TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-994 in Patients With Narcolepsy With or Without Cataplexy (Narcolepsy Type 1 or Narcolepsy Type 2)

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington MA 02421 USA		
Study Number:	TAK-994-1501		
Study Phase	2		
IND Number:	142658	**EudraCT Number:**	2020-000777-24
Compound:	TAK-994		
Date:	15 January 2021	**Version/Amendment Number:**	Amendment 3

Amendment History:

Date	Amendment Number	Region
15 January 2021	Amendment 3	Global
05 June 2020	Amendment 2	Global
13 March 2020	Amendment 1	Global
26 November 2019	Initial version	Global

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

1.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc., 95 Hayden Avenue Lexington, MA 02421, United States	**Compound:** TAK-994
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-994 in Patients With Narcolepsy With or Without Cataplexy (Narcolepsy Type 1 or Narcolepsy Type 2)	**IND No.:** 142658 **EudraCT Number:** 2020-000777-24
Study Identifier: TAK-994-1501	**Phase:** 2

Study Design:

This is a phase 2, randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics (PK), [redacted] of multiple oral doses of TAK-994 administered to subjects with narcolepsy type 1 (NT1) or type 2 (NT2). The study will be conducted in 4 parts (A, B, C, and D) as follows:

Part A: Part A will include subjects with NT1 only.

In Cohort A1 subjects will receive TAK-994 or matching placebo twice daily (BID) (with randomization ratio of 2:1) orally as a tablet formulation for 28 days; Cohort A1 will enroll 18 subjects. Sentinel dosing on the first 9 subjects (Cohort A1a) will be performed. Dosing for the next 9 subjects (Cohort A1b) may be adjusted based on the safety and/or efficacy data from the first 9 subjects. Overall randomization ratio for the 18 subjects in Cohort A1 will remain at 2:1. Based on Cohort A1 data, decision to enroll Cohort A2 will be made.

Cohort A2 is an **optional** cohort that, if executed, may enroll 9 to 18 subjects. Based on the Cohort A1 data, if additional data are needed, 9 subjects will be randomized in a 2:1 ratio to receive oral TAK-994 at the determined dose level or placebo in a double-blinded fashion. Based on the data from these first 9 subjects, an additional 9 subjects may be enrolled in this cohort in a 2:1 ratio. In both cohorts, subjects will be enrolled to receive TAK-994 BID or matching placebo orally as a tablet formulation for 28 days.

Part B: Part B will enroll approximately 112 subjects with NT1 for 56 days of treatment. Part B will have 4 parallel arms with subjects randomized to 1 of 3 different TAK-994 dose levels (dose 1, 2 or 3) or placebo in 1:1:1:1 ratio, to receive TAK-994 or matching placebo BID for 56 days. In each arm, approximately 21 to 28 subjects will be enrolled. Doses will be determined based on the available and emerging safety, tolerability, PK, [redacted] data from Part A. See Section 6.1 for details.

Part C (China-specific): Part C will enroll 12 to 18 subjects with NT1 in a single Cohort (C1) with a ratio of 2:1 to receive TAK-994 BID or matching placebo for 56 days. See Section 6.1 for details.

Part D: Part D will include subjects with NT2. Subjects will be randomized in a ratio of 2:1 to receive TAK-994 BID or matching placebo orally for 28 days. Sentinel dosing on the first 9 subjects (Cohort D1a) will be performed. Dosing for the next 9 subjects (Cohort D1b) may be adjusted based on the safety and/or efficacy data from the first 9 subjects. Overall randomization ratio for the 18 subjects in Cohort D1 will remain at 2:1. See Section 6.1 for details.

Cohort D2 is an **optional** cohort that, if executed, may enroll 9 to 18 subjects. Based on the Cohort D1 data, if additional data are needed, Cohort D2 will enroll 9 subjects, which will be randomized with a ratio of 2:1 to receive oral TAK-994 at the determined dose level or placebo in a double-blinded fashion. Based on the data from these first 9 subjects, an additional 9 subjects may be enrolled in this cohort in a 2:1 ratio. In both cohorts, subjects will be enrolled to receive TAK-994 BID or matching placebo) orally as a tablet formulation for 28 days.

For Part B, the randomization will be stratified by baseline weekly cataplexy rate (WCR) (<8 vs ≥8) and regions/countries (ie, North America, Japan, South Korea, and Europe).

For Part C, the randomization will be stratified by baseline WCR (<8 vs ≥8).
For other parts, the randomization will be stratified by regions/countries (North America, Japan, South Korea, and Europe.

Both blinded and unblinded data review will be performed by the sponsor at the end of each cohort for those cohorts that will be run sequentially. In these data reviews, available safety, tolerability, and PK [redacted] data will be used to determine the dosing regimen for the subsequent cohort(s).

Part A and Part D:

For subjects in Parts A and D, there will be 3 periods including screening (up to 45 days, including a baseline period), study treatment (Days 1-28), and follow-up (Day 29 to 35, ±2 days). During the screening period, subjects will undergo screening assessments to determine eligibility.

After the initial screening visit, eligible subjects must discontinue prior medication following the guidelines below (as applicable for each subject):

1. Stimulant medications: minimum of 7 days or 5 half-lives before Day -2 check-in.
2. Anticataplexy medications (Part A subjects only): The anticataplexy medication washout should start at least 21 days before Day -2 to allow for confirmation of cataplexy eligibility criterion. See Section 9.3.2.7 for details.
3. Sodium, and/or multisalt oxybate: at least 4 weeks before Day -2 check-in.

For subjects in Part A not taking any medications that require washout at screening, the 14 consecutive days of recording of daily cataplexy may commence at any time after the screening visit.

Subjects will check-in and remain as inpatients between Days -2 to 2. Baseline assessments will occur on Days -2 to Day 1 before randomization and dose. Subjects who met all selection criteria will be randomized on Day 1 to receive TAK-994 or matching placebo for 28 days. Randomized subjects will stay overnight in clinic on days as indicated in Section 3.0, Schedule of Study Procedures. Subjects will need to travel to the clinic for the fitting of ABPM device. Alternatively, the site staff may consider confining the subject the evening before fitting of the ABPM device according to subject and site preferences. The second scenario may require additional stays at the clinic (see Section 3.0 and Section 9.2.6 for details).

On other days during the treatment period, subjects will continue TAK-994 or placebo at home. Study assessments and visits will be conducted throughout the study as described in the Schedule of Study Procedures. A follow-up visit will be conducted at Day 35 (±2 days). Blood samples for PK assessment will be collected at specified timepoints over the duration of treatment.

Part B and Part C:

For subjects in Part B and C, the study will consist of 3 periods including screening (up to 45 days, including a baseline period), study treatment (Days 1-56), and follow-up (Day 57-63 ±2 days). During the screening period, subjects will undergo screening assessments to determine eligibility. After the initial screening visit, eligible subjects must discontinue prior medication following the guidelines below (as applicable for each subject):

1. Stimulant medications: minimum of 7 days or 5 half-lives before Day -2 check-in
2. Anticataplexy medications: The anticataplexy medication washout should start at least 21 days before Day -2 to allow for confirmation of cataplexy eligibility criterion. See Section 9.3.2.7 for details.
3. Sodium, and/or multisalt oxybate: at least 4 weeks before Day -2 check-in.

For subjects not taking any medications at screening that require washout, the 14 consecutive days of recording of daily cataplexy may commence at any time after the screening visit.

Subjects will then check-in and remain as inpatient between Days -2 to 2. Baseline assessments will occur on Days -2 to Day 1 prior to randomization. Subjects who meet all selection criteria will be randomized on Day 1 to receive TAK-994 or matching placebo for 56 days. Randomized subjects will stay overnight in clinic on the days indicated in the schedule of assessments in Section 3.0 of this protocol. On other days during the treatment period, subjects will continue TAK-994 or placebo at home. Study assessments and visits will be conducted throughout the study period according to Section 3.0, Schedule of Study Procedures. A follow-up visit will be conducted at Day 63 (±2 days).

Blood samples for PK assessment will be collected at specified timepoints over the duration of treatment and follow-up. Safety and tolerability will be evaluated in all study parts by adverse events (AEs), clinical laboratory

evaluations, vital signs, electrocardiograms (ECGs), ambulatory blood pressure monitoring (ABPM), physical examination findings, and suicidality assessment. Ongoing medical monitoring will occur during the study with stopping rules in place for pretreatment events, AEs, liver function test (LFT) abnormalities, suicidality, blood pressure (BP) increase, insomnia, and other reasons.

The end of the study is defined as when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit, withdraws from the study, or is lost to follow-up.

OBJECTIVES

PART A and PART D

Primary Objective:

- To assess the safety and tolerability of TAK-994 following multiple oral doses in subjects with narcolepsy with (NT1) or without cataplexy (NT2).

Secondary Objective:

- To characterize the PK of TAK-994 in subjects with narcolepsy with (NT1) or without cataplexy (NT2).

Additional/Exploratory Objectives:

[redacted]

PART B and PART C

Primary Efficacy Objectives:

- To assess the efficacy of TAK-994 on reducing excessive daytime sleepiness as measured by prolongation of sleep onset in MWT procedure.

Secondary Objectives:

- To assess the efficacy of TAK-994 on WCR and ESS reduction.
- To assess the safety and tolerability of TAK-994 following chronic administration.

Additional/Exploratory Objectives:

[redacted]

Subject Population: Male and female subjects with NT1 or NT2 (aged 18 to 65 years, inclusive).

Number of Subjects:	**Number of Sites:**
Approximately 202 subjects will be enrolled: • Part A (Cohort A1a and A1b): approximately 18 subjects • Part A, Cohort A2 (optional): approximately 9-18 subjects with NT1. • Part B: approximately 112 subjects with NT1. • Part C (China-specific Cohort C1): approximately 12-18 subjects with NT1. • Part D (Cohort D1a and D1b): approximately 18 subjects with NT2. • Part D, Cohort D2 (optional): approximately 9-18 subjects with NT2.	Up to 100 sites globally
Dose Levels: Initial dose for Cohort A1a: 240 mg daily (120 mg BID); Other parts/cohorts: TBD	**Route of Administration:** Oral (tablets)
Duration of Treatment: 28 days (Parts A and D) or 56 days (Parts B and C)	**Study Duration:** Screening and Baseline: up to 45 days Treatment period: 28 days (Parts A & D); 56 days (Parts B & C) Safety follow-up period: 7±2 days

Main Criteria for Inclusion:

To be eligible for randomization on Day 1, subjects must:

- Be male or female, aged 18 to 65 years (inclusive), at the time of informed consent.
- Be judged in good health by the investigator based on clinical evaluations including laboratory safety tests. See Section 7.1 for details.
- Have a body mass index ≥17.0 and ≤40.0 kg/m^2 at the screening visit).
- Have a diagnosis of NT1 (Parts A, B, and C) or NT2 (Part D) (as per International Classification of Sleep Disorders-3rd Edition) made by [redacted] multiple sleep latency test (MSLT) performed within the past 10 years meeting the minimal acceptable criteria for the proper performance of the [redacted] MSLT as outlined by ICSD-3 criteria. Note: If there is a potential subject with a diagnosis of NT1 or NT2 whose diagnostic [redacted] MSLT was performed more than 10 years ago or is not available, special exemptions, ie, ability of the site to repeat the diagnostic [redacted] MSLT will be considered on a case-by-case basis after discussions between the investigator and the sponsor or designee.
- Have ≥10 ESS score at Day -1.
- Part A: The human leukocyte antigen (HLA) genotype should test positive for HLA-DQB1*06:02 - (positive results for either homozygous or heterozygous alleles will be considered "positive" and acceptable). However, if the HLA test is negative (ie, negative for the heterozygous allele) and the PI feels strongly that the subject has narcolepsy with cataplexy (NT1) then a discussion should be initiated between the PI and the sponsor or designee about the advisability of doing a spinal tap to determine the subject's cerebrospinal fluid (CSF) orexin-1 (OX-1) level. If the CSF result shows the OX-1 concentration is either less than or equal to 110 pg/mL, or less than one-third of mean values obtained in normal subjects with the same standardized assay, then the diagnosis of NT1 is established allowing the subject to be enrolled and randomized. If the CSF OX-1 concentration is >110 pg/mL then the subject will not be allowed to continue in the study. Subjects previously excluded in Part A for being HLA negative will not be included in Part B.
- Parts B and C: HLA genotyping will be done for these subjects as well; however, HLA test results are not a study entry criteria. Subjects who present with CSF testing results indicating OX-1 concentration either less than or equal to 110 pg/mL, or less than one-third of mean values obtained in normal subjects with the same standardized assay, may be considered for enrollment into Parts B and C after a discussion with the sponsor or designee. For all subjects in Parts B and C, site staff will complete the cataplexy questionnaire during screening. This questionnaire along with a copy of the most recent [redacted] MSLT report will be submitted to the sponsor for adjudication by a committee of experts in the field of narcolepsy/cataplexy to be chosen by the sponsor. This committee will to determine eligibility for the study and the committee's determination will be final for study entry criteria. Additional documentation may be requested by the sponsor.
- For Parts A, B, and C, during the screening period, the subject must have ≥4 partial or complete episodes of cataplexy/week (WCR), averaged over 2 weeks (14 consecutive days) minimum. WCR recording taken during the following period will be considered for study eligibility: after the patient has stopped taking anticataplexy medications for at least 7 days (minimum 7-day washout) and completed before study Day -2. Refer to Section 9.3.2.7 for details.
- Be willing to discontinue all medications used for the treatment of NT1 or NT2.
- BP <140 mmHg (systolic) and <90 mmHg (diastolic). The subject may have a history of hypertension and be on antihypertensive medication treatment as long as the BP meets these criteria. BP measurements should be obtained after the subject has been resting for a minimum of 10 minutes and will be repeated 3 times. The median BP obtained will be used.

Main Criteria for Exclusion:

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

- Has a positive pregnancy test or is a lactating/nursing female subject.
- Has a known hypersensitivity to any component of the formulation of TAK-994 or related compounds.
- Has a risk of suicide according to endorsement of Item 4 or 5 of the screening/baseline visit Columbia Suicide Severity Rating Scale and/or has made a suicide attempt in the previous 12 months.

- Has a screening ECG with a QT interval with Fridericia's correction method >450 ms (men) or >470 ms (women).
- Has a resting pulse rate outside of the range of 40 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes.
- Has renal creatinine clearance ≤50 mL/min.
- Has LFTs (alanine aminotransferase, aspartate aminotransferase) higher than 1.5× ULN at screening.
- Is an excessive (>600 mg/day) caffeine user 1 week before the study screening.
- Has a history of cancer (does not apply to carcinoma in situ that has been resolved without further treatment or basal cell skin cancer); these subjects may be included after approval by the sponsor or designee.
- Has past or current epilepsy or seizure, except for febrile seizure in childhood.
- Has a lifetime history of major psychiatric disorder (such as bipolar disorder or schizophrenia), a current active major depressive disorder (MDD), or has had active MDD in the past 6 months.
- Has a clinically significant history of head injury or head trauma per the judgment of the investigator.
- Has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation; known coronary artery disease, a history of myocardial infarction, angina, cardiac rhythm abnormality, or heart failure.
- Has current or recent (within 6 months) gastrointestinal disease expected to influence the absorption of drugs. See Section 7.2 for details.
- Subjects on fluoxetine (any dose) or on ≥300 mg per day of venlafaxine will be excluded due to the drug's long elimination half-life or clinically significant tapering/washout difficulties. See Section 7.3 for a complete list of medications that are not allowed during the treatment period and the guidelines for washout for stimulant, anticataplexy, antidepressant medications and sodium, and/or multisalt oxybate, when applicable.
- Be unwilling to abstain from driving and operating dangerous or hazardous machinery during study participation, starting from when narcolepsy medications are discontinued and extending until after the follow-up visit (Day 35 ±2 days or Day 63 ±2 days as applicable).
- Has a medical disorder (including moderate to severe sleep apnea syndrome with or without treatment with mandibular advanced device hypoglossal nerve stimulation and/or positive airway pressure therapy), other than narcolepsy, associated with excessive daytime sleepiness, or has any other medical condition (eg, anxiety, depression, epilepsy, heart disease, or significant hepatic, pulmonary, or renal disease) that requires the subject to take excluded medications or at the time of screening the subject is being treated with nasal /oro-nasal positive airway pressure for any reason. See Section 7.2 for details.
- Has a usual bedtime later than 2400 (12:00 AM, midnight) or an occupation requiring nighttime shift work or variable shift work within the past 6 months or travel within more than 3 time zones, within 14 days before Study Day -2.
- The subject has a nicotine dependence that is likely to have an effect on sleep (eg, a subject who routinely awakens at night to smoke) and/or an unwillingness to discontinue all smoking and nicotine use during the confinement portions of the study.

