed procedures are performed. The requirements of informed consent are described in Appendix B.

9.1.1.1 Assignment of Screening and Randomization Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur before randomization or allocation. Each subject will be assigned only 1 screening number. Screening numbers must not be reused for different subjects. Any subject who is screened multiple times will be assigned a new screening number for each screening event.

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be reassigned to another subject. A single subject cannot be assigned more than 1 randomization number.

9.1.1.2 Study Drug Assignment

On Day 1 of Treatment Period 1, subjects will be assigned a randomization number in ascending numerical order at the clinical site. The randomization number encodes the sequence in which each subject will receive TAK-925 LD mg, TAK-925 HD mg, modafinil, or placebo, according to the randomization schedule generated before the study. Each subject will be dispensed blinded study drug, labeled with his/her unique randomization number, throughout the study.

9.1.2 Inclusion and Exclusion

Each subject will be assessed through randomization, according to the eligibility criteria provided in Section 7.0.

9.1.3 Medical History, Demographics, and Prior and Concomitant Medications

Qualified site personnel will collect subject significant medical history (past and concurrent medical conditions), per the site's standard of care and appropriate clinical judgment, and also subject demographics.

Qualified site personnel will review subject prior and concomitant medication use. Medications are defined as prescription and over-the-counter drugs, vaccines, supplements, nutraceuticals, and PO herbal preparations.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Examination

Qualified site personnel will conduct full physical examinations.

9.2.2 Height and Weight

Body weight and height will be obtained with the subject's shoes off, and jacket or coat removed.

9.2.3 BMI

BMI equals a subject's weight in kilograms divided by height in meters squared (BMI=kg/m^2). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4, round down, and 0.5 to 0.9, round up.

9.2.4 Vital Signs

Body temperature will be measured with an oral (temperature taken at floor of the mouth) or tympanic thermometer. The same method (ie, oral or tympanic) must be used for all subsequent measurements for each individual subject and should be the same for all subjects.

Subjects should rest in a bed with the head of the bed at 30 degrees for at least 5 minutes before vital signs are measured. Vital signs will include HR, respiratory rate, SBP, and DBP. The same method (eg, same size cuff, manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

Subjects should continue to rest in a bed with the head of the bed at 30 degrees from the time of dosing until 4 hours postdose except to stand for the measurement of standing vital signs (if needed) or other trial-related procedure.

9.2.5 Continuous Monitoring with Digital Technology

BP data will be collected using a wrist- or finger-based device for measurement of radial arterial pressure or digital arterial pressure. BP and HR will be continuously monitored during the confinement period. BP data will be collected during the NPSG on the first night of the study and continuously during study drug infusion such that time points of BP collection during these periods are approximately matched.

9.2.6 12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Subjects may need to be shaved to ensure proper lead placement.

Subjects should be resting in a semirecumbent position for at least 5 minutes before each ECG measurement.

QTcF intervals will be calculated in this study.

For each treatment period, a predose ECG will be obtained within approximately 1 hour before study drug dosing. This measurement will be used as the baseline assessment. The principal investigator should arrange to have a study cardiologist available as needed to review ECG tracings with abnormalities.

During each treatment period, if a subject demonstrates an increase in QTcF interval ≥40 milliseconds compared with a predose baseline measurement, the ECG will be repeated within 5 minutes. The average value of the QTcF interval from the 2 ECGs will represent the value at that time point. If the average QTcF interval increase from baseline for any postdose time point is ≥40 milliseconds, the subject will continue to be monitored by repeat 12-lead ECGs every 60 minutes for at least 4 hours or until the QTcF interval is within 40 milliseconds of the baseline value. If prolongation of the QTcF interval ≥40 milliseconds persists, a consultation with a study cardiologist may be appropriate and the sponsor should be notified.

If the QTcF interval is ≥500 milliseconds, the sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be monitored by telemetry (until the QTcF interval is <500 milliseconds) or should be considered for transfer to a location where closer monitoring is available.

If the subject has unstable hemodynamics, or has any clinically significant dysrhythmias noted by telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

The following ECG parameters will be recorded: HR, PR interval, QRS interval, QT interval, QTcF interval, and the interpretation of the ECG profile by the principal investigator.

9.2.7 Study Drug Administration

On Day 1 of each treatment period, trial drug (TAK-925 LD mg, TAK-925 HD mg, modafinil [300 mg], or placebo) will be administered as described in Section 7.4.1.