Main Criteria for Evaluation and Analyses:

PART A and PART D

Primary Endpoints

The primary endpoints assessing safety and tolerability are:

- Number of subjects with at least 1 treatment-emergent AE (TEAE) during the study.
- Number of subjects with at least 1 markedly abnormal value (MAV) for post dose laboratory values during the study.
- Number of subjects with at least 1 MAV for vital signs during the study.
- Number of subjects with at least 1 MAV for ECGs during the study.

Secondary Endpoints

The secondary endpoints assessing the PK of TAK-994 are:

- Day 1: maximum observed concentration [C_{max}], time to reach C_{max} [t_{max}], area under the concentration-time curve [AUC] from time 0 to time of the last quantifiable concentration [AUC_{last}].
- Day 28: C_{max}, t_{max}, area under the concentration-time curve during a dosing interval, where τ is the length of the dosing interval [AUCτ].

Additional/Exploratory Endpoints

[redacted]

PART B and PART C

Primary Endpoint:

The primary endpoint assessing efficacy is:

- Change from baseline in average sleep latency from MWT to Week 8.

Secondary Endpoints:

The secondary endpoints assessing efficacy are:

- Change from baseline in the ESS total score to Week 8.
- WCR at Week 8.

The secondary endpoints assessing safety are:

- Number of subjects with at least 1 treatment-emergent AE (TEAE) during the study.
- Number of subjects with at least 1 markedly abnormal value (MAV) for post dose laboratory values during the study.
- Number of subjects with at least 1 MAV for vital signs during the study.
- Number of subjects with at least 1 MAV for ECGs during the study.

Additional/Exploratory Endpoints:

[redacted]

[redacted]

Statistical Considerations:

Primary analyses of endpoints will be performed on each study part separately. Additional analyses may be performed on pooled data across the study parts of the same dose level and populations. Details will be described in the statistical analysis plan (SAP).

Safety Analysis:

TEAEs, safety clinical laboratory measurements, vital signs, and 12-lead ECG parameters will be summarized. Linear mixed-effect models for repeated measures will be used to evaluate the drug effect on change from baseline in BP and heart rate.

Twenty-four-hour ABPM mean profiles will be plotted at baseline and post dose days by treatment groups. ABPM parameters will be derived from 24-hour ABPM monitoring at baseline and post dose days, such as mean 24-hour BP, day, and nighttime mean BP. Observed values and change from baseline in these parameters will be summarized by treatment groups. Change from baseline in these parameters to post dose days will be analyzed using analysis of covariance or linear mixed effects models for repeated measures, as appropriate (Details will be described in the SAP). Effect of TAK-994 on these ABPM parameters will be evaluated through estimates of difference between TAK-994 treatment groups and placebo and 95% CIs.

PK Analysis:

Individual plasma concentrations of TAK-994 in subjects with NT1 or NT2 will be presented in a data listing and summarized by day, and nominal sampling time point using descriptive statistics for each treatment (arithmetic mean, SD, coefficient of variation, median, minimum, maximum, and geometric mean). Individual plasma noncompartmental analysis PK parameters obtained in NT1 and in NT2 will be tabulated and summarized descriptively by day for each treatment. As data permit, the 4β-hydroxycholesterol/cholesterol ratio, measured predose throughout the treatment period, will also be summarized descriptively for each treatment to assess cytochrome P-450 (CYP)3A4/5 activity over time.

TAK-994 plasma concentration-time data collected in this study will be combined with other clinical study data to develop a population PK model of TAK-994 in subjects with NT1 or NT2. The objectives and details of this modeling approach will be described in a separate analysis plan, and the results of this analysis will be reported separately.

Efficacy [redacted] Analysis:

Observed sleep latency from MWT, ESS, WCR (applicable parts only), and [redacted], and change from baseline (or shift tables) will be summarized by visit by treatment and overall. Change from baseline in the sleep latency from MWT and ESS scores will be analyzed using linear mixed-effect models for repeated measures. Baseline will be included as a covariate. CSF orexin levels may be included as a covariate in the model (applicable cohorts only). In addition, Bayesian models may be used on the change from baseline in the mean sleep latency from the MWT score and change from baseline in the total ESS score to evaluate the posterior probability of the true TAK-994 effect in delaying the sleep onset to >8, 14, and 20 minutes and reducing the ESS (>4 points reduction) for specific parts and subgroups. Details will be included in the SAP. [redacted]

[redacted]

Sample Size Justification:

PARTS A, C and D:

In Parts A, C and D, the number of subjects planned are not based on statistical hypothesis testing consideration. They are considered sufficient for dose selection under a typical multiple rising dose design.

PART B:

In Part B, change from baseline in the mean sleep latency, change from baseline in the total ESS score and postdose WCR will be used to evaluate the true TAK-994 effect on delaying the sleep onset (>14 minutes prolongation over placebo), reducing ESS (>8 points reduction over placebo) and reducing WCR (>50% reduction over placebo) at a dose level.

A sample size of 21 in each group will have 98% power to detect a 14-minute difference in means of change from baseline between a TAK-994 dose group and placebo in sleep latency using a 2-sample t-test with a 5% 2-sided significance level. The power to detect an 8-point reduction in means of change from baseline between a TAK-994 dose group and placebo in the total ESS score is estimated to be approximately 95% using a 2-sample t-test with a 5% 2-sided significance level. The power to detect a 50% reduction in WCR from that of placebo group is estimated to be approximately 93% using a 2-incidence-rate ratio test using Poisson model with a 5% 2-sided significance level.

A fixed sequence of tests with MWT at high and middle doses first followed by ESS at high and middle doses and WCR at high and middle doses will be applied. The overall power for the entire testing procedure is approximately 75% (the square of the product of the power of each individual test at a dose level, 98%, 95%, and 93% respectively) under the assumption that these 3 endpoints are independent at difference dose levels. The overall power may be higher or lower than 75% depending on the assumed correlation structure of these 3 endpoints. There is no known reliable data to support any particular assumption on the correlation structure.

To allow for a 25% dropout rate, 28 subjects per group will be enrolled for Part B. The enrollment can be stopped once the number of evaluable 21 subjects is reached. A blinded sample size re-estimation will be performed before Part B starts. The change in the sample size of Part B after the re-evaluation, along with justification, will be documented in the clinical study report.

The SD for the change from baseline in the sleep latency is assumed to be 11 minutes. The SD for the change from baseline in the ESS score is assumed to be 7 points. The incidence rate of WCR at baseline is assumed to be 3.

1.1 Protocol Amendment 3 Summary of Changes

Protocol Amendment 3 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 3. The primary reasons for this amendment are to:

- Updated to include recent clinical and nonclinical study data.
- Change the study eligibility criteria to better define how the presence of cataplexy is established for participants in Part B and C cohorts.
- Clarify and revise several protocol sections, including the Schedule of Study Procedures to allow more flexibility for the study participants and the site personal.
- Revise the statistical analysis strategy to reduce the number of times the sponsor unblinded team reviews the data.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Throughout the document	Text has been edited to provide additional guidelines.	To provide more guidance to the site, so that data can be collected consistently, allowing for some flexibility for the subject's travel etc.
2.	Section 1.0 STUDY SUMMARY Section 6.0 Study Design Section 8.1.4 Randomization Code Creation and Storage	Overall study description changed to provide clarity around start of each part and cohort in relation to the first cohort in Part A. For Cohort A1, new term Cohort A1a and Cohort A1b have been added for clarity. For Cohort D1, new term Cohort D1a and Cohort D1b have been added for clarity. South Korea has been added to the list of countries where this study will be conducted.	To provide further guidance about sentinel cohorts dosing. New country has been added where this study will enroll subjects.

Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
3.	Section 1.0 STUDY SUMMARY Section 7.1 Inclusion Criteria Section 7.3 Excluded Medications, Supplements, and Dietary Products Table 7.a Section 9.3.2.7 ePRO Measures	Excluded medications and wash-out a. Required washout period for anticataplexy medications when weekly cataplexy rate counting for study eligibility can start has been revised as follows: *Anticataplexy medications (eg, tricyclic antidepressents, SSRI, and SNRI) washout should start at least 21 days before Day -2 to allow for confirmation of cataplexy eligibility criterion.* b. In addition, baseline for completing all medication washout (as applicable) has been specified as Day -2. c. Topical steroid has been permitted to treat adverse events (AEs) during study period. d. Centrally acting antihistamines (eg, Loratadine) are prohibited.	a. This is done to accommodate the cataplexy recording during screening period. c. Topical steroids have been included as they are not expected to impact subject safety if used during the study. Clarification has been added regarding which antihistamines are prohibited during the study
4.	Section 1.0 STUDY SUMMARY	Updated the number of sites (approximately 100 sites globally)	Update has been made
5.	Section 1.0 STUDY SUMMARY Section 3.0 SCHEDULES OF STUDY PROCEDURES Section 5.1 Study Objectives Section 5.2 Endpoints Section 6.3.3.3 Efficacy [redacted] Endpoints Section 9.3.2.6 Cognitive Assessments	[redacted]	[redacted]

Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
			[redacted]
6.	Section 1.0 STUDY SUMMARY Section 5.2.4 Primary Endpoint-PART B and PART C Section 5.2.6 Additional/Exploratory Endpoints-[redacted]	Changes in efficacy endpoints (Parts B and C): Change from baseline in sleep latency from Maintenance of Wakefulness Test (MWT) to Week 8 is now a primary endpoint (it was secondary in Protocol Amendment 2 [PA2]). [redacted]	Instead of both MWT and ESS, the sponsor decided to use only MWT as the primary endpoint for both B and C. The time duration has been changed from [redacted] to 8 weeks to have a longer efficacy measurement.
7.	Section 1.0 STUDY SUMMARY Section 7.1 Inclusion Criteria #8 Section 9.1.2.1 The Cataplexy Questionnaire	Subject eligibility for human leukocyte antigen genotype criteria has been revised and cataplexy questionnaire has been added.	Update has been made
8.	Section 1.0 STUDY SUMMARY Section 7.2 Exclusion Criteria#26	Study exclusion criterion regarding pre-existing conditions has been revised.	Update has been made
9.	Section 1.0 STUDY SUMMARY Section 3.0 SCHEDULES OF STUDY PROCEDURES Table 3.e, Table 3.g, Table 3.i, Table 3 k, Table 3 m Section 5.1.3 Additional/ Exploratory Objectives--[redacted]	[redacted]	[redacted]

Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
	Section 5.1.6 Additional/ Exploratory Objectives-[redacted] Section 5.2.3 Additional/Exploratory Endpoints-[redacted] Section 5.2.6 Additional/Exploratory Endpoints-[redacted] Section 11.1.6.4 Other Safety Parameters		
10.	Section 1.0 STUDY SUMMARY Section 11.1.4 Efficacy [redacted] Analysis Section 11.3 Determination of Sample Size	Change in statistical consideration has been explained.	Part B is a dose-ranging part designed to better characterize the efficacy and safety of TAK-994 to inform late phase development. A fixed sequence statistical hypothesis testing procedure will be applied to evaluate the efficacy of TAK-994 at 3 dose levels via key efficacy endpoints, MWT, ESS, & WCR, while maintaining the overall family-wise type 1 error rate at 0.05 level.
11.	Section 1.0 STUDY SUMMARY Section 6.0 STUDY DESIGN AND DESCRIPTION Section 8.1.4 Randomization Code Creation and Storage	Randomization in Part B and stratification criteria has been added.	Update has been made
12.	Section 1.0 STUDY SUMMARY Section 3.0 SCHEDULES OF STUDY PROCEDURES ABPM footnotes in Table 3.a, Table 3.c, Table 3.e, Table 3.g, Table 3.i, Table 3 k, Table 3 m Section 7.4.1 Dosing Instructions Section 9.2.6.1 ABPM	Ambulatory blood pressure monitoring guidance text has been revised.	ABPM guideline text has been modified to clarify procedure that should be used for this study and because of these modifications additional flexibility was added for the subjects and the sites.

Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
13.	Section 4.3 Benefit/Risk Profile Section 6.3.1.2 Rationale for Study Design Section 6.3.3.1 Safety Endpoints Section 9.2.11.1.2 Chemistry	Glutamate dehydrogenase level and fluoride level measurements have been deleted based on new clinical study data.	Data review from recently completed healthy volunteer study (TAK-994-1001) indicated that pooled aggregate summaries of all cohorts in the of GLDH and fluoride change from baseline by visit date showed that there was no clinically meaningful difference between the active and placebo arms. Therefore, these assessments have been deleted from this Amendment.
14.	Section 3.0 SCHEDULES OF STUDY PROCEDURES ePRO footnotes in: Table 3.a, Table 3.c, Table 3.e, Table 3.g, Table 3.i, Table 3.k, Table 3 m Section 997.3.3 Alcohol Section 9.3.2.7 ePRO Measures	Items to be captured in the electronic patient-reported outcome diary have been revised.	Text has been revised to allow capturing alcohol consumption in the ePRO diary. Also, alternative approach has been added, in case ePRO diary becomes unavailable.
15.	Section 1.0 STUDY SUMMARY Section 3.0 SCHEDULES OF STUDY PROCEDURES [redacted]	Text has been revised to provide additional guidelines [redacted]	Clarification has been added
16.	Section 3.0 SCHEDULES OF STUDY PROCEDURES	Text has been revised to provide additional guidance to the sites regarding collection of blood pressure readings	Text has been revised to provide additional guidance to the sites regarding collection of BP readings
17.	Section 3.0 SCHEDULES OF STUDY PROCEDURES Table 3 f, Table 3.l	Text has been revised to provide clarity to the sites regarding the timing of postdose electrocardiogram.	To provide clarity to the sites regarding the timing of post-dose ECG

Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
18.	Section 3.0 SCHEDULES OF STUDY PROCEDURES Table 3.a, Table 3.c, Table 3.e, Table 3.i, Table 3.k, Table 3.m	Text has been added to further clarify timing of alcohol screens when overnight stay does not occur.	To further clarify timing of alcohol screens when overnight stay does not occur.
19.	Section 3.0 SCHEDULES OF STUDY PROCEDURES Table 3.a, Table 3.c, Table 3.e,Table 3.i, Table 3.k, Table 3 m	Text has been added to further clarify timing of urine drug screen when overnight stay does not occur.	
20.	Section 3.0 SCHEDULES OF STUDY PROCEDURES Table 3 f, Table 3.l,	A practice assessment of cognitive testing has been added on Day -2 to familiarize the subjects with the task requirements.	Update has been made
21.	Section 4.1.3 Clinical Study Experience	Text has been revised with recently completed phase 1 study (TAK-994-1001) unblinded data.	Update has been made
22.	Section 6.1 Study Design Section 6.2 Dose Selection and Cohort Progression Section 6.3.2 Rationale for Dose	Text have been revised regarding the dose selection rules, and dose rationale,	Revision and update
23.	Section 2.0 STUDY SCHEMATICS Figure 2.b Section 3.0 SCHEDULES OF STUDY PROCEDURES Table 3.e (PARTs B and C) Section 6.1 Study Design Section 9.3.3.2 CSF Orexin Measurements (FOR Subjects with NT1 only)	Additional text has been added to clarify that cerebrospinal fluid (CSF) testing will not be offered if such testing is not approved by local health authorities.	Update has been made
24.	Section 6.5.5.1 Criteria for Premature Termination or Suspension	This revision was done to revise stopping criteria for Part B to account for the multiple arm, parallel nature of Part B which includes 112 subjects.	Update has been made

Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
25.	Section 1.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Inclusion criterion #13: Lower limit of BMI for study entry has been changed from 18 to 17 kg/m^2 to consider the patient population in Asia.	Lower limit of BMI for study entry has been changed from 18 to 17 kg/m^2 to consider patient population in Asia.
26.	Section 7.2 Exclusion Criteria	Exclusion criterion #1: Study entry criteria have been clarified for subjects who have recently participated in other studies that may be noninterventional or have required a participant to take an investigational medicinal product.	Update has been made
27.	Section 1.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Exclusion criterion #11: Based on the safety results from Study TAK-994-1001, study entry criteria for liver function tests (alanine aminotransferase, aspartate aminotransferase) have been adjusted.	Update has been made
28.	Section 7.2 Exclusion Criteria	Exclusion criterion #22: Clarity added to criteria regarding "surgical interventions" that are exclusionary for this study.	Clarification has been added
29.	Section 7.2 Exclusion Criteria	Exclusion criterion #26: Flexibility added to allow clinician discretion in cases where a change in clinical status would yield different results.	Update has been made
30.	Section 7.2 Exclusion Criteria	Exclusion criterion #42: Revised to clarify that the site may need to draw a laboratory sample (prothrombin time [PT]/international normalized ratio [INR], activated partial thromboplastin time) during the screening period to allow subject time to read the informed consent and to think about agreeing to the procedure.	Clarification has been added