9.2.8 C-SSRS

Suicidal ideation will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures (see Section 3.0). Two versions of the C-SSRS will be used in this study: the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS. Any suicidal ideation or suicidal behavior during trial periods detected by C-SSRS will be recorded as AEs. The

investigator will ensure that any suicidal ideation or behavior is medically addressed, including assessment and treatment by qualified medical personnel.

9.2.9 Drug-Liking VAS

Following recovery sleep in each treatment period, subjects will undergo a self-administered 100-point (0 = strongly dislike to 100 =strongly like) drug-liking VAS to assess abuse potential.

9.2.10 Actigraphy

Subjects will be monitored with actigraphy from Day -6 through Day -1 of each treatment period to confirm that subjects have a normal sleep-wake cycle (defined as at least 6 hours of sleep per night, and other criteria as specified in the inclusion/exclusion criteria). The actigraphy will be deployed on Day -6 and used continuously until subjects arrive at the study site. Actigraphy data will not be collected while subjects are confined.

9.2.11 Sleep Deprivation

Subjects will be required to stay awake in between MWT tests. During the MW study, subjects will be instructed to sit quietly and remain awake for as long as possible during each of the 40-minute MWT sessions. Each MWT test will be terminated after 40 minutes of wakefulness or after the onset of an EEG-detected sleep signal lasting up to 30-second epoch of any sleep stage.

9.2.12 AE Monitoring

AE monitoring begins after signing of the informed consent form. Changes in subject health status from the baseline assessment until study drug administration should be captured in the subject's medical history. A complete description of AE collections and procedures is provided in Section 10.0.

9.2.13 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. Samples will be taken on the days stipulated in the Schedule of Study Procedures (Section 3.0).

9.2.13.1 Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

Erythrocytes (RBCs)	Leukocytes (WBCs) with absolute differential
Hematocrit	Platelets
Hemoglobin	

Abbreviations: RBCs, red blood cells; WBCs, white blood cells.

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Chloride
Alkaline phosphatase	Creatinine
ALT	GGT
AST	Glucose
Bilirubin (total), if above ULN total bilirubin will be fractionated	Potassium
Blood urea nitrogen	Protein (total)
Calcium	Sodium
Carbon dioxide	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transferase; ULN, upper limit of normal.

If subjects experience ALT or AST >3× ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

If ALT or AST remains elevated >3× ULN on these 2 consecutive occasions, the investigator must contact the medical monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, and discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE.

Please refer to Section 7.5 for subject discontinuation criteria regarding abnormal LFTs and Section 10.2.8.4 for guidance on reporting abnormal LFTs.

Urinalysis

Urinalysis will consist of the following tests:

Blood	Nitrite
Glucose	Protein

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of red blood cells/high-power field, white blood cells/high-power field, and casts.

9.2.13.2 Diagnostic Screening

Serum

The serum diagnostic screening assessment will include the following tests:

HIV	Hepatitis screen (HBsAg, HCV)

Abbreviations: HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Alcohol Screen

Subjects will undergo an alcohol breath test. A urine alcohol test may be performed at the discretion of the investigator.

Urine Drug Screen

The urine drug screening assessment will include the following tests:

Amphetamines	MDMA
Barbiturates	Methadone/metabolite
Benzodiazepines	Opiates
Buprenorphine/metabolite	Oxycodone/oxymorphone
Cannabinoids	Phencyclidine
Cocaine/metabolites	

Abbreviation: MDMA, 3,4-methylenedioxy-methamphetamine.

9.3 PK, Biomarker, PD, and Pharmacogenomic Samples

9.3.1 PK, Biomarker, PD, and Pharmacogenomic Evaluations

Samples for PK, biomarker, PD, and pharmacogenomic (PGx) analysis will be collected as specified in the Schedule of Study Procedures (Section 3.0). Please refer to the Laboratory Manual for information on the collection, processing, and shipment of samples to the central laboratory.

The decision as to which plasma samples collected will be assayed for evaluation of PK will be determined by the sponsor. If indicated, these samples may also be assayed and/or pooled to measure metabolites in an exploratory manner.

It is anticipated that the total blood volume drawn in this study will be approximately 285 mL.

Primary specimen collection parameters are provided in Table 9.a.

Table 9.a Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Blood sample for PGx	Blood	DNA	Blood sample for PGx analysis	Optional
Plasma sample for PK	Blood	Plasma	Plasma sample for PK	Mandatory

Abbreviations: PGx, pharmacogenomic; PK, pharmacokinetics.

9.3.2 PK Measurements

The PK parameters of TAK-925 and its metabolites M-I and M-II 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.

The following PK parameters will be calculated from plasma concentrations of TAK-925 and its metabolites M-I and M-II, as data permit:

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

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

The PK profile of modafinil has already been reported and will not be evaluated in this study.

9.3.2.1 Plasma for PK Measurements

Blood samples (one 3-mL sample per scheduled time) for PK analysis of TAK-925 will be collected into chilled blood collection tubes (vacutainer) containing the anticoagulant dipotassium ethylenediaminetetraacetic acid (K_2EDTA) according to the schedules in Section 3.0.

The actual time of sample collection will be recorded on the source document and eCRF. Sampling time points may be adjusted based on the preliminary emerging concentration data collected from prior subject(s), but the total number of samples collected per subject should not exceed the planned number.

Instructions for collecting, processing, and shipping of PK samples are provided in the Laboratory Manual.

9.3.2.2 PK Sample Analysis

Plasma concentrations of TAK-925 and its metabolites MI and MII will be measured by a validated high-performance liquid chromatography with tandem mass spectrometry assay. Part of the archival plasma samples may be used for potential analysis of unknown metabolite characterization, if appropriate.

9.3.3 Biomarker Measurements

EEG will be used as the primary translational biomarker to assess the efficacy of TAK-925. There is the potential to add other biomarkers which are reported to be increased by sleep disturbances, including serum superoxide dismutase, plasma Aβ42, low-density lipoprotein receptor-related protein, and soluble receptors for advanced glycation end products [30,31]. However, as the study is being conducted in healthy normal subjects who are undergoing only 1 night of sleep deprivation in each period, the likelihood of finding significant changes, as well as changes related to study drug, is low. Therefore, fluid biomarkers will not be collected in this study.

9.3.4 PD Measurements

The PD assessments described below will be performed according to the Schedule of Study Procedures in Section 3.0. Additional details regarding these PD assessments are provided in the Study Manual.

9.3.4.1 PSG

Subjects will undergo an 8-hour (11:00 PM-7:00 AM) NPSG to exclude any sleep disorders. The PSG will be evaluated shortly after completion utilizing the American Academy of Sleep Criteria Scoring to ensure that subjects do not have an abnormal PSG before randomization into the study (scoring criteria specified in study manual). The Day -1 PSG will be performed once; subsequent treatment periods will not require the NPSG before dosing and testing.

When the final MWT test and cognitive testing has been completed, subjects will be allowed to sleep (recovery sleep) for at approximately 6 hours. PSG recording will be done during this time.

9.3.4.2 MWT

The MWT is a validated objective measure that evaluates a person's ability to remain awake under soporific conditions for a defined period of time. As there is no biological measure of wakefulness, this is measured indirectly by the inability or delayed tendency to fall asleep. This tendency to fall asleep is measured via EEG-derived sleep latency in MWT.

9.3.4.3 KSS

The KSS is a 9-item Likert-type rating scale for assessing subjective sleepiness. 1 = very alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy (but not fighting sleep), 9 = very sleepy (fighting sleep). This scale measures the subjective level of sleepiness at a particular time during the day. On this scale subjects indicate which level best reflects the psycho-physical sate experienced in the last 10 minutes.

9.3.4.4 CCBT

The CCBT is a computer-based cognitive assessment system consisting of a battery of several neuropsychological tests relevant to the effects of sleep deprivation. The cognition areas covered by the battery include reaction time, processing speed, attention and sustained vigilance, and episodic memory. The test battery will take approximately 20 minutes.

9.3.4.5 POMS

The POMS is a well-validated self-report measure of mood states. The original English version consists of 65 items, consisting of adjectives which are rates with regard to the participant's current mood on a 6-point Likert scale ranging from 0 (not at all) to 5 (extremely). Answers provide standardized scores for 6 identified subscales: anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, tension-anxiety, and vigor-activity. Higher scores indicate more negative mood states, except for vigor-activity for which lower scores denote a more negative mood state.

9.3.5 PGx Measurements

9.3.5.1 Blood Sample for DNA PGx Measurements

Sampling of whole blood for PGx analysis is optional in this study and will only be performed for subjects who provide consent to participate in this assessment.