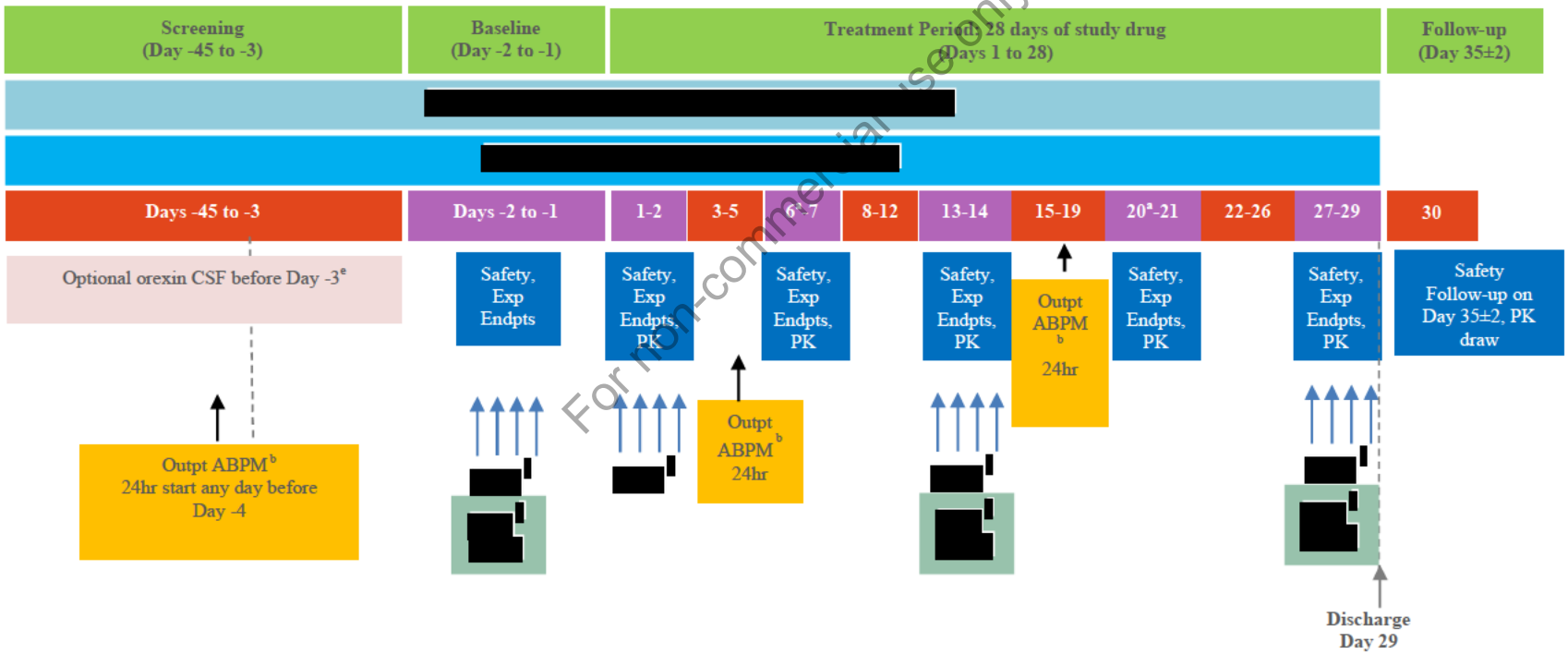
Protocol Amendment 03			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
31.	Section 7.3.3 Alcohol	Guidance text related to alcohol consumption (Parts B and C) has been updated.	Update has been made
32.	Section 8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs	Clarification has been provided for unused drug to be returned to the site.	Clarification has been added
33.	Section 10.2.8.1 Collection Period	AE collection timepoint has been revised to ensure all AEs are collected until 30 days or 5.5 half-lives, whichever is longer, because after 5.5 half-lives no significant investigational product should be circulating for the product to be linked to an AE.	Update has been made
34.	Section 4.1.2 Summary of Nonclinical Data	New data has been added	Update has been made
35	Appendices G, H and I have been added	Appendix G: Criteria for Identification of Markedly Abnormal Laboratory Values-Hematology and Serum Chemistry Appendix H: Criteria for Identification of Markedly Abnormal Laboratory Values for Vital Signs Appendix I: Criteria for Identification of Markedly Abnormal Laboratory Values for ECGs	Clarification has been added

2.0 STUDY SCHEMATICS

A schematic of the study timing and assessments is provided in Figure 2.a (PART A), Figure 2.b (PARTs B-C), and Figure 2.c (PART D)

Figure 2.a Study Schematic (PART A)

Red indicates outpatient status; purple indicates inpatient status.



ABPM: ambulatory blood pressure monitoring; CSF: cerebrospinal fluid; [redacted] Endpts: endpoints; Exp: exploratory; hr: hour; [redacted]; Outpt: outpatient; PK: pharmacokinetic(s).

[a] Days 7 and 21 are clinical visits with optional inpatient overnight stays on Days 6 and 20, based on the subject's availability to travel. If the patient does not stay overnight on days 6 and 20, they must not have anything by mouth past midnight, before they arrive at the clinic on the next day. See Schedule of assessments for additional instructions.

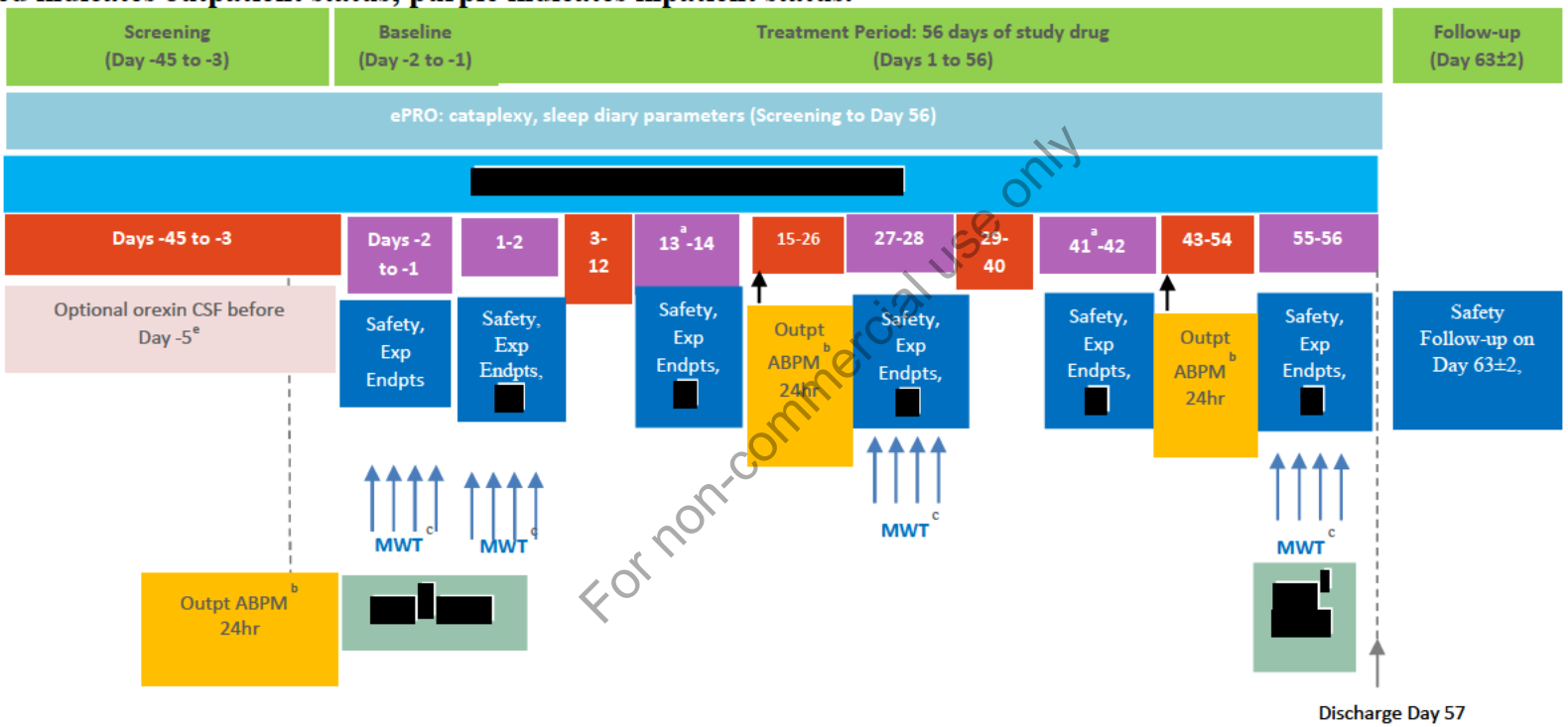
[b] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. See Schedule of assessments for additional instructions.

[redacted]

[c] For subjects participating in the optional CSF sampling, these samples may be collected any day before Day -3 so long as they are not collected within 24 hours in advance of another study procedure, ie, APBM.

Figure 2.b Study Schematic (PARTs B-C)

Red indicates outpatient status; purple indicates inpatient status.



ABPM: ambulatory blood pressure monitoring; CSF: cerebrospinal fluid; ePRO: electronic patient-reported outcome; Endpts: endpoints; Exp: exploratory; hr: hour; MWT: Maintenance of Wakefulness Test; [redacted]; NT1: narcolepsy type 1 (narcolepsy with cataplexy); Outpt: outpatient; [redacted] Red indicates outpatient status; purple indicates inpatient status.

Days 14 and 42 are in-clinic visits with optional inpatient overnight stays on Days 13 and 41, based on the subject's availability to travel. If the patient does not stay overnight on days 13 and 41, they must not have anything by mouth past midnight, before they arrive at the clinic on the next day.

[b] ABPM readings will be obtained over approximately 24-hour period. See Schedule of assessments for additional instructions.

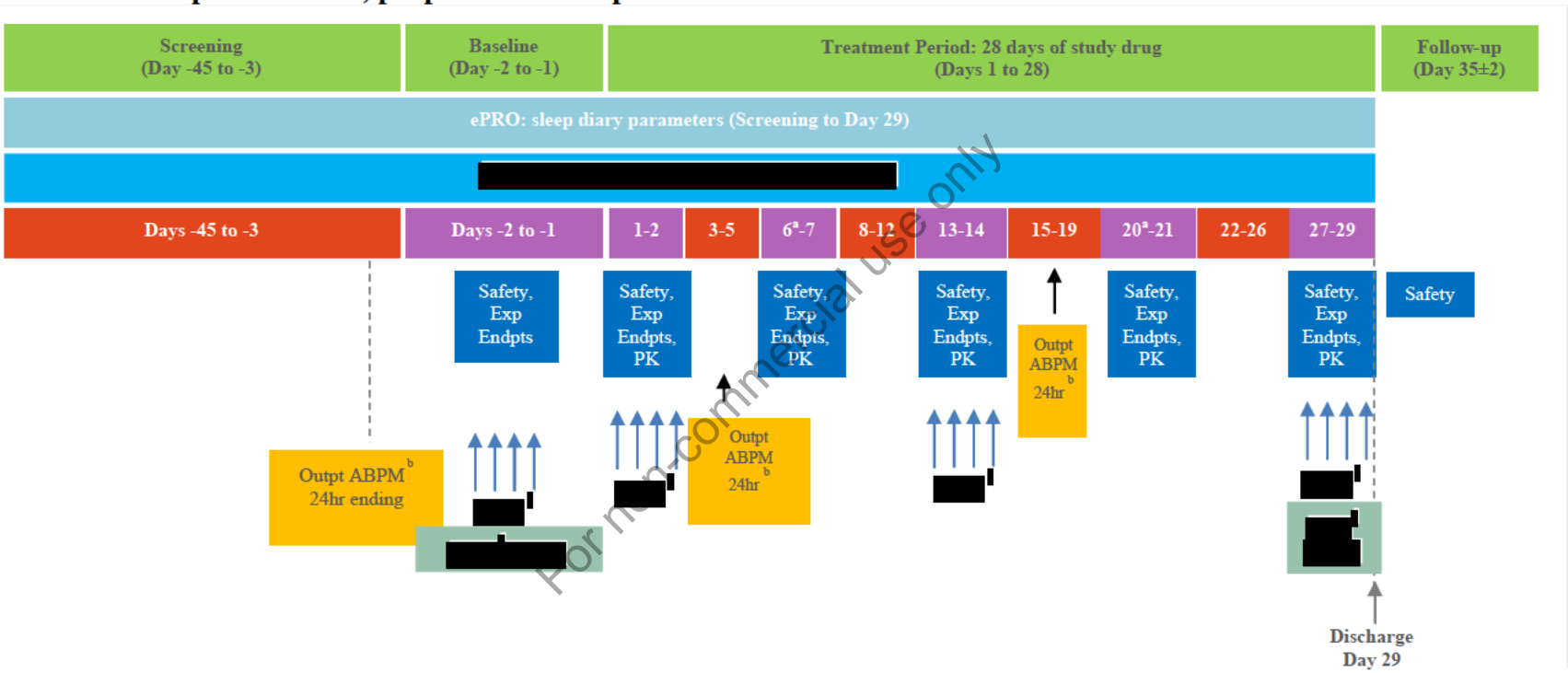
[c] For MWT, confinement will start on evening of Days -2 with MWT done on Days -1 and 1, again on Day 27 with MWT performed on Day 28, and on Day 55 with MWT done on Day 56 with discharge on Day 57.

P [redacted]
u

[b] For subjects participating in the optional CSF sampling, these samples may be collected any day prior to Day -5 so long as they are not collected within 24 hours in advance of another study procedure ie APBM. Optional CSF sampling substudy, may not be available in every region. See Section 9.3.3.2 for details.

Figure 2.c Study Schematic (PART D)

Red indicates outpatient status; purple indicates inpatient status.



ABPM: ambulatory blood pressure monitoring; ePRO: electronic patient-reported outcome; Endpts: endpoints; Exp: exploratory; hr: hour; [redacted] NT2: narcolepsy type 2 (narcolepsy without cataplexy); Outpt: outpatient; PK: pharmacokinetic(s).

[a] Days 7 and 21 are clinical visits with optional inpatient overnight stays on Days 6 and 20, based on the subject's availability to travel. If the patient does not stay overnight on days 6 and 20, they must not have anything by mouth past midnight, before they arrive at the clinic on the next day

[b] ABPM readings will be obtained over approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour period. See Schedule of assessments for additional instructions

[redacted]

3.0 SCHEDULES OF STUDY PROCEDURES

3.1 NT1: PART A-Cohorts A1-A2

3.1.1 Screening Through Day 15 (PART A, Cohorts A1-A2)

Table 3.a Schedule of Study Procedures for Screening Through Day 15 (PART A, Cohort A1-A2)

Day [a]	Screening -45 to -3 [c]	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
Administrative Procedures													
Informed consent or e-consent [b]	X												
Inclusion/exclusion criteria [c]	X	X											
NT1 medication washout [d]	X												
Medical history/Demographics/Prior Medication	X												
Concomitant medication review	X	X	X	X		X		X	X		X	X	
Clinical Procedures/Assessments													
Physical examination [e]	X	X										X	
Funduscopic examination and CSF collection for orexin (optional) [f]	X												
Height and BMI calculation	X												
Weight	X	X											
Vital signs	See Table 3.b												
ABPM [g]	X						X						X (15-20)
12-lead standard ECG	See Table 3.b												
HLA genotyping (HLA-DQB1*06:02) [h]	X												
C-SSRS	X	X							X		X		
TAK-994/placebo administration [i]					X	X	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X		X	X		X	X	
[redacted]													

Table 3.a Schedule of Study Procedures for Screening Through Day 15 (PART A, Cohort A1-A2)

Day [a]	Screening -45 to -3 [c]	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
[redacted]													
Laboratory Procedures/Assessments													
Hematology and blood chemistry [m]	X	X				X			X			X	
Pregnancy test [n]	X		X						X			X	
FSH assessment (optional; postmenopausal women only)	X												
Urinalysis [o]	X	X				X			X			X	
PT/INR and aPTT	X												
Alcohol screening [p]	X	X						X			X		
Urine drug screen [q]	X	X						X			X		
Hepatitis and HIV screen	X												
[redacted]													
PK Evaluations													
Plasma sample for TAK-994 PK	See Table 3.b												
Blood sample for CYP3A4/5 activity	See Table 3.b												

ABPM: ambulatory blood pressure monitoring; AE: adverse event; aPTT: activated partial thromboplastin time; BMI: body mass index; [redacted] CSF: cerebrospinal fluid; C-SSRS: Columbia–Suicide Severity Rating Scale; CYP: cytochrome P-450; ECG: electrocardiogram; [redacted]; ET: early termination; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; [redacted]; INR: international normalized ratio; LP: lumbar puncture; [redacted]; NT1: narcolepsy type 1 (narcolepsy with cataplexy); [redacted]

Table 3.a Schedule of Study Procedures for Screening Through Day 15 (PART A, Cohort A1-A2)

Day [a]	Screening -45 to -3 [c]	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
[redacted]													

[redacted] PK: pharmacokinetic(s); PT: prothrombin time; [redacted]

PART A: Patients will be enrolled in 2:1 ratio to receive TAK-994 or placebo for 28 days, twice daily.