PGx is the study of variations of DNA characteristics as related to drug response. There is increasing evidence that an individual's genetic background may impact the PK (absorption, distribution, metabolism, and excretion), PD (pharmacologic effects), and/or clinical effects (efficacy and/or safety) of a drug.

PGx research in this study may be conducted to understand how individual genetic variation in subjects impacts their response to study drug treatment. This information may also be used, for example, to develop a better understanding of the safety and efficacy of TAK-925 and other study drugs, to increase understanding of the disease/condition being studied and other related conditions, to gain a better understanding of the drug pharmacology, and to generate information needed for research, development, and regulatory approval of tests to predict response to TAK-925.

One 5-mL whole blood sample for DNA isolation will be collected at Day -1 from each consented subject in the study. If necessary and feasible, a second aliquot of blood may be taken at a later time point if isolation of DNA from the first sample was not successful or possible.

Since, PGx is an evolving science, many genes and their functions are not yet fully understood. Future data may suggest a role of these genes in drug response, which may lead to additional hypothesis-generating exploratory research and diagnostic development on stored samples.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

9.3.5.2 Biological Sample Retention and Destruction

In this study, blood samples for PGx analysis will be collected as described in Section 9.3.5.1. The genetic material will be initially stored at a vendor or comparable laboratory, under contract to Takeda, with validated procedures in place, and then preserved and retained at a long-term storage vendor, or a comparable laboratory, with validated procedures in place, for up to but not longer than 15 years from the end of the study when the study report is signed, or if less, the maximum period permitted under applicable law or until consent is withdrawn.

The sponsor and vendors working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access, and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier as in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code

numbers; the samples are stripped of all personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The sample identifier will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided a PGx sample for DNA analysis can withdraw their consent at any time and request disposal of a stored sample. Any remaining sample that can be identified as coming from the subject will be destroyed. The investigator and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

9.3.6 Confinement

Subjects will report to the clinical site on Day -1 in each treatment period and will leave after completion of all study-related procedures on Day 2.

At the discretion of the investigator, subjects may be requested to remain in the clinical site longer.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug.

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a preexisting condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters maybe considered AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication

of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before the signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, to capture this important safety information consistently in the database.

AEs associated with an overdose will be documented on AE case report forms (CRFs) according to Section 10.0.

- SAEs of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild:	An AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
Severe:	An AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which a causal relationship is at least a reasonable possibility, ie, the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.2.3 Start Date

The start date of the AE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.2.4 End Date

The end date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.5 Pattern of AE (Frequency)

Episodic AEs (eg, headache) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.2.6 Action Taken With Study Treatment

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication had not yet started or dosing with study medication was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

- Recovered/resolved – subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis has or signs/symptoms have almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to the baseline value; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving."
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has become worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved."
- Recovered/ Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – an AE that is considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until approximately 30 days after the last dose of investigational product. For subjects who discontinue before the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing an SAE before the first exposure to investigational product must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious AEs that begin before the first exposure to investigational product, related or unrelated to the study procedure, need not be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the

changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with study drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

When an SAE occurs through the AE collection period it should be reported according to the procedure outlined below:

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study medication(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Appendix 14.1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

If information is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and

fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.2.8.4 Reporting of Abnormal LFTs

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.8.3. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.2.13.1 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, suspected unexpected serious adverse reactions will be submitted within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted before database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

The safety set will consist of all subjects who were 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.

11.1.1.2 PK Set

The PK analysis set will consist of all subjects who received at least 1 dose of study drug and have at least 1 measurable plasma concentration.

11.1.1.3 PD Set

The PD analysis set will consist of all subjects who received at least 1 dose of study drug and have at least 1 evaluable PD endpoint.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed by treatment sequence and overall. Descriptive statistics will be used to summarize data for continuous variables such as age and weight (number of subjects [N], mean, median, SD, minimum, and maximum) and for categorical variables such as sex, ethnicity, and race (number and percentage of subjects within each category). Medical history and medication history will be listed by subject.

11.1.3 PK Analysis

Plasma concentrations of TAK-925 and its metabolites M-I and M-II and PK parameter estimates will be listed for each subject and summarized using descriptive statistics by each time point for each dose.

Additionally, the relationships between TAK-925 plasma concentrations and selected measures of efficacy (eg, MWT, CCBT, and KSS) and safety (eg, BP) will be explored as deemed appropriate.

11.1.4 PD Analysis

11.1.4.1 Primary and Secondary Analyses

Sleep latency on the MWT will be summarized (N, mean, median, SD, minimum, and maximum) by treatment and time.

The effect of TAK-925 will be evaluated with a mixed effects model appropriate for a 4-period crossover study. The response variable in the model will be the observed value of sleep latency. The model will contain fixed effects for sequence, period, treatment (TAK-925 LD, TAK-925 HD, modafinil, and placebo), time (as a categorical variable), and the treatment-by-time interaction, and a random effect for subject.

The estimated mean sleep latency for each treatment and the associated standard error and 95% CI will be extracted from the model at each time, along with all treatment differences and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over all timepoints at which an MWT is performed, will also be extracted from the model using an appropriate contrast. The study objectives will be addressed using the results of the average treatment difference across all time points.

A similar analysis will be performed for the KSS.

11.1.4.2 Exploratory Analyses

CCI

[redacted]

11.1.5 Safety Analysis

Unless stated otherwise, baseline for safety parameters is defined as the last measurement collected before study drug administration, and summary statistics will be N, mean, median, SD, minimum, and maximum.

11.1.5.1 AEs

All AEs will be coded by system organ class and preferred term using MedDRA (Medical Dictionary for Regulatory Activities). TEAEs will be summarized by treatment.

11.1.5.2 Clinical Laboratory Evaluations

Clinical laboratory test data will be summarized for baseline, postdose, and changes from baseline by treatment and time. Only the scheduled measurements will be included in the summary.

11.1.5.3 Vital Signs

HR and BP data will be summarized for baseline (defined as Day -1 of each treatment period), postdose, and change from time-matched baseline by treatment and time. Only the scheduled measurements will be included in the summary.

The change from time-matched baseline will be analyzed using a statistical model of the same form as for the primary endpoint. The estimated 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 all treatment differences and associated standard errors, 95% CIs, and p-values. The same quantities, averaged over all postdose timepoints, will also be extracted from the model using an appropriate contrast.

All other vital signs will be summarized for baseline (pre-dose on Day 1 of each period), postdose, and change from baseline by treatment and time.

11.1.5.4 ECGs

ECG data will be summarized for baseline, postdose, and changes from baseline by treatment and time. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

11.1.5.5 C-SSRS

C-SSRS data will be listed.

11.1.5.6 Drug-liking VAS

Drug-liking VAS data will be listed.

11.1.5.7 POMS

POMS data will be summarized for baseline, postdose, and changes from baseline by treatment and time.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 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 [1]. 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.

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 [20], 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.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or the sponsor's designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

13.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and, if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study, and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

Subjects who consented and provided a PGx sample for DNA and RNA analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. Notify sponsor of consent withdrawal.

13.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, the FDA, the Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 13.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with

this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

13.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

13.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

13.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Study contact numbers can be found in the Study Manual, the communication plan, or other similar documents provided to the site.

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Provence)

_____

Location of Facility (Country)

14.1.3 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified for specific study-related activities will perform these activities in full or in partnership with the sponsor.

14.1.4 List of Abbreviations

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
Ca^{2+}	calcium
CCBT	Cambridge Cognition Computerized Battery of Tests
C_{eoi}	plasma concentration observed at the end of infusion
CFR	Code of Federal Regulations
CL	total clearance after intravenous administration
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EDS	excessive daytime somnolence
EEG	electroencephalogram
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HD	high dose
HED	human equivalent dose
HIV	human immunodeficiency virus
HR	heart rate

ICH	International Conference on Harmonisation
ICSD-3	International Classification of Sleep Disorders, 3rd edition
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
KSS	Karolinska Sleepiness Scale
LD	low dose
LFT	liver function test
M-I, M-II	metabolites of TAK-925
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
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
PTE	pretreatment event
QTcF	QT interval with Frederica correction method
REM	rapid eye movement
SAE	serious adverse event
SBP	systolic blood pressure
$t_{1/2z}$	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
WT	wild type

15.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using MedDRA. Drugs will be coded using the World Health Organization Drug Dictionary.