[a] In-clinic visits (marked with clear cells) allow ±1-day window. Outpatient periods are marked with grey cells. Confinement is optional on Days 6 and 20. Check-in should occur in the afternoon on Days -2, 13, and 27. Check-in should occur in the morning on Days 7 and 21 if optional stay does not occur on nights of Days 6 and 20. If the patient does not stay overnight on days 6 and 20, they must not have anything by mouth past midnight, before they arrive at the clinic on the next day. Discharge days are the last day of each confinement period.

[b] Informed consent may be performed by e-consent.

[redacted]

[d] NT1 medication washout before baseline (minimum of 7 days or 5 half-lives for stimulant medications and minimum of 14 days or 5 half-lives for anticataplexy medications, whichever is longer) (see exemptions in Section 7.3).

[e] Full physical examination will be performed at screening and at final discharge (or ET visit). On all other timepoints, an abbreviated physical examination will be done.

[f] Fundoscopic exam will be performed only in those who elect CSF collection and will be evaluated before CSF collection. Coagulation laboratory tests for subjects participating in the optional CSF collection (for orexin); a CSF sample should be taken before Day -3 via LP. Subjects will be required to meet all specified protocol eligibility requirements. Before any LP can be performed, the results of the most recent coagulation panel must be reviewed by the investigator and must indicate that the LP can be performed safely.

[g] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device the following morning. If the subject does not opt to confine the evening before the ABPM, and is travelling to the site for the ABPM fitting the morning of, **they should delay their morning dose of study medication (8 AM ±2 hours)** that day, and take their study drug right after the ABPM device begins recording the measurements in the clinic that morning. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts that morning. Subjects will need to return to the clinic the next day to have the device removed and data downloaded. See Section 9.2.6.1 and study manual for additional details. Below are the timepoints in which ABPM readings should be collected between screening and Day 15:

- **Baseline** ABPM should occur once during screening period starting any day up to Day -4 (ending on Day -3).
- The second (first double-blind) ABPM reading should be collected between Days 3 and 6 (starting no later than the morning of Day 5, if subject is checking into the clinic on Day 6 or starting no later than Day 6 if subject is checking into the clinic on Day 7).

[h] The HLA genotype will be determined only at screening. See Section 9.2.11.2.4.

[i] Each subject in this study will be instructed to take study drug twice daily. Please see Section 7.4.1 for specific dosing instructions.

[redacted]

Table 3.a Schedule of Study Procedures for Screening Through Day 15 (PART A, Cohort A1-A2)

Day [a]	Screening -45 to -3 [c]	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15

[m] Hematology and blood chemistry procedures should occur after at least 8 hours of fasting and predose at all indicated timepoints.

[n] Pregnancy test is required for women of childbearing potential only. Urine hCG testing will be done at screening, within approximately 24 hours before the first study drug administration on Day -1 and at check-in for all other scheduled visits. See Central Laboratory Reference Document for additional details.

[o] Urinalysis: For additional details regarding urinalysis, refer to the Central Laboratory Reference Document.

[p] Alcohol screening: At screening visit, alcohol screening will be done initially with a breathalyzer and if positive, a serum ethanol level will be obtained. For all other timepoints a breathalyzer will be done at check-in. If optional stay does not occur on Day 6, alcohol screening should be done on Day 7 at check-in.

[q] Urine drug screen: May be repeated at any time at the investigator's discretion. Additional details to be found in the Central Laboratory Reference Document. If optional stay does not occur on Day 6, urine drug screen should be done on Day 7 at check-in.

[redacted]

Table 3.b Applicable PK, [redacted] and Safety Assessment Timing for Screening Through Day 15 (PART A, Cohorts A1-A2)

Procedure	Predose				Treatment Period								
Day	-45 to -3	-2	-1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
Primary Specimens													
Plasma sample for TAK-994 PK[a]				Pre AM dose	1, 3, 5, 7, 9, 12, 14 h post AM dose	24 h after Day 1 AM dose but should be collected before Day 2 AM dose			Pre AM dose			Pre AM dose, and 1, 3, 5, 7, 9, 12 h post AM dose	
Blood sample for CYP3A4/5[b]				Pre AM dose					Pre AM dose			Pre AM dose	
Vital Signs/ ECGs													
BP and pulse rate measurements [c]	X	X	Approx. 8 AM, and to match the time at 1, 3, 5, 7, 9, 12, 14 h post Day 1 AM dose.	Pre AM dose	1, 3, 5, 7, 9, 12, 14 h post AM dose	24 h post Day 1 AM dose but should be collected before Day 2 AM dose		X	Pre AM dose		X	Pre AM dose, and 1, 3, 5, 7, 9, 12 h post AM dose	
Respiratory rate and temperature [d]	X	X	X [e]	Pre AM dose [e]	X	Pre AM dose [e]		X	Pre AM dose [e]			Pre AM dose [e]	
12-lead standard ECG [f]	X	X		Pre AM dose	X	Pre AM dose		X	Pre AM dose		X	Pre AM dose	
[redacted]													

Approx: approximately; BP: blood pressure; CYP: cytochrome P-450; ECG: electrocardiogram; [redacted] PK: pharmacokinetic(s); Post: postdose; Pre: pre AM dose; [redacted]

[a] PK is to be done closest to the specified time. ECG, BP, and pulse, should be done near specified times before the PK.

[b] Blood samples for measurement of 4β-hydroxycholesterol/cholesterol ratio to assess CYP3A4/5 activity will be obtained.

[c] On Days 13 and 27, vital signs (pulse rate, BP) will be taken after subject check-in to the site. On optional Days 6 and 20, vital signs may be taken after subject check-in to the site; vital signs should also be taken in the morning of Days 7 and 21 before dosing.

[d] Respiratory rate and body temperature will also be taken once with the first vital sign measurement (pulse rate, BP) at screening and at the times shown. On optional Days 6 and 20, readings may be taken after subject check-in to the site and also in the morning of Days 7 and 21 before dosing.

[e] For these timepoints, respiratory rate and temperature will be taken with first BP, pulse rate assessment.

[f] On Days 13 and 27, ECG will be performed after subject check-in to the site. On optional days 6 and 20, ECG may be performed after subject check-in to the site; otherwise ECG should occur in the mornings of Days 7 and 21 before dosing.

[redacted]

3.1.2 Day 16 Through Day 35 (PART A, Cohorts A1-A2)

Table 3.c Schedule of Study Procedures for Day 16 Through Day 35 (PART A, Cohorts A1-A2)

Day [a]	16-19	20	21 [a]	22-26	27	28	Day 29 Discharge	Day 30	ET [b]	ET on Scheduled Visit [b]	Day 35 ±2 Follow-Up Visit
Administrative Procedures											
NT1 medication restart [c]											X
Concomitant medication review		X	X		X	X	X	X	X	X	X
Clinical Procedures/Assessments											
Physical examination [d]							X		X	X	X
Weight						X			X	X	
Vital signs	See Table 3.d										
ABPM [e]	X (D15-20)										
12-lead standard ECG	See Table 3.d										
C-SSRS			X		X				X	X	X
TAK-994/placebo administration [f]	X	X	X	X	X	X					
AE monitoring		X	X		X	X	X	X	X	X	X
[redacted]											

Table 3.c Schedule of Study Procedures for Day 16 Through Day 35 (PART A, Cohorts A1-A2)

Day [a]	16-19	20	21 [a]	22-26	27	28	Day 29 Discharge	Day 30	ET [b]	ET on Scheduled Visit [b]	Day 35 ±2 Follow-Up Visit
Laboratory Procedures/Assessments											
Hematology and blood chemistry [k]			X			X	X		X	X	X
Pregnancy testing [l]			X			X			X	X	
Urinalysis [m]			X			X	X		X	X	X
Alcohol screening [n]			X		X				X	X	
Urine drug screen [o]			X		X				X	X	
[redacted]											
PK Evaluations											
Plasma sample for TAK-994 PK	See Table 3.d										
Predose sample for CYP3A4/5 activity	See Table 3.d										

ABPM: ambulatory blood pressure monitoring; AE: adverse event; BP: blood pressure; [redacted] C-SSRS: Columbia –Suicide Severity Rating Scale; CYP: cytochrome P-450; ECG: electrocardiogram; [redacted] ET: early termination; hCG: human chorionic gonadotropin; [redacted] NT1: narcolepsy type 1 (narcolepsy with cataplexy); [redacted] PK: pharmacokinetic(s); [redacted]

[a] In-clinic periods (indicated by clear cells) allow a ±1-day window. Outpatient periods are marked with grey cells. Confinement is optional on Days 6 and 20. Check-in should occur in the afternoon on Days -2, 13, and 27. Check-in should occur in the morning on Days 7 and 21 if optional stay does not occur on nights of Days 6 and 20, and all assessments will be done accordingly. If the patient does not stay overnight on days 6 and 20, they must not have anything by mouth past midnight, before they arrive at the clinic on the next day. Discharge days are the last day of each confinement period.

[b] If the subject does not complete all treatment and study specific assessments, he/she will be requested to come to the clinic for an ET visit. If the subject completes all treatment and study specific assessments, the ET visit is not applicable.

[c] Earliest restart of NT1 medication used before washout should be restarted as per the subject's treating physician.

[d] Full physical examination will be performed at screening and at discharge (or ET visit). On all other timepoints, an abbreviated physical examination will be done.

[e] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device the following morning. If the subject does not opt to confine the evening before the ABPM, and is travelling to the site for the ABPM fitting the morning of, they should delay their morning dose of study medication (8 AM ±2 hours) that day, and take their study drug right after the ABPM device begins recording the measurements in the clinic that morning. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts that morning. Subjects will need to return to the clinic the next day to have the device removed and data downloaded. See Section 9.2.6.1 and study manual for additional details. Below are the timepoints in which ABPM readings should be collected between Day 16-35:

- The third (second double-blind) ABPM reading should be collected between Days 15 and 20 (starting no later than the morning of Day 19 if the subject is checking into the clinic on Day 20 or starting no later than the morning of Day 20 if subject is checking in on Day 21).

[f] Each subject in this study will be instructed to take study drug twice daily. Please see Section 7.4.1 for specific dosing and mealtimes instructions

Table 3.c Schedule of Study Procedures for Day 16 Through Day 35 (PART A, Cohorts A1-A2)

Day [a]	16-19	20	21 [a]	22-26	27	28	Day 29 Discharge	Day 30	ET [b]	ET on Scheduled Visit [b]	Day 35 ±2 Follow-Up Visit
[redacted]											

[k] Hematology and blood chemistry procedures should occur after at least 8 hours of fasting and predose at the indicated timepoints.

[l] Pregnancy test is required for women of childbearing potential only. Urine hCG testing will be done within approximately 24 hours before first study drug administration on Day -1 and at check-in for all other scheduled visits. See Central Laboratory Reference Document for additional details.

[m] Additional details about urinalysis may be found in the Central Laboratory Reference Document.

[n] For all visits where indicated, at check-in alcohol screening will be done initially with a breathalyzer and if positive, a serum ethanol level will be obtained. If optional stay does not occur on Day 20, alcohol screening should be done on Day 21 at check-in.

[o] Urine drug screen: May be repeated at any time at the investigator's discretion. Additional details to be found in Central Laboratory Reference Document. If optional stay does not occur on Day 20, urine drug screen should be done on Day 21 at check-in.

Table 3.d Applicable PK, [redacted] and Safety Assessment Timing for Day 16 Through Day 35 (PART A, Cohorts A1-A2)

Procedure	Day in Treatment Period						Postdose/Follow-Up				
Day	16-19	20	21	22-26	27	28	29	30	ET	ET on Scheduled Visit	Follow-Up 35 (±2 days)
Primary Specimens											
Plasma sample for TAK-994 PK[a]			Pre AM Dose			Pre AM dose, and 1, 3, 5, 7, 9, 12, 14 h post AM dose [a]	24 h post Day 28 AM dose	48 h post Day 28 AM dose[b]	X	X	
Blood sample for CYP3A4/5			Pre AM Dose			Pre AM Dose					
Vital Signs/ ECGs											
BP and pulse rate measurements [c]		X	Pre AM Dose		X	Pre AM dose, and 1, 3, 5, 7, 9, 12 and 14 h post AM dose	24 h post Day 28 AM dose		X	X	X
Respiratory rate and temperature [d]		X	Pre AM Dose		X	Pre AM Dose	X		X	X	X
12-lead standard ECG [e]		X	Pre AM Dose		X	Pre AM Dose	X		X	X	X
[redacted]											

BP: blood pressure; CYP: cytochrome P-450; ECG: electrocardiogram; ET: early termination; [redacted] PK: pharmacokinetic(s); [redacted]

[a] PK is to be done closest to the specified time. ECG, BP, and pulse, should be done near specified times before the PK.

[b] If the optional stay does not occur on the night of Day 29, subjects should be discharged on Day 29 after all study assessments are completed and be instructed to return to the clinic on Day 30 for the last 48-hour PK assessment. and then schedule their follow-up visit no later than Day 37 assessment.

[c] Vital signs (pulse rate, BP) will be obtained as indicated. On Days 13 and 27, vital signs will be taken in unit after subject check-in to the site. On optional Days 6 and 20, vital signs will be taken after subject check-in to the site; vital signs should also be taken in the morning of Days 7 and 21 before dosing.

[d] For these timepoints, respiratory rate and temperature will be taken with first BP, pulse rate assessment. On optional Days 6 and 20, readings will be taken after subject check-in to the site and also in the morning of Days 7 and 21 before dosing.

[e] On Days 13 and 27, ECG will be performed after check-in to the site. On optional Days 6 and 20, ECG may be performed after subject check-in to the site, otherwise ECG will be done on the following day.

[redacted]

3.2 NT1: PART B and PART C

3.2.1 Screening Through Day 15 (PART B and PART C)

Table 3.e Schedule of Study Assessment for Screening Through Day 15 (PART B and PART C [Cohort C1])

Day[a]	Screening[c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1		2	3-12	13	14	15
Administrative Procedures				Predose	Postdose					
Informed consent[b]	X									
Inclusion/exclusion criteria[c]	X	X								
NT1 medication washout[d]	X									
Medical history/demographics/prior medication review	X									
Cataplexy questionnaire	X									
Concomitant medication review	X	X	X	X		X		X	X	
Clinical Procedures/Assessments										
Physical examination[e]	X	X							X	
Funduscopic examination and CSF collection for orexin (optional)[f]	X									
Height and BMI calculation	X									
Weight	X	X								
Vital signs	See Table 3.f									
ABPM[g]	X						X			
12-lead standard ECG	See Table 3.f									
HLA genotyping (HLA-DQB1*06:02)[h]	X									
C-SSRS	X	X								
[redacted]										
TAK-994/placebo administration[i]					X	X	X	X	X	X
AE monitoring	X[u]	X	X	X	X	X		X	X	
[redacted]										

Table 3.e Schedule of Study Assessment for Screening Through Day 15 (PART B and PART C [Cohort C1])

Day[a]	Screening[c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1	2	3-12	13	14	15
[redacted]									
Laboratory Procedures/Assessments									
Hematology and blood chemistry[m]	X		X		X			X	
Pregnancy testing[n]	X		X					X	
FSH assessment (optional; postmenopausal women only)	X								
Urinalysis[o]	X		X		X			X	
Alcohol screening[p]	X	X					X		
Urine drug screen[q]	X	X					X		
Hepatitis and HIV screen	X								
[redacted]									

ABPM: ambulatory blood pressure monitoring; AE: adverse event; BMI: body mass index; [redacted] CSF: cerebrospinal fluid; C-SSRS: Columbia-Suicide Severity Rating Scale; [redacted] ECG: electrocardiogram; [redacted] FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; ICSD-3: International Classification of Sleep Disorders, 3rd edition; LP: lumbar puncture; MSLT: Multiple Sleep Latency Test; [redacted]

Table 3.e Schedule of Study Assessment for Screening Through Day 15 (PART B and PART C [Cohort C1])

Day[a]	Screening[c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1	2	3-12	13	14	15
[redacted] NT1: narcolepsy type 1 (narcolepsy with cataplexy); [redacted] PT: prothrombin time.									

Part B is a 4-treatment group parallel design with subjects randomized to 1 of 3 different TAK-994 dose levels or placebo. Part C will recruit subjects in China to be randomized in a ratio of 2:1 to receive TAK-994 twice daily or matching placebo.

[a] In-clinic periods are indicated by clear cells, allows a ±1-day window. Outpatient periods are marked with grey cells. Check-in should occur in the afternoon on Days -2, 13 (optional), 27, 41 (optional) and 55; otherwise, check-in should occur in the morning if optional stay does not occur on nights of Days 13 or 41. If the patient does not stay overnight on days 13 and 41, they must be instructed to not have anything by mouth past midnight, before they arrive at the clinic on the next day. Discharge days are the last day of each confinement period.

[b] Informed consent may be performed by e-consent.

[c] If no [redacted] MSLT has been performed within the past 10 years, meeting the minimal acceptance criteria as outlined by the ICSD-3 criteria, special exemptions, i.e. ability of the site to repeat the diagnostic [redacted] MSLT will be considered on a case-by-case basis after discussions between the investigator and the sponsor or designee.