15.1 CRFs (Electronic and Paper)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change of, modification of, or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs including the audit trails, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source

documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

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17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's

legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 5 half-lives PLUS 90 days after the last dose of study drug. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this study will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives PLUS 90 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

In studies with no risk of fetotoxicity/teratogenicity/genotoxicity: Male subjects are not required to use barrier contraception.

Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
   - Non-Hormonal Methods:
     - Intrauterine device.
     - Bilateral tubal occlusion.
     - Vasectomized partner (provided that partner is the sole sexual partner of the study participant and that the vasectomized partner has received medical assessment of the surgical success.

  - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month before the first dose until 5 half-lives PLUS 30 days after last dose.

- Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method (Evaluate on compound-by-compound and protocol-by-protocol basis and obtain clinical pharmacology justification).
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
    - Oral †.
    - Intravaginal † (eg, ring).
    - transdermal †.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation1 initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
    - Oral †.
    - Injectable.
    - Implantable.

2. If genotoxicity/teratogenicity/embryotoxicity is unlikely to be caused by the investigational drug, comparator, background therapy or standard of care medications effective methods of contraception (there may be a higher than 1% failure rate) are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.

- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.
- Sexual abstinence is NOT an acceptable method of contraception.

4. Subjects will be provided with information on highly effective/effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and sperm donation during the study.
5. During the study, all subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?

Pregnancy

Women of childbearing potential will not be included in this study.

Any pregnancies in the female partner of a male subject during the study or for 5 half-lives PLUS 90 days after the last dose, should also be recorded following authorization from the subject's partner.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Pregnancies in female partners of subjects randomized to placebo need not be followed.

If the female partner of a male subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the male subject received (blinded or unblinded, as applicable).

All pregnancies in female partners of male subjects who were on active study drug (including comparator, if applicable) will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

Appendix E Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Removed Sustained Attention to Response Task (SART) assessment throughout protocol and updated study schematic accordingly.

The primary change occurs in Section 3.0 SCHEDULE OF STUDY PROCEDURES

Description of change: Removed SART under pharmacodynamic evaluations.

Rationale for Change: Change in rating vendor who required change in rating scales.

The following sections also contain this change:

- Section 1.0 STUDY SUMMARY
- Section 2.0 STUDY SCHEMATIC
- Section 5.1.3 Exploratory Objectives
- Section 5.2.4 Exploratory Endpoints
- Section 6.1 Study Design
- Section 6.2.3.2 Secondary Endpoints
- Section 6.2.4 Critical Procedures Based on Study Objectives: Timing of Procedures
- Section 6.3 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters
- Section 9.3.4 PD Measurements
- Section 11.1.1.3 PD Set
- Section 11.1.4.2 Exploratory Analyses
- Section 14.1.4 List of Abbreviations
- Section 16.0 REFERENCES

Change 2: Replaced Cogstate Cognitive Computerized Battery of Tests with Cambridge Cognition Computerized Battery of Tests (CCBT).

The primary change occurs in Section 5.1.3 Exploratory Objectives

Initial wording:	CCI [redacted]
Amended or new wording:	CCI [redacted]

Rationale for Change: Change in rating vendor who required change in rating scales.

The following sections also contain this change:

- Section 1.0 STUDY SUMMARY
- Section 2.0 STUDY SCHEMATIC
- Section 3.0 SCHEDULE OF STUDY PROCEDURES
- Section 5.1.3 Exploratory Objectives
- Section 6.2.3.2 Secondary Endpoints
- Section 9.3.4.4 CCBT
- Section 14.1.4 List of Abbreviations

Change 3: Updated alcohol consumption restrictions.	
The primary change occurs in Section 7.3.3 Alcohol	
Rationale for Change: Align protocol text with exclusion criteria.	
Initial wording:	Subjects will refrain from consuming alcohol 7 days before the screening visit and follow-up visit and from 7 days before and until the last PK blood sample has been collected in each treatment period. At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 alcoholic beverage is approximately equivalent to: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz]) per day.
Amended or new wording:	~~Subjects will refrain from consuming alcohol 7 days before the screening visit and follow-up visit and from 7 days before and until the last PK blood sample has been collected in each treatment period. At all other times, a~~**A**lcohol consumption is not **allowed during the entire study** ~~limited to no more than approximately 3 alcoholic beverages or equivalent (1 alcoholic beverage is approximately equivalent to: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz]) per day~~.
Change 4: Updated caffeine consumption restrictions.	
The primary change occurs in Section 7.3.4 Caffeine	
Rationale for Change: Align protocol text with exclusion criteria.	
Initial wording:	Subjects will refrain from consuming caffeinated beverages 24 hours before the screening visit and follow-up visit and from 24 hours before and until the last PK blood sample has been collected in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than 6 units per day (1 unit=120 mg of caffeine).
Amended or new wording:	Subjects will refrain from consuming caffeinated beverages 24 hours before the screening visit and follow-up visit and from 24 hours before and until the last PK blood sample has been collected in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to amounts of no more than ~~6 units per day (1 unit=120 mg of caffeine)~~ **400 mg/day**.