[d] NT1 medication washout before Day -2 (see details in Section 7.3).

[e] Full physical examination will be performed at screening and at discharge (or ET visit). On all other timepoints, an abbreviated physical examination will be performed.

[f] Subject to local laboratory regulations and guidelines (including limitations on sample export) as well as institutional review board/independent ethics committee approval. In those subjects participating in optional CSF testing for orexin levels, fundoscopic examination and coagulation laboratory tests should be performed and evaluated by the investigator to ensure that the LP can be performed safely. The CSF sample should be obtained before Day -5 via LP. Subjects will be required to meet all specified protocol eligibility requirements.

[g] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device the following morning. If the subject does not opt to confine the evening before the ABPM and is travelling to the site for the ABPM fitting the morning of, **they should delay their morning dose of study medication (8 AM ±2 hours)** that day, and take their study drug right after the ABPM device begins recording the measurements in the clinic that morning. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts that morning. Subjects will need to return to the clinic the next day to have the device removed and data downloaded. See Section 9.2.6.1 and study manual for additional details. Below are the timepoints in which ABPM readings should be collected from screening to Day 15:

- Baseline ABPM should occur once during screening period starting any day up to Day -4 (ending on Day -3).
- The second (first double-blind) ABPM reading should be collected between Days 3 and 12 (starting no later than the morning of Day 12 ending on Day 13 or starting no later than the morning of Day 13 if the subject is checking into the clinic on Day 14).

[h] The HLA genotype will be determined only at screening. See Section 9.2.11.2.4.

[i] Each subject in this study will be instructed to take study drug twice daily. Please see Section 7.4.1 for specific dosing and mealtimes instructions.

[redacted]

Table 3.e Schedule of Study Assessment for Screening Through Day 15 (PART B and PART C [Cohort C1])

Day[a]	Screening[c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1	2	3-12	13	14	15
[redacted]									

[m] Hematology and blood chemistry procedures should occur after at least 8 hours of fasting and predose.

[n] Pregnancy test is required for women of childbearing potential only. Serum pregnancy test will be done at screening and final discharge/early termination. At all other timepoints, urine hCG testing will be done. Urine hCG testing will be done within approximately 24 hours before first study drug administration on Day -1 and at check-in for all other scheduled visits. Pregnancy testing can be repeated at any time at the investigator's discretion.

[o] For additional details regarding urinalysis, refer to the Central Laboratory Reference Document.

[p] At screening visit, alcohol screening will be done initially with a breathalyzer and if positive, a serum ethanol level will be obtained. For all other timepoints a breathalyzer will be done at check-in. If optional stay does not occur on Day 13, alcohol screening should be done on Day 14 at check-in.

[q] Urine drug screen: May be repeated at any time at the investigator's discretion. Additional details to be found in Central Laboratory Reference Document. If optional stay does not occur on Day 13, urine drug screen should be done on Day 14 at check-in. For confirmatory urine drug screen, please refer to Section 9.2.11.2.3.

[redacted]

Table 3.f Applicable [redacted], Efficacy and Safety Assessment Timing: Screening Through Day 15 (PARTs B-C)

Procedure	Predose				Treatment Period					
Day	-45 to -3	-2	-1	1 Predose	1 Postdose	2	3-12	13	14	15
Primary Specimens										
[redacted]										
Vital Signs/ ECGs										
BP and pulse rate measurements [b]	X	X	Approx. 8 AM, and to **match the timepoints** when 1, 3, 5, 7, 9, 12, 14 h post Day 1 AM dose will happen	Pre AM dose	Approx. at 1, 3, 5, 7, 9, 12, 14 h post AM dose	A 24 h after Day 1 AM dose, but should be collected before Day 2 AM dose		X	Pre AM dose	
Respiratory rate and temperature [c]	X	X	X	Pre AM dose	X	X		X	X	
12-lead standard ECG [d]	X			Pre-AM dose	X	Pre AM dose		X	Pre AM dose	
[redacted] **Efficacy Evaluations**										
MWT [e]			To **match the timepoints** when 2, 4, 6, and 8 h post Day 1 AM dose will happen		2, 4, 6, and 8 h post AM dose					
[redacted]										

Approx: approximately; BP: blood pressure; [redacted] CYP: cytochrome P-450; ECG: electrocardiogram; [redacted] Post: postdose; [redacted]

[a] PK is to be done closest to the specified time. ECG, BP, and pulse, should be done near specified times before the PK.
[b] Vital signs will be taken as indicated. Vital signs should be taken in unit after subject check-in to the site before the confinement period on Day -2. On Days -45 (or the first screening visit) and -2, blood pressure reading will be collected 3 times and the median result used to assess eligibility. If optional Days 13 and 41 occur, vital signs should be done after subject check-in to the site on these days. If optional Days 13 and 41 do not occur, vital signs should be done after check-in on Day 14 and 42.
[c] Respiratory Rate and body temperature will also be taken once with the first vital sign assessment (pulse rate, BP) at screening and the times indicated. If subjects check-in on optional Days 13 and 41 occur, readings should be done after subject check-in to the site on these days. Otherwise, readings should be done after check-in on Day 14 and 42.
[d] ECG will be done at screening, and at all timepoints mentioned. On Day 1, the postdose ECG may occur any time after the first dose; it does not need to occur before the second dose. If optional overnight stays on Day 13 and 41 occur, ECG should be performed after subject check-in to the site on these days. If optional Days 13 and 41 do not occur, ECG should occur in the mornings of Day 14 and 42 before dosing.
[e] The MWT should be done as close as possible to the specified times;
[redacted]

3.2.2 Day 16 Through Day 32 (PART B and PART C)

Table 3.g Schedule of Study Procedures for Day 16 Through Day 32 (PART B and PART C)

Day [a]	16-25	26	27	28	29	30	31	32
Administrative Procedures								
NT1 medication restart [b]								
Medical history/demographics								
Concomitant medication review			X	X				
Clinical Procedures/Assessments								
Physical examination [c]				X				
Vital signs (pulse rate, systolic, and diastolic BP)	See Table 3 h							
ABPM [d]	X (15-25)							
12-lead ECG standard	See Table 3 h							
TAK-994/placebo administration [e]	X	X	X	X	X	X	X	X
[redacted]								
AE monitoring			X	X				
[redacted]								
Laboratory Procedures/Assessments								
Hematology and blood chemistry [j]				X				

Table 3.g Schedule of Study Procedures for Day 16 Through Day 32 (PART B and PART C)

Day [a]	16-25	26	27	28	29	30	31	32
Pregnancy testing [k]				X				
Urinalysis [l]				X				
Alcohol screening [m]			X					
Urine drug screen [n]			X					
[redacted]								

ABPM: ambulatory blood pressure monitoring; AE: adverse event; BP: blood pressure; [redacted] C-SSRS: Columbia–Suicide Severity Rating Scale; [redacted]; ECG: electrocardiogram; [redacted] patient-reported outcome; [redacted]; ET: early termination; hCG: human chorionic gonadotropin; [redacted] NT1: narcolepsy type 1 (narcolepsy with cataplexy); [redacted]

[a] In-clinic visits are indicated by clear cells and allow a ±1-day window. Outpatient periods are marked with grey cells. Check-in should occur in the afternoon of Day 27 for Day 28 in-patient assessments. Discharge days are the last day of each confinement period.

[b] Earliest restart of NT1 medication used before washout; to be restarted as per the subject's treating physician.

[c] Physical examination: Full physical examination will be performed at screening and at discharge (or ET visit). On all other timepoints, an abbreviated physical examination will be done.

[d] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device the following morning. If the subject does not opt to confine the evening before the ABPM, and is travelling to the site for the ABPM fitting the morning of, **they should delay their morning dose of study medication (8 AM ±2 hours)** that day, and take their study drug right after the ABPM device begins recording the measurements in the clinic that morning. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts that morning. Subjects will need to return to the clinic the next day to have the device removed and data downloaded. See Section 9.2.6.1 and study manual for additional details.

- The third (second double-blind) ABPM reading should be collected between Day 15 and 25 (starting no later than the morning of Day 25 ending on Day 26).

[e] Each subject in this study will be instructed to take study drug twice daily. Please see Section 7.4.1 for specific dosing and mealtimes instructions.

[redacted]

[j] Hematology and blood chemistry procedures should occur after at least 8 hours of fasting and predose.

[k] Pregnancy test is required for women of childbearing potential only. Serum pregnancy test will be done at screening and final discharge/early termination. At all other timepoints, urine hCG testing will be done. Urine hCG testing will be done within approximately 24 hours before first study drug administration on Day -1 and at check-in for all other scheduled visits. Pregnancy testing can be repeated at any time at the investigator's discretion.

Table 3.g Schedule of Study Procedures for Day 16 Through Day 32 (PART B and PART C)

Day [a]	16-25	26	27	28	29	30	31	32

[l] Additional details about urinalysis may be found in the Central Laboratory Reference Document.

[m] For all indicated timepoints, alcohol screening will be done initially with a breathalyzer at check-in and if positive, a serum ethanol level will be obtained.

[a] Urine drug screen: May be repeated at any time at the investigator's discretion. Additional details to be found in the Central Laboratory Reference Document. For confirmatory urine drug screen, please refer to Section 9.2.11.2.3.

Table 3.h Applicable [redacted], Efficacy and Safety Assessment Timing for Day 16 Through Day 32 (PARTs B-C)

Procedure	Day in Treatment Period			
Day	16-26	27	28	29-32
Primary Specimens				
[redacted]				
Vital Signs/ ECGs				
BP and pulse rate measurements [b]		X	Pre AM dose, and 1, 3, 5, 7, 9, 12h post AM dose	
Respiratory rate and temperature [b]		X	Pre AM Dose	
12-lead standard ECG [c]			Pre AM Dose	
[redacted]				

BP: blood pressure; [redacted] CYP: cytochrome P-450; ECG: electrocardiogram; MWT: Maintenance of Wakefulness Test; [redacted] PK: pharmacokinetic(s); [redacted]

[b] On Day 27, pre-dose vital signs will be taken in unit after subject check-in to the site. Vital signs will also be taken in the morning of Day 28 before dosing and at other times indicated.

[c] On Day 28, ECG will be performed.

[redacted]

3.2.3 Day 33 Through Day 63 (PART B and PART C)

Table 3.i Schedule of Study Procedures for Day 33 Through Day 63 (PARTs B-C)

Day[a]	33-40	41	42	43-54	55	56	Day 57 Discharge[p]	ET[b]	ET on Scheduled Visit[b]	Day 63 ±2 Follow-Up Visit[q]
Administrative Procedures										
NT1 medication restart[c]										X
Medical history/Demographics/prior medication										
Concomitant medication review		X	X		X	X	X	X	X	X
Clinical Procedures/Assessments										
Physical examination[d]			X			X		X	X	X
Weight						X		X	X	
Vital signs	See Table 3.j									
ABPM[e]				X						
12-lead ECG standard	See Table 3.j									
C-SSRS						X		X	X	X
TAK-994/placebo administration[f]	X	X	X	X	X	X				
[redacted]										
AE monitoring		X	X		X	X	X	X	X	X
[redacted]										

Table 3.i Schedule of Study Procedures for Day 33 Through Day 63 (PARTs B-C)

Day[a]	33-40	41	42	43-54	55	56	Day 57 Discharge[p]	ET[b]	ET on Scheduled Visit[b]	Day 63 ±2 Follow-Up Visit[q]
[redacted]										
Laboratory Procedures/Assessments										
Hematology and blood chemistry[j]			X			X		X	X	X
Pregnancy testing[k]			X			X		X	X	X
Urinalysis[l]			X			X		X	X	X
Alcohol screening[m]		X			X			X	X	
Urine drug screen[n]		X			X			X	X	
[redacted]										

ABPM: ambulatory blood pressure monitoring; AE: adverse event; [redacted] C-SSRS: Columbia–Suicide Severity Rating Scale; [redacted]; ECG: electrocardiogram; [redacted]; ET: early termination; hCG: human chorionic gonadotropin; [redacted]; NT1: narcolepsy type 1 (narcolepsy with cataplexy); [redacted]

[a] In-clinic period are indicated by clear cells and allow a ±1-day window. Outpatient periods are marked with grey cells. Check-in may occur in the afternoon of Day 41 for visit day 42; Day 42 is a clinical visit with optional inpatient overnight stay on Day 41, based on the subject's availability to travel. If the patient does not stay overnight on Day 41, they must not have anything by mouth past midnight, before they arrive at the clinic on the next day. Discharge days are the last day of each confinement period. Check-in should occur in the afternoon for Day 55 for visit days 56-57.

[b] If the subject does not complete all treatment and study specific assessments, he/she will be requested to come to the clinic for an ET visit. If the subject completes all treatment and study specific assessments, the ET visit is not applicable.

[c] Earliest restart of NT1 medication used before washout should be restarted as per the subject's treating physician.

[d] Full physical examination will be performed at screening and at discharge (or ET visit). On all other timepoints, an abbreviated physical examination will be performed.

Table 3.i Schedule of Study Procedures for Day 33 Through Day 63 (PARTs B-C)

Day[a]	33-40	41	42	43-54	55	56	Day 57 Discharge[p]	ET[b]	ET on Scheduled Visit[b]	Day 63 ±2 Follow-Up Visit[q]

[e] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device the following morning. If the subject does not opt to confine the evening before the ABPM, and is travelling to the site for the ABPM fitting the morning of, **they should delay their morning dose of study medication (8 AM ±2 hours)** that day, and take their study drug right after the ABPM device begins recording the measurements in the clinic that morning. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts that morning. Subjects will need to return to the clinic the next day to have the device removed and data downloaded. See Section 9.2.6.1 and study manual for additional details. The following timepoint should be collected for Days 33 to 63:

- The last (third double-blind) ABPM reading should be collected between Day 43 and Day 54 (starting no later than the morning of Day 53 and ending on Day 54).

[f] Each subject in this study will be instructed to take study drug twice daily. Please see Section 7.4.1 for specific dosing and mealtimes instructions.

[i] [redacted]

[j] Hematology and blood chemistry procedures should occur after at least 8 hours of fasting and predose.

[k] Pregnancy test is required for women of childbearing potential only. Serum pregnancy test will be done at Screening and Day 56 /ET visit. At all other timepoints, urine hCG testing will be done. Urine hCG testing will be done within approximately 24 hours before first study drug administration on Day -1 and at check-in for all other scheduled visits. Pregnancy testing can be repeated at any time at the investigator's discretion.

[l] Additional details on urinalysis may be found in the Central Laboratory Reference Document.

[m] For all indicated timepoints, alcohol screening will be done initially with a breathalyzer at check-in and if positive, a serum ethanol level will be obtained. Breathalyzer will be done during check-in to the clinic. If optional stay does not occur on Day 41, alcohol screening should be done on Day 42 at check-in.

[n] Urine drug screen may be repeated at any time at the investigator's discretion. Additional details to be found in the Central Laboratory Reference Document. If optional stay does not occur on Day 41, urine drug screen should be done on Day 42 at check-in. For confirmatory urine drug screen, please refer to Section 9.2.11.2.3.

[p] [redacted]

Table 3.i Schedule of Study Procedures for Day 33 Through Day 63 (PARTs B-C)

Day[a]	33-40	41	42	43-54	55	56	Day 57 Discharge[p]	ET[b]	ET on Scheduled Visit[b]	Day 63 ±2 Follow-Up Visit[q]

[p] Part B only: Subjects at participating sites (countries) who enroll into the open-label extension study, all assessments for Day 57 should be done before the first dose of open-label extension.

[q] Part B only: Subjects at participating sites (countries) who enroll into the open-label extension study, may not require the follow up visit for this study.

Table 3.j Applicable [redacted] and Safety Assessment Timing for Day 33 Through Day 63 (PARTs B-C)

Procedure	Day in Treatment Period						Postdose Assessments/Follow-Up			
Day	33-40	41	42	43-54	55	56	Day 57 discharge [f]	ET	ET on Scheduled Visit	Follow-Up 63 (±2 days) [g]
Primary Specimens										
[redacted]										
Vital Signs/ ECGs										
BP and pulse rate measurements [b]		X	Pre AM dose		X	Pre, and 1, 3, 5, 7, 9, 12 and 14 h post AM dose	24 h post Day 56 AM dose	X	X	X
Respiratory rate and temperature		X	X		X	X	X	X	X	X
12-lead standard ECG [c]			Pre AM dose			X	X	X	X	X
[redacted]										

BP: blood pressure; [redacted]; ECG: electrocardiogram; ET: early termination; [redacted] Pre: predose; [redacted]

[b] On Days 42, vital signs will be taken pre-dose. On all other timepoints, vital signs will be taken as indicated. Day 42 is clinical visits with optional inpatient overnight stays on Day 41, based on the subject's availability to travel.

[c] On Days 42, ECG will be performed pre-dose, unless it has been done on Day 41; Day 42 is clinical visit with optional inpatient overnight stays on Day 41, based on the subject's availability to travel.

[redacted]

[f] Part B only: Subjects at participating sites (countries) who enroll into the open-label extension study, all assessments for day 57 should be done before the first dose of open-label extension.

[g] Part B only: Subjects at participating sites (countries) who enroll into the open-label extension study, may not require the follow up visit for this study.

3.3 NT2: PART D (Cohorts D1 and D2)

3.3.1 Screening Through Day 15 (Part D, Cohorts D1 and D2)

Table 3.k Schedule of Study Procedures for Screening Through Day 15 (Cohorts D1 and D2)

Day [a]	Screening [c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
Administrative Procedures													
Informed consent [b]	X												
Inclusion/exclusion criteria [c]	X	X											
NT2 medication washout [d]	X												
Medical History/Demographics/ Prior Medication	X												
Concomitant medication review	X	X	X	X		X		X	X		X	X	
Clinical Procedures/Assessments													
Physical examination [e]	X	X										X	
Height and BMI calculation	X												
Weight	X	X											
Vital signs	See Table 3.1												
ABPM [f]	X						X (3-6)						X (15-20)
12-lead ECG standard	See Table 3.1												
C-SSRS	X	X							X		X		
TAK-994/placebo administration [g]					X	X	X	X	X	X	X	X	X
[redacted]													
AE monitoring	X	X	X	X	X	X		X	X		X	X	
[redacted]													

Table 3.k Schedule of Study Procedures for Screening Through Day 15 (Cohorts D1 and D2)

Day [a]	Screening [c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
[redacted]													
Laboratory Procedures/Assessments													
Hematology and blood chemistry [k]	X		X			X			X			X	
Pregnancy testing [l]	X		X						X			X	
FSH assessment (optional; postmenopausal women only)	X												
Urinalysis [m]	X		X			X			X			X	
Alcohol screening [n]	X	X						X			X		
Urine drug screen [o]	X	X						X			X		
Hepatitis and HIV screen	X												
[redacted]													
PK Evaluations													
Plasma sample for TAK-994 PK	See Table 3.1												
Predose blood sample for CYP3A4/5 activity	See Table 3.1												

ABPM: ambulatory blood pressure monitoring; AE: adverse event; aPTT: activated partial thromboplastin time; BMI: body mass index; BP: blood pressure; [redacted] C-SSRS: Columbia–Suicide Severity Rating Scale; CYP: cytochrome P-450; ECG: electrocardiogram; [redacted] ET: early termination; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; HLA: human leukocyte antigen; ICSD-3: International Classification of Sleep Disorders, 3rd edition; INR: international normalized ratio; MSLT: Multiple Sleep Latency Test; [redacted] NT2: narcolepsy type 2

Table 3.k Schedule of Study Procedures for Screening Through Day 15 (Cohorts D1 and D2)

Day [a]	Screening [c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
(narcolepsy without cataplexy); [redacted]													
PK: pharmacokinetic(s); [redacted] PT: prothrombin time													

[a] In-clinic visits (marked with clear cells) allow ±1-day window. Outpatient periods are marked with grey cells. Check-in should occur in the afternoon on Days -2, 6, 13, 20 and 27. If optional stay does not occur on Days 6 and 20, check-in should occur in the morning of Days 7 and 21. If the patient does not stay overnight on days 6 and 20, they should be instructed to not have anything by mouth past midnight, before they arrive at the clinic on the next day. Discharge days are the last day of each confinement period.

[b] Informed consent may be performed by e-consent.

[c] If no [redacted] MSLT has been performed within the past 10 years, meeting the minimal acceptance criteria as outlined by the ICSD-3 criteria, special exemptions, ie, ability of the site to repeat the diagnostic [redacted] MSLT will be considered on a case-by-case basis after discussions between the investigator and the sponsor or designee.

[d] NT2 medication washout before day -2 (minimum of 7 days or 5 half-lives for stimulant medications). See Section 7.3 for details.

[e] Physical examination: Full physical examination will be performed at screening and at discharge (or ET visit). On all other timepoints, an abbreviated physical examination will be done as medically required.

[f] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device the following morning. If the subject does not opt to confine the evening before the ABPM, and is travelling to the site for the ABPM fitting the morning of, **they should delay their morning dose of study medication (8 AM ±2 hours)** that day, and take their study drug right after the ABPM device begins recording the measurements in the clinic that morning. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts that morning. Subjects will need to return to the clinic the next day to have the device removed and data downloaded. See Section 9.2.6.1 and study manual for additional details. Below are the timepoints in which ABPM readings should be collected between screening and Day 15:

- Baseline ABPM should occur once during screening period starting any day up to Day -4 (ending on Day -3).
- The second (first double-blind) ABPM reading should be collected between Days 3 and 6 (starting no later than the morning of Day 5, if the subject is checking into the clinic on Day 6 or starting no later on Day 6 if subject is checking into the clinic on Day 7).

[g] Each subject in this study will be instructed to take study drug twice daily Please see Section 7.4.1 for specific dosing and mealtimes instructions.

[redacted]

Table 3.k Schedule of Study Procedures for Screening Through Day 15 (Cohorts D1 and D2)

Day [a]	Screening [c] -45 to -3	Check-in/ Baseline -2	Baseline -1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
[redacted]													

Hematology and blood chemistry procedures should occur after at least 8 hours of fasting and predose.

[l] Pregnancy test is required for women of childbearing potential only. Serum pregnancy test will be done at Screening and final discharge (or early termination). At all other timepoints, urine hCG testing will be done. Urine hCG testing will be done within approximately 24 hours before first study drug administration on Day -1 and at check-in for all other scheduled visits. Pregnancy testing can be repeated at any time at the investigator's discretion.

[m] For additional details regarding urinalysis, refer to the Central Laboratory Reference Document.

[n] At screening visit, alcohol screening will be done initially with a breathalyzer and if positive, a serum ethanol level will be obtained. For all other timepoints a breathalyzer will be done at check-in. If optional stay does not occur on Day 6, alcohol screening should be done on Day 7 at check-in.

[o] Urine drug screen: May be repeated at any time at the investigator's discretion. Additional details to be found in the Central Laboratory Reference Document. If optional stay does not occur on Day 6, urine drug screen screen should be done on Day 7 at check-in. For confirmatory urine drug screen, please refer to Section 9.2.11.2.3.

[redacted]

Table 3.1 Applicable PK, [redacted] and Safety Assessment Timing for Screening Through Day 15 (PART D, Cohorts D1 and D2)

Procedure	Predose				Treatment Period								
Day	-45 to -3	-2	-1	1 Predose	1 Postdose	2	3-5	6	7	8-12	13	14	15
Primary Specimens													
Plasma sample for TAK-994 PK [a]				Pre AM dose	1, 3, 5, 7, 9, 12, 14 h post AM dose [a]	24 h after Day 1 AM dose but should be collected before Day 2 AM dose			Pre AM dose			Pre, and 1, 3, 5, 7, 9, 12h post AM dose [a]	
Blood sample for CYP3A4/5				Pre AM dose					Pre AM dose			Pre AM dose	
Vital Signs/ ECGs													
BP and pulse rate/heart rate measurements [b]	X	X	Approx. 8 AM, and to **match the timepoints** when 1, 3, 5, 7, 9, 12, 14 h post Day 1 AM dose	Pre AM dose	1, 3, 5, 7, 9, 12, 14 h post AM dose	24 h post but should be collected before Day 2 dose		X	Pre AM dose		Approx. 2000 (12 h post AM dose)	Pre AM dose, and 1, 3, 5, 7, 9, 12 h post AM dose	
Respiratory rate and temperature [c]	X	X	X	Pre AM dose	X	Pre AM dose		X	Pre AM dose		X	Pre AM dose	
12-lead standard ECG [d]	X	X		Pre AM dose	X	Pre AM dose		X	Pre AM dose		X	Pre AM dose	
[redacted]													

Approx: approximately; BP: blood pressure; [redacted]; CYP: cytochrome P-450; ECG: electrocardiogram; [redacted]; PK: pharmacokinetic(s); Post: postdose; Pre: predose; [redacted].

PK: When feasible, PK can be collected at home. ECG, BP, and pulse, should be done near specified times before the PK.

[b] Vital signs will be taken as indicated. On Days -45 (or first screening visit, as applicable) and Days -2, BP readings should be taken 3 times and the median measurement should be used to assess eligibility. Vital signs should be taken in unit after subject check-in to the site before the confinement periods on Days -2, 7, 13, 21, and 27; On optional Days 6 and 20, vital signs will be taken after subject check-in to the site in the evenings.

[c] Readings should be taken in unit after subject check-in to the site before the confinement periods on Days -2, 7, 13, 21, and 27; On optional Days 6 and 20, readings will be taken after subject check-in to the site in the evenings.

[d] ECG will be performed after subject check-in to the site in the evening before the confinement periods or in the mornings before dosing. On Day 1, the postdose ECG may occur any time after the first dose; it does not need to occur before the second dose. If the patient does not stay overnight on days 6 and 20, ECGs will be done predose on days 7 and 21.

[redacted]

3.3.2 Day 16 Through Day 35 (PART D, Cohorts D1 and D2)

Table 3.m Schedule of Study Procedures for Day 16 Through Day 35 (PART D, Cohorts D1 and D2)

Day [a]	16-19	20	21	22-26	27	28	Day 29 Discharge	ET [b]	ET on Scheduled Visit [b]	Day 35 ±2 Follow-Up Visit
Administrative Procedures										
NT2 medication restart [c]										X
Medical history/Demographics/ Prior medication										
Concomitant medication review		X	X		X	X	X	X	X	X
Clinical Procedures/Assessments										
Physical examination [d]							X	X	X	X
Weight						X		X	X	
Vital signs	See Table 3 n									
ABPM [e]	X (15-20)									
12-lead ECG standard See Table	See Table 3 n									
C-SSRS			X		X			X	X	X
TAK-994/placebo administration [f]	X	X	X	X	X	X				
[redacted]										
AE monitoring		X	X		X	X	X	X	X	X
[redacted]										

Table 3.m Schedule of Study Procedures for Day 16 Through Day 35 (PART D, Cohorts D1 and D2)

Day [a]	16-19	20	21	22-26	27	28	Day 29 Discharge	ET [b]	ET on Scheduled Visit [b]	Day 35 ±2 Follow-Up Visit
[redacted]										
Laboratory Procedures/Assessments										
Hematology and blood chemistry [j]			X			X		X	X	X
Pregnancy testing [k]			X			X		X	X	
Urinalysis [l]			X			X		X	X	X
Alcohol screening [m]		X			X			X	X	
Urine drug screen [n]		X			X			X	X	
[redacted]										
PK Evaluations										
Plasma sample for TAK-994 PK	See Table 3 n									
Predose sample for CYP3A4/5 activity	See Table 3 n									

ABPM: ambulatory blood pressure monitoring; AE: adverse event; BP: blood pressure; [redacted] C-SSRS: Columbia–Suicide Severity Rating Scale; CYP: cytochrome P-450; ECG: electrocardiogram; [redacted] ET: early termination; hCG: human chorionic gonadotropin [redacted] NT2: narcolepsy type 2 (narcolepsy without cataplexy); [redacted] PK: pharmacokinetic(s); [redacted]

[a] In-clinic visits are marked by clear cells and allow a ±1-day window. Outpatient periods are marked with grey cells. Check-in should occur in the afternoon on Days 20 (optional) and 27. If the patient does not stay overnight on Day 20, they must not have anything by mouth past midnight, before they arrive at the clinic on the next day. Discharge days are the last day of each confinement period.

[b] If the subject does not complete all treatment and study specific assessments, he/she will be requested to come to the clinic for an ET visit. If the subject completes all treatment and study specific assessments, the ET visit is not applicable.

[c] Earliest restart of NT2 medication used before washout; to be restarted as per the subject's treating physician.

[d] Full physical examination will be performed at screening and at discharge (or ET visit). On all other timepoints, an abbreviated physical examination will be done.

[e] ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device the following morning. If the subject does not opt to confine the evening before the ABPM, and is travelling to the site for the ABPM fitting the morning of, **they should delay their morning dose of study medication (8 AM ±2 hours)** that day, and take their study drug right after the ABPM device begins recording the measurements in the clinic that morning. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts that morning. Subjects will need to return to the clinic the next day to have the device removed and data downloaded. See Section 9.2.6.1 and study manual for additional details. Below are the timepoints when ABPM should be collected between Days 16 and 35:

- The third (second double-blind) ABPM reading should be collected between Days 15 and 20 (starting no later than the morning of Day 19 if subject is checking into clinic on Day 20 or starting

Table 3.m Schedule of Study Procedures for Day 16 Through Day 35 (PART D, Cohorts D1 and D2)

Day [a]	16-19	20	21	22-26	27	28	Day 29 Discharge	ET [b]	ET on Scheduled Visit [b]	Day 35 ±2 Follow-Up Visit

morning of Day 20 if subject is checking into clinic on Day 21).

[f] Each subject in this study will be instructed to take study drug twice daily. Please see Section 7.4.1 for specific dosing and mealtimes instructions.

[redacted]

[j] Hematology and blood chemistry procedures should occur after at least 8 hours of fasting and predose.

[k] Pregnancy test is required for women of childbearing potential only. Serum pregnancy test will be done at screening and discharge/ET. At all other timepoints, urine hCG testing will be done. Urine hCG testing will be done within approximately 24 hours before first study drug administration on Day -1 and at check-in for all other scheduled visits. Pregnancy testing can be repeated at any time at the investigator's discretion.

[l] Urinalysis-Additional details about urinalysis may be found in the Central Laboratory Reference Document.

[m] For all indicated timepoints, alcohol screening will be done initially with a breathalyzer at check-in and if positive, a serum ethanol level will be obtained. If optional stay does not occur on Day 20, alcohol screening should be done on Day 21 at check-in.

[n] Urine drug screen: May be repeated at any time at the investigator's discretion. Additional details to be found in the Central Laboratory Reference Document. If optional stay does not occur on Day 20, urine drug screen should be done on Day 21 at check-in.

[redacted]

Table 3.n Applicable PK, [redacted] and Safety Assessment Timing for Day 16 Through Day 35 (PART D, Cohorts D1 and D2)

Procedure	Day in Treatment Period						Postdose/Follow-Up			
Day	16-19	20	21	22-26	27	28	29	ET	ET on Scheduled Visit	Follow-Up 35 (±2 days)
Primary Specimens										
Plasma sample for TAK-994 PK [a]			Pre AM dose			Pre, and 1, 3, 5, 7, 9, 12, 14 h post AM dose [a]	24 h post Day 28 AM dose	X	X	
Blood sample for CYP3A4/5			Pre AM dose			Pre AM dose				
Vital Signs/ ECGs										
BP and pulse rate measurements [b]		X	Pre AM dose		X	Pre, and 1, 3, 5, 7, 9, 12 and 14 h post AM dose	24 h post Day 28 AM dose	X	X	X
Respiratory rate and temperature [c]		X	Pre AM dose		X	Pre AM dose [c]	X	X	X	X
12-lead standard ECG [d]			Pre AM dose		X	X	X	X	X	X
[redacted]										

BP: blood pressure; [redacted] CYP: cytochrome P-450; ECG: electrocardiogram; ET: early termination; [redacted] PK: pharmacokinetic(s); Pre: predose; [redacted].

[a] PK: When feasible, PK can be collected at home. ECG, BP, and pulse, should be done near specified times before the PK.

[b] Vital signs will be taken as indicated. Vital signs should be taken in unit after subject check-in to the site before the confinement periods on Days -2, 7, 13, 21 and 27 (before dosing); On optional Days 6 and 20, vital signs will be taken after subject check-in to the site in the evenings;

[c] Respiratory rate and temperature will be taken with the first vital sign assessment (pulse rate, BP) after subject check-in to the site before the confinement periods on Days -2, 7, 13, 21 and 27 (before dosing); On optional Days 6 and 20, readings will be taken after subject check-in to the site in the evenings.

[d] On Days 13 and 27, ECG will be performed after subject check-in to the site in the evening before the confinement periods of Days 14 and 28. On optional Days 6 and 20, ECG will be performed after subject check-in to the site in the evenings; otherwise ECG should occur in the mornings of Days 7 and 21 before dosing.

[redacted]

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Background

The orexinergic system is a major wake-promoting system of the brain. It is comprised of 2 types of wake promoting orexin (OX) neurons, localized in a specific region of the lateral and posterior hypothalamus and have excitatory projections to wide areas of the central nervous system (CNS) including the basal forebrain and brainstem nuclei involved in maintaining wakefulness (ie, cholinergic neurons if the reticular activating system [RAS], histaminergic tuberomammillary nucleus, noradrenergic locus coeruleus, dopaminergic ventral lateral area, and the serotonergic dorsal raphe nucleus. The OX system acts to coordinate and synchronize the wake-promoting centers of the brain and when absent (ie, in patients with NT1, sleep/wake instability results). The orexinergic system is also involved in several other functions, such as feeding, reward, and sympathetic activity.