Change 5: Updated smoking restrictions.

The primary change occurs in Section 7.3.5 Smoking

Rationale for Change: Align protocol text with inclusion criteria.

Initial wording:	Tobacco or nicotine-containing products are restricted for 1 hour before the PSG and 40 minutes before the MWT. No excessive consumption per day is allowed (>10 cigarettes/day) during the study.
Amended or new wording:	~~Tobacco~~ **Smoking** or **use of** nicotine~~-containing~~ **or tobacco** products ~~are restricted for 1 hour before the PSG and 40 minutes before the MWT. No excessive consumption per day is allowed (>10 cigarettes/day)~~ **is not allowed** during the **entire** study.

Change 6: Added dose levels selected for the low dose (LD) and high dose (HD).

The primary change occurs in Section. 6.2.2 Rationale for Dose.

Initial wording:	This study will evaluate 2 dose levels of TAK-925, LD and HD. The dose level of HD will be determined once study TAK-925-1001 has completed the dose escalations in the healthy normal cohorts. The maximum dose of the healthy cohorts in TAK-925-1001 was originally 134.4 mg and an amendment is being planned to increase the maximum dose to 420 mg. The HD may be equivalent to the highest dose level (plasma concentration expected to be approximately 883 ng/mL, which is the estimated observed plasma concentration at steady state when 420 mg is administered) where safety and tolerability of 9-hour IV infusion of TAK-925 is confirmed in the TAK-925-1001 study. The aim of the LD is to evaluate a dose that will result in effects on wakefulness (as assessed by the MWT) that are greater than those seen on placebo, but a dose that is pharmacologically different than the HD in concentration. The LD will also be considered above or equal to the dose level that is expected to achieve a target concentration associated with effects on wakefulness, which is equivalent to the human equivalent dose (HED) calculated based on WT monkey pharmacology studies as described below. CCI [redacted] This difference will be taken into consideration when choosing the LD in sleep-deprived healthy subjects.

Amended or new wording:

~~This~~ **Based on the currently available information, this** study will evaluate 2 dose levels of TAK-925~~, LD and~~ HD. The a low dose ~~level~~ of ~~HD will be determined once study TAK-925-1001 has completed the dose escalations in the healthy normal cohorts. The maximum~~ **44 mg (LD) and high** dose o~~f the healthy cohorts in~~ CCI [redacted] -**112** mg. CCI [redacted] ~~.~~ **The HD of 112** mg ~~is administered) where~~ **was selected based on the safety and tolerability ~~of~~ results in adult subjects from the ongoing FIH TAK-925-1001 study. Doses up to and including 134.4 mg, the maximum dose tested so far in healthy volunteers, were safe and well tolerated with no severe AEs or SAEs. All subjects dosed with 112 mg TAK-925 had acceptable safety and tolerability during the** 9-hour IV infusion ~~of TAK-925 is confirmed in the TAK-925-1001 study. The aim of the .~~ **The 44 mg** LD ~~is~~ **was selected** to evaluate a dose that ~~will~~ **may** result in effects on wakefulness (as assessed by the MWT) that are greater than those ~~seen on~~ of placebo, ~~but a dose that is~~ CCI [redacted] ~~This difference will be~~ **Thus, the potential difference in the pharmacological response to TAK-925 has also been** taken into consideration when choosing the LD **and HD** in sleep-deprived healthy subjects.

Rationale for Change: Doses selected based on currently available safety and tolerability results in healthy adult subjects in the ongoing TAK-925-1001 study.

The following sections also contain this change:

- Section 1.0 STUDY SUMMARY
- Section 5.1.2 Secondary Objectives

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	08-May-2018 20:54 UTC
	Biostatistics Approval	09-May-2018 15:18 UTC
	Clinical Science Approval	09-May-2018 19:40 UTC