Two orexinergic neuropeptides, OX-A and OX-B, have been identified to date. These neuropeptides exert effects via 2 types of G-protein coupled OX receptors: orexin type-1 receptor (OX1R) and orexin type-2 receptor (OX2R). OX-A has a high affinity to OX1R and OX2R, and OX-B has a high affinity to OX2R. The 2 types of OX receptors have a distinct distribution in the arousal network: the locus coeruleus contains only OX1Rs, the tuberomammillary nucleus contains only OX2Rs, and both receptor types occur in the dorsal raphe nucleus and ventral tegmental area. The 2 types of OX receptors also make distinct contributions to the regulation of arousal. OX2Rs in the tuberomammillary nucleus are essential for the maintenance of wakefulness, whereas both receptor types are required for the inhibition of rapid eye movement (REM) sleep [1].

The pathological loss of orexinergic neurons is associated with the development of NT1 [2]. Narcolepsy is a rare, acquired, chronic neurologic disorder that alters sleep-state stability. The cardinal symptom of narcolepsy is excessive daytime sleepiness (EDS), described as a sudden overpowering need to sleep during the day normal periods of alertness. Intrusion of REM sleep phenomena into wakefulness also can also occur. These REM-like phenomena may include cataplexy (sudden loss of muscle tone triggered by strong emotions), hypnagogic/hypnopompic hallucinations (hallucinatory phenomenon that can include mental, auditory, tactile or uncinate events typically occurring during at the transitions into and out of sleep), and sleep paralysis (similar to cataplexy, ie, acute onset of muscle atonia accompanied by a somatic feeling of general paralysis, usually occurring during the transition from wakefulness into sleep). Disturbed nighttime sleep (DNS) is a common narcolepsy related symptom, with difficulty maintaining continuous nocturnal sleep manifested by frequent awakenings with prompt return back into sleep. Together, these 5 clinical features (EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS) comprise the narcolepsy symptom pentad. It has been estimated that only 20% to 30% of patients have all components of the pentad at any one time. NT2 or narcolepsy without cataplexy accounts for 20% to 40% of all cases of narcolepsy but it is important to know

that cataplexy onset can occur many years after the onset of EDS (cases of 10- to 20-year delay have been described).

Narcolepsy has been classified by the International Classification of Sleep Disorders, 3rd edition (ICSD-3) diagnostic criteria [3,4] as either NT1 or NT2, on the basis of the presence or absence of cataplexy and on levels associated with demonstrably absent or low levels of OX1 in the cerebrospinal fluid (CSF) (if measured). NT1 is characterized by EDS and the presence of cataplexy. CSF levels of OX are absent or less than one-third of normal (typically <110 pg/mL). In contrast, patients with NT2 do not have cataplexy, and CSF levels of OX1 are greater than one-third the normal value (above 110 pg/mL) for the laboratory doing the assay. Both in NT1 and NT2, patients have exhibit sleep-onset REM periods on polysomnography/multiple sleep latency test (MSLT) testing and have average sleep onset latencies of the MSLT of <8 minutes averaged over 5 naps. Approximately 70% of those with narcolepsy are classified as having NT1.

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*06:02 [5,6]. The proposed etiology involves T-cell-mediated destruction of OX-producing neurons in the hypothalamus [6-8]. Loss of OX-producing neurons is reflected by low CSF OX levels [9]. The pathophysiology of NT2 is not well understood.

Based on the aforementioned data 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 a pathophysiology-directed mechanism of action. 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 EDS and cataplexy.

TAK-994 is a first-in-class, orally available, highly selective OX2R agonist being developed by Takeda for the treatment of narcolepsy with or without cataplexy (NT1 or NT2).

4.1.2 Summary of Nonclinical Data

In both OX/ataxin-3 transgenic (Tg) mice and non-Tg mice, oral administration of TAK-994 (1, 3, and 10 mg/kg) during the sleep phase (daytime) dose-dependently increased wakefulness time for 1 hour after dosing. Statistically significant effects in OX/ataxin-3 Tg and non-Tg mice were observed at 3 and 10 mg/kg, respectively, with the minimum effective dose approximately 3 times lower in OX/ataxin-3 Tg than non-Tg mice. In addition, TAK-994 (3 and 10 mg/kg) administered orally to OX/ataxin-3 Tg mice significantly improved fragmentation of wakefulness, decreased the number of wakefulness episodes, and increased the duration of wakefulness episodes for 1 hour after dosing. The statistically significant effects were observed at 10 mg/kg for the number of wakefulness episodes ($p \leq 0.01$) and 3 and 10 mg/kg for the duration of wakefulness episodes ($p \leq 0.05$ at 3 mg/kg, $p \leq 0.01$ at 10 mg/kg). TAK-994 (3 mg/kg) also significantly suppressed cataplexy-like episodes for 3 hours after administration in OX/ataxin-3 Tg mice in active phase. TAK-994 at 30 mg/kg significantly increased wakefulness time for 1 hour after administration in wild-type mice in sleep phase ($p \leq 0.05$). In contrast, TAK-994 at 30 mg/kg did not significantly increase wakefulness time for 1 hour after administration in OX2R knockout mice. These results suggest that TAK-994 shows an arousal effect through OX2R activation in mice. In addition, the

arousal effect of TAK-994 was not diminished after 14 days subchronic administration in OX/ataxin-3 Tg mice. Thus, TAK-994 may have a low risk of OX2R desensitization. TAK-994 (3 and 10 mg/kg) was administered orally to monkeys, diurnal animals with monophasic sleep/wake patterns, during their sleep phase. TAK-994 at 10 mg/kg significantly increased wakefulness time for 8 hours after administration.

In safety pharmacology studies, no CNS effects were observed in a CNS observational battery in rats at 50 mg/kg, although biting or licking of the chamber floor or ceiling and/or biting or licking of the tail were observed during respiratory measurements at 1 and 2 hours postdose at ≥50 mg/kg. Decreased body temperature was noted at ≥200 mg/kg. A decrease in locomotor activity was observed in 1 animal at 1000 mg/kg at 4 hours postdose; this animal exhibited the lowest body temperature. These behavioral changes were considered due to the pharmacological action of TAK-994 because OX2R agonists have been reported to increase locomotor activity and bursts of stereotypy in rats [10].

In vitro cardiovascular assessments revealed an inhibitory effect of TAK-994 on the human ether-à-go-go-related gene (hERG) current at 5 and 50 µg/mL; the half-maximal inhibitory concentration was 37.47 µg/mL in hERG-transfected HEK293 cells. In vivo cardiovascular studies revealed blood pressure (BP) increases at ≥20 mg/kg (10 mg/kg twice daily [BID]) in conscious telemeterized monkeys. Prolongation of the PR interval and shortening of the QT/corrected QT intervals observed at ≥100 mg/kg and 1000 mg/kg, respectively, were deemed to be of no toxicological importance because of the low magnitude of these changes. During a 1-week study of repeated oral administration of TAK-994 (100 mg/kg) in conscious telemeterized monkeys, increased BP and heart rate were observed on the first day of dosing; these findings were attenuated on the second dosing day and had disappeared by the final dosing day. Evaluation of respiratory function in rats revealed an increased respiratory rate at ≥50 mg/kg, an increased minute volume and decreased enhanced pause ([Penh], an index of airway constriction) at ≥200 mg/kg, and an initially decreased and then increased Penh at 1000 mg/kg.

Plasma protein binding rates for TAK-994 ranged from 94.2% to 98.5% in rats, monkeys, and humans. TAK-994 was a substrate for P-glycoprotein (Pgp) but was not a substrate for breast cancer resistance protein (BCRP).

Metabolite profiling from in vitro studies showed that TAK-994 is mainly metabolized via cytochrome P-450 (CYP)3A4; no human-specific metabolites have been identified from early in vitro screening in hepatocytes. Treatment of cryopreserved human hepatocyte cultured preparations with TAK-994 (up to 30 µmol/L) showed that TAK-994 has little or no induction potency for CYP1A2 but does have induction potency for CYP2B6, CYP2C8, CYP2C9, and CYP3A4. TAK-994 inhibited CYP3A4/5 activities with a half-maximal inhibitory concentration value of 14 µmol/L (without preincubation) and 9.0 µmol/L (with preincubation) but had little or no inhibition for other CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6). A study in human liver microsomes revealed that TAK-994 had direct inhibitory effects and some time-dependent inhibitory effects on CYP3A4/5 activity.

Based on in vitro transporter studies, TAK-994 inhibited the Pgp- and BCRP-mediated transport of typical substrates with the 50% inhibitory concentrations (IC_{50}) of 11.3 and 30.1 µmol/L.

TAK-994 inhibited the organic anion transporting polypeptide (OATP)1B1-, organic anion transporter (OAT)3-, organic cation transporter (OCT)1-, multidrug and toxin extrusion transporter (MATE)1-, and bile salt export pump-mediated transport of typical substrates with the IC_{50}s of from 33.8 to 58.3 μmol/L. TAK-994 also inhibited the OATP1B1- and OATP1B3-mediated transport of typical substrates after pre-incubation with TAK-994 for 30 minutes with the IC_{50}s of 3.28 and 22.7 μmol/L. TAK-994 did not inhibit the OAT1-, OCT2-, and MATE2-K-mediated transport of typical substrates up to the maximum concentration of 100 μmol/L (IC_{50} >100 μmol/L).

At a mean C_{max} value of 756 ng/mL in plasma (1.61 μM; unbound C_{max} ~ 0.061 μM) following oral administration of TAK-994 200 mg BID in human subjects, the potential exists for drug-drug interactions when TAK-994 is co administered with drugs that are inhibitors or inducers of CYP3A or Pgp or substrates of CYP3A, Pgp, BCRP or OATP1B1 based on Food and Drug Administration (FDA) Guidance for Industry "In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions".

A 13-week repeat dose toxicity in rats at dose levels of 0, 50, 150, and 1500 mg/kg/day with a 4-week recovery period was conducted. No deaths or moribundities occurred. Adverse fluorosis was observed at 1500 mg/kg/day with evidence of increased fluoride levels in the incisors and plasma. Fractures and whitening of the incisors were observed from Weeks 9 and 11, respectively and throughout the recovery period in both sexes at 1500 mg/kg/day, and single cell necrosis and/or degeneration of the ameloblasts in both sexes and pulp stone in males were observed at the end of the dosing period at 1500 mg/kg/day. Basophilic granules were also observed in the femur at 1500 mg/kg/day as a fluoride-related precipitation; however, it was not considered to be adverse because there was no associated morphological abnormality in the bone. Slight decreases in body weight gain and food consumption were observed at 150 mg/kg/day and in females at 50 mg/kg/day with more noticeable decreases at 1500 mg/kg/day that corresponded with the fracturing of incisors in the latter part of the dosing period. Nonadverse minimal increased diffuse vacuolation was observed in the adrenal gland with no organ weight changes or indication of adrenal dysfunction and minimal diffuse hypertrophy of the acinar cells in the submandibular gland was observed and considered secondary to the fractured incisors. In the liver, hypertrophy of the centrilobular hepatocytes was observed in both sexes at ≥150 mg/kg/day and it was accompanied by increased liver weight in females, indicative of an induction of hepatic drug-metabolizing enzymes and was considered to be nonadverse.

There were no clinical signs or decreased body weights suggestive of withdrawal signs/symptoms during the recovery period, and the adverse findings including the abnormalities in the incisors partially or fully recovered following a 4-week recovery period.
Based on the adverse fluorosis of incisors at 1500 mg/kg, the no-observed-adverse-effect level (NOAEL) of TAK-994 was 150 mg/kg for both sexes. The C_{max} and area under the concentration-time curve from time 0 to 24 hours (AUC_{24}) mean values at 150 mg/kg/day were 6030 ng/mL and 78,900 h*ng/mL and 13,200 ng/mL and 198,000 h*ng/mL in males and females, respectively, on Day 91.

A 13-week repeat-dose oral toxicity study in monkeys at dose levels of 0, 30, 100, and 500 mg/kg BID (0, 60, 200, and 1000 mg/kg/day) with a 4-week recovery period was conducted. Yellow-green stool was observed in males and females at 500 mg/kg BID throughout the dosing period that was considered nonadverse because there were no findings suggesting damage to the digestive tract. Vomiting was observed several times per animal at 500 mg/kg BID that was considered nonadverse because of low frequency and lack of abnormalities (eg, dehydration) in the general condition or an imbalance of plasma electrolytes. Slightly low body weight gain was noted in males at 500 mg/kg BID. Low food consumption was sporadically noted in females at ≥100 mg/kg BID with no corresponding effects on the body weight. There were observations of high ALP in females at 500 mg/kg BID, high triglycerides in males at ≥30 mg/kg BID and females at 500 mg/kg BID, low total cholesterol in males at ≥30 mg/kg BID and females at 500 mg/kg BID, and low creatine phosphokinase in females at 500 mg/kg BID. These changes were considered to be nonadverse because they were slight changes and there were no microscopic correlates. Hypertrophy of hepatocytes with an increased liver weight in males and females was observed at 500 mg/kg BID and was considered to be associated with the induction of hepatic drug-metabolizing enzymes. The analysis of hepatic microsomal drug-metabolizing enzyme activity revealed increases in 7-ethoxyresorufin O-deethylase activity (males at ≥30 mg/kg BID and females at ≥100 mg/kg BID), aminopyrine N-demethylase activity (males at 500 mg/kg BID and females at ≥100 mg/kg BID), and p-nitrophenol uridine 5′-diphosphate-glucuronosyltransferase activity (females at ≥100 mg/kg BID). Diffuse hypertrophy of the follicular cells of the thyroid gland was observed in males at 500 mg/kg BID, which might be associated with the induction of hepatic drug-metabolizing enzymes. These findings were considered to be nonadverse. There were no clinical signs or body weight changes suggestive of withdrawal symptoms during the recovery period, and all TAK-994-related changes observed during the dosing period recovered after a 28-day recovery period. Based on these results, the NOAEL was 500 mg/kg BID for both sexes. The plasma C_{max} of 21,700 and 15,100 ng/mL, and plasma AUC_{24} of 307,000 and 155,000 h*ng/mL in males and females, respectively, at 500 mg/kg BID on Day 91. TAK-994 was not genotoxic in vitro or in vivo. A definitive embryo-fetal development study of TAK-994 in pregnant Sprague-Dawley rats at doses of 0 (0.5% [w/v] methylcellulose), 30, 100, and 1000 mg/kg/day by once daily (QD) oral gavage was completed. Decreases in body weights and food consumption were observed dose-dependently at ≥100 mg/kg/day, and these changes were especially marked at 1000 mg/kg/day in dams. Decreases in body weights and the number of ossified bones were noted in male and female fetuses at 1000 mg/kg/day. Based on these results, the NOAEL was 30 mg/kg/day for maternal toxicity (C_{max} and AUC_{24} of 3760 ng/mL and 51,600 h*ng/mL, respectively, on gestational day 17) and 100 mg/kg/day for embryo-fetal toxicity (C_{max} and AUC_{24} of 6990 ng/mL and 103,000 h*ng/mL, respectively, on gestational day 17).

A definitive embryo-fetal development study of TAK-994 in pregnant New Zealand white rabbits at doses of 0 (0.5% [w/v] methylcellulose), 20, 50, and 150 mg/kg/day by QD oral gavage was completed. Decreased body weights, body weight gain, and food consumption, as well as scant or no feces, were noted in does at 150 mg/kg/day. The changes were considered to be the cause of abortion observed in 6 does at this dose. At 50 and 20 mg/kg/day, body weight gain between GDs 7 and 9 was low compared to the control group. However, because these were transient and

minimal changes and there were no TAK-994- related effects on body weight gain throughout the dosing period (GDs 7 to 21), they were not considered to be adverse. Adequate evaluation was not achieved in embryos/fetuses at 150 mg/kg/day because the number of does decreased to 12 due to abortion in 6 does at 150 mg/kg/day. However, at this dose, slightly decreased numbers of ossified middle phalanges of the forelimbs and hindlimbs were noted in fetuses of the 12 does with sustained pregnancy. Based on these results the NOAEL was 50 mg/kg/day for maternal and embryo-fetal toxicity (C_{max} and AUC_{24} of 3310 ng/mL and 15,200 h*ng/mL, respectively, on gestational day 20).

In a 1-week, non-pregnant rabbit oral toxicokinetic/tolerability study, decreases in food consumption, body weight, and feces were noted at 1000 mg/kg; 1 animal died, and 1 animal was euthanized at this dose level. The maximum tolerable dose in this study was 300 mg/kg/day. TAK-994 absorption of ultraviolet-visible light at 290 to 700 nanometers was below the threshold for direct phototoxicity; thus, no direct phototoxicity is anticipated.

A 4-week repeat-dose toxicity study with TAK-994 was conducted in non-Tg littermates of CByB6F1-Tg(HRAS)2Jic (nonTg rasH2) mice (10/sex/group, 8 weeks of age at the start of dosing) [Study report B-8529]. TAK-994 was administered by oral gavage at doses of 0 QD, 300 QD, 2000 QD, and 4000 (2000 BID) mg/kg/day. The purpose of this study was to establish a suitable dose range for the 6-month carcinogenicity study in Tg-rasH2 mice. No deaths occurred, and no TAK-994-related abnormal clinical signs were observed. At 2000 and 4000 mg/kg/day, body weights and food consumption were transiently decreased on Week 1 and/or 2. However, the body weights later increased and at the end of the study there were no differences between the control group and the 2000 mg/kg/day group although body weights at 4000 mg/kg/day were still lower than the control group values. An adverse hepatocellular injury (single cell necrosis of the periportal hepatocytes) associated with elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, and glutamate dehydrogenase (GLDH) in the clinical chemistry were observed at ≥300 mg/kg/day. While the single cell necrosis of the periportal hepatocytes was observed in several animals in both sexes at 300 mg/kg QD at a minimal grade, increased incidences and/or severity (minimal to mild grade) were noted in both sexes at ≥2000 mg/kg QD. Additionally, atrophy of hepatocytes and hyperplasia of oval cells which was considered to be a regenerative response to the hepatocellular injury were observed in the periportal area at ≥300 mg/kg QD and at ≥2000 mg/kg/day, respectively. A low blood urea nitrogen, which was possibly related to impaired urea cycle function in the liver, was observed in males at ≥2000 mg/kg/day, suggesting a deteriorated hepatocellular function at ≥2000 mg/kg/day. Other than the above, macroscopically large liver size in both sexes at 4000 mg/kg/day, increased liver weight in males at ≥2000 mg/kg/day and in females at ≥300 mg/kg/day, and hypertrophy of the centrilobular hepatocytes at ≥300 mg/kg/day were observed, which were indicative of induction of drug metabolizing enzymes. In the female reproductive organs, atrophy of the ovary, uterus and vagina was observed microscopically at ≥2000 mg/kg/day, and these findings indicate the disruption of the estrus cycle and are considered adverse. In conclusion, hepatocellular injury including single cell necrosis of the periportal hepatocytes at ≥300 mg/kg/day and adverse atrophic changes in the female reproductive organs at ≥2000 mg/kg/day were observed; therefore, a NOAEL was not established in this study. An additional 4-week repeat-dose toxicity study of

TAK-994 was conducted in nonTg rasH2 mice with a 7-day sacrifice to investigate the effects of shorter dose period on TAK-994-induced hepatotoxicity. TAK-994 was administered QD by oral gavage to male and female nonTg rasH2 mice (4/group/sex for the 7-day dosing groups and 10/group/sex for the 4-week dosing groups) at doses of 0, 300, and 2000 mg/kg/day for the 7-day dosing groups and 0, 50, 100, and 300 mg/kg/day for the 4-week dosing groups. No deaths occurred, and no TAK-994-related abnormal clinical signs were observed in any group. There were slight decreases of body weight gain, which resulted in -6%, -8%, and -8% of mean body weights in females at 50, 100, and 300 mg/kg/day, respectively, compared to the control value. In the liver, atrophy of periportal hepatocytes in males at 300 mg/kg/day and hypertrophy of centrilobular hepatocytes in both sexes at 300 mg/kg/day were observed. The hypertrophy of centrilobular hepatocytes was in correlation with increased liver weights, which were indicative of induction of drug metabolizing enzymes.

No adverse hepatocellular injury such as single cell necrosis of hepatocytes was observed at any dose in the 4-week dosing although atrophy of periportal hepatocytes at 300 mg/kg/day was in the same direction as that of the previous 4-week study, and thus 300 mg/kg/day was considered to be marginal to induce the hepatotoxicity in mice. Therefore, based on the findings in both studies, overall NOAEL of TAK-994 for mice was concluded to be 100 mg/kg/day (AUC_{24} of 17,000 and 30,600 h*ng/mL in males and females, respectively).

Plasma levels of free fluoride ion were determined in a 1-week repeat-dose study in mice, which revealed not only remarkably high concentrations of plasma fluoride in TAK-994 groups on Day 1 (C_{max} [μmol/L] on Day 1: 10.9 for males and 5.9 for females at 0 mg/kg/day, 65.5 for males and 66.7 for females at 300 mg/kg/day, and 77.2 for males and 85.7 for females at 1000 mg/kg/day), but also they were increased after repeated dosing of TAK-994 (C_{max} [μmol/L] on Day 7: 5.2 for males and 5.1 for females at 0 mg/kg/day, 106.0 for males and 122.5 for females at 300 mg/kg/day, and 210.9 for males and 213 for females at 1000 mg/kg/day). Repeated dosing of TAK-994 to mice also caused a decrease of plasma TAK-994 exposure concomitantly with findings that were indicative of induction of hepatic drug-metabolizing enzymes such as a dose dependent increase of liver weights; therefore, the increased fluoride level after the repeated dosing was considered to be the result of increased metabolic defluorination of TAK-994 by the induction of hepatic drug-metabolizing enzymes.

The in vitro and in vivo metabolic profiles of TAK-994 in humans (in vitro only), mice, rats and monkeys suggest marked qualitative and quantitative species differences in TAK-994 metabolism. Thus, in mice the proportion of TAK-994 that undergoes the reactive metabolic pathway of defluorination/arene oxide formation followed by glutathione conjugation appears to be considerably larger than in other species, especially if compared to monkey and human. Based on the results of the rat and monkey toxicology studies, in vitro and in vivo metabolite profiling, the hepatotoxicity observed in non-Tg rasH2 mice appears to be related to species-specific metabolic conversion of TAK-994 via a reactive metabolite pathway. In addition, the TAK-994 exposure decrease was noted in mice suggesting some enzyme induction involved in the TAK-994 metabolism. The induction is also considered to involve in the increase of the reactive metabolite formation in mice. Therefore, the hepatotoxicity observed in non-Tg rasH2 mice is likely of limited relevance to human safety assessment. The human risk of hepatocellular injury is further

mitigated by the fact that there was no liver toxicity detected in either rat or non-human primate 13-week studies at equal plasma exposures; the mouse liver findings were of minimal severity at plasma exposure levels approximately 10-fold above anticipated therapeutically efficacious levels; accompanied by monitorable liver enzyme (potentially also free fluoride) changes; and would be expected to be readily reversible upon cessation of treatment.

Please refer to the TAK-994 Investigator's Brochure (IB) for more information on the investigational product.

4.1.3 Clinical Study Experience

Study TAK-994-1001 was the first-in-human (FIH), randomized, double-blind, placebo-controlled, single and multiple rising oral dose study to evaluate the safety, tolerability, PK, [redacted] of TAK-994 that was conducted in healthy subjects. Male and female subjects of nonchildbearing potential, aged 18 to 55 years (inclusive) were enrolled in Parts A, B, C, E, whereas, subjects ≥65 years were enrolled in Part D.

The data from study TAK-994-1001 reveal no major safety concerns.

TAK-994 was considered to be safe and well tolerated up to 450 mg single dose and 200 mg BID repeat dose both in healthy adults and elderly. The maximum repeated dose tested in healthy volunteers was 200 mg twice daily and it was well tolerated. There were no deaths or serious adverse events (SAEs) in the study. All reported treatment-emergent adverse events (TEAEs) were mild or moderate in severity, except 1 severe TEAE syncope, that was not related to study drug. Two subjects discontinued due to TEAEs (1 due to presyncope/near syncope and the other due to ALT increased/elevated ALT).

A higher frequency of renal and urinary TEAEs were reported in subjects receiving TAK-994 compared with subjects receiving placebo. Renal and urinary adverse events (AEs) were reported (incontinence, pollakiuria, micturition urgency, dysuria) in 24 subjects (only 1 subject in the placebo group); however, no subjects discontinued due to these AEs. These were mild or moderate in intensity and all events resolved. Frequency of these TEAEs was not dose dependent. Therefore, the sponsor is including a bladder questionnaire to monitor these symptoms in the current amendment.

A total of 24 subjects (only 2 subjects in placebo group and rest in the TAK-994 group) also reported insomnia within the first 2 to 3 days of first dose; however, no subjects discontinued due to these AEs. These were mild or moderate in intensity and all events resolved. Higher number of insomnias were noted in the TAK-994 treated group compared with the placebo, in a dose-independent manner.

BP elevation (approximately 4 to 12 mm Hg on average in systolic BP) was observed on Day 1 at some dose levels; however, the elevations were not sustained beyond Day 4. There appears to be no clear dose response relationship for BP elevation.

Pooled aggregate summaries of all cohorts in the healthy volunteer study (TAK-994-1001) of GLDH and fluoride assessed change from baseline by visit date. The analysis showed that there was no clinically meaningful difference between the active and placebo arms. Three subjects

exposed to TAK-994 had ALT elevations. All events were mild, related, and resolved without treatment. One subject in Part E who received TAK-994 200 mg experienced TEAEs of ALT increased/elevated ALT (MedDRA PT = Transaminitis) according to liver function test (57 U/L) on Day 1. This event was continuous, mild in intensity and considered related to study drug by the investigator. The subject did not receive any other dose and discontinued from the study on Day 7.

Following single- and multiple-dose oral administration of TAK-994 to healthy subjects under fasted conditions, TAK-994 was readily absorbed into the systemic circulation, with most median t_{max} at 2 hours. After single-dose administration, peak exposure increased near dose proportionally, while total exposure increased slightly greater than dose proportionally. At steady-state, peak and total exposure of TAK-994 appeared to increase dose proportionally when comparing the BID dose regimens where TAK-994 was administered at the same amount for 14 consecutive days.

After single-dose administration, TAK-994 displayed a multiexponential disposition phase with an estimated mean terminal elimination half-life ranging from 3 to 12.5 hours across doses. Additionally, there were no apparent dose-related trends in TAK-994 clearance across the groups assessed.

TAK-994 exposure does not appear to accumulate after QD or BID dosing in any of the dose groups and study parts (≤9%). The only exception was the 120 mg AM/60 mg PM dose group in study Part B where it appears to marginally accumulate (≤18%).

Urinary excretion of TAK-994 was less than 0.62% in all dose groups and study parts. Overall, urinary excretion of TAK-994 was minimal and not impacted by dose level.

Ingesting a high-fat, high-calorie meal immediately before administering TAK-994, significantly increases the mean peak concentration by 53% and total exposure of TAK-994 by 25%. Ingesting a standardized, non–high-fat meal with TAK-994, increased mean peak concentration by 42% but had no effect on total exposure.

The estimated CSF to plasma concentration ratios for TAK-994 C_{max} and AUC at steady-state were 2.92% and 2.05%, respectively, which are similar to the previously reported mean plasma free fraction of TAK-994, thus indicating TAK-994 readily crosses the blood brain barrier.

Given 120 mg BID TAK-994, healthy elderly subjects appear to have slightly higher TAK-994 exposure (C_{max} and AUCs) by approximately 20% to 60%, compared with healthy subjects of the same dose regimen in study Part B.

TAK-994 exposure in Japanese subjects appears similar to those in non-Japanese subjects treated with a single dose and repeated doses of TAK-994.
The approximate 50% increase of 4β-hydroxycholesterol to cholesterol ratio in TAK-994–treated subjects suggests TAK-994 is a weak CYP3A4/5 inducer.

4.2 Rationale for the Proposed Study Design

Nonclinical pharmacology studies showed that wake-promoting effects of TAK-994 were observed following chronic dosing for up to 14 days. The available nonclinical information;

emerging clinical safety, tolerability, and PK profiles of single doses of TAK-994; and results from TAK-994-1001 study in healthy subjects support this study, which is designed to evaluate the safety, tolerability, PK, [redacted] of multiple oral doses of TAK-994 in subjects with NT1 and NT2.

Additional rationale relating to the study design, TAK-994 dose administered, and study endpoints is provided in Section 6.3.

4.3 Benefit/Risk Profile

This randomized, double-blind, placebo-controlled study will include safety/tolerability, PK, [redacted] evaluations in subjects with NT1 or NT2 after multiple dose oral administration of TAK-994.

Patients with NT1 are deficient in OX and hence are the first individuals who would most benefit from treatment with an OX2R agonist. If TAK-994 is efficacious for EDS and catalepsy, subjects receiving the drug may benefit during the period of study drug administration. Subjects will also receive medical examinations and information about their overall health. Results of the study are critical in planning future clinical studies with TAK-994, and it is possible that the information obtained in the study will be beneficial to patients with narcolepsy in the future.

In non-clinical pharmacology studies, TAK-994 showed strong wakefulness promoting effects in wild type animals who have normal OX levels. This observation, and preliminary safety/tolerability data from the recently completed TAK-994-1001 study in healthy subjects further support evaluating TAK-994 [redacted] in the NT2 patient population. The NT2 population has OX levels that may range from 30% to 100% of normal values.

Safety data informing the risk profile for TAK-994 are limited to the mode of action, data from nonclinical toxicology studies, and current and emerging safety and tolerability data from TAK-994-1001. Based on nonclinical safety pharmacology data, the primary potential risk is increased BP. A safety pharmacology study of TAK-994 in monkeys found mild to moderate degrees of transient elevated BP at all doses tested on initial dosing, although effects on BP and heart rate were no longer observed at 7 days of dosing. The cardiovascular effects noted in preclinical models with OX2R agonists are considered potentially on-mechanism based on published literature [11]. To mitigate this risk, BP will be measured frequently in this study; stopping rules for individual subjects, cohorts, and the overall study as well as the treatment of increased BP have been established and are noted in Section 6.5.5.1 and Section 7.5, respectively.

The AEs that have occurred in TAK-994-1001 FIH study have primarily been graded as mild. AEs generally increased in number with increasing dose or exposure. The tolerability of 200 mg BID in the MRD cohort was acceptable although there were urinary System Organ Class TEAEs. AEs of urinary frequency and urgency have been reported, and this will be monitored in the current study.

Other effects in nonclinical studies included vomiting at high doses and minor changes in ECG parameters. ECG findings in the study were considered nonadverse and monitoring for these events is a standard part of clinical studies. Additionally, it is possible that a long half-life may result in insomnia, which has been seen in healthy subjects in Study TAK-994-1001. Though insomnia is thought less likely to occur in NT1 patients due to their marked OX deficiency, stopping rules have been created for severe and/or persistent insomnia (Section 6.5.5).

The TAK-994-related hepatocellular injury observed in the initial non-Tg rasH2 mice is thought to be of limited relevance to human safety risk assessment. A subsequent 1-month study in non-Tg rasH2 mice at lower doses provided a NOAEL for the liver findings, which for AUC was 4-fold over the maximum expected clinical exposures (120 mg BID). Moreover, there were no adverse liver findings in the 13-week Good Laboratory Practice toxicology studies in rats and nonhuman primates at plasma exposures vastly exceeding the levels at which the minimal single cell necrosis was seen in non-Tg rasH2 mice, thus providing further evidence that the liver toxicity observed in mice was likely species-specific. Liver function tests will be monitored throughout the study. Proposed monitoring in the Schedule of Assessments are felt to be sufficient to adequately monitor for evidence of injury. See Section 7.5 and Section 6.5.5.1 for individual and cohort stopping rules related to LFT changes.

This study has been designed to mitigate potential safety risks based on clinical and nonclinical findings. The principal mitigation strategy for these risks includes appropriate selection of the study population; intermittent use of the inpatient clinical research unit setting, which permits close monitoring and rapid institution of appropriate care as needed; appropriate specified monitoring procedures; periodic laboratory tests, ECGs, and vital signs assessments; and utilization of experienced staff trained in study procedures. In addition, ambulatory monitoring of BP will occur before baseline and at steady state in order to evaluate the effects of TAK-994 on BP in the ambulatory setting.

Overall, there is manageable risk associated with the proposed study. Potential risks relating to the study include the following:

- Study procedure-specific risks, including issues relating to blood collection for safety and PK assessments (eg, venipuncture may cause bruising).
- Acute hypersensitivity/anaphylactic reactions to new chemical entities, which is always a possible risk in any clinical study. Appropriate procedures will be used to manage such possible risks.
- This study also includes an optional CSF collection (single sample) for assessment of CSF OX levels. CSF OX levels are of interest as the level may potentially correlate with the [redacted] for a given drug level. CSF collection is an established procedure with the typical risks associated with lumbar puncture. There is a very low risk of CNS infection. Subjects may experience low back pain during needle insertion and for a brief time after the procedure and postural headache after the procedure. Very rare risks include the risk of meningitis, nerve root injury, and hematoma resulting in spinal cord compression. These risks will be detailed in the informed consent documentation.

Review of data supports a favorable benefit/risk ratio for this study of TAK-994. To date, the observed nonclinical and clinical safety data for TAK-994, including mild and manageable AEs, are acceptable considering its potential clinical benefit.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objective--PART A and PART D

- To assess the safety and tolerability of TAK-994 following multiple oral doses in subjects with narcolepsy with or without cataplexy (NT1 or NT2).

5.1.2 Secondary Objective--PART A and PART D

- To characterize the PK of TAK-994 in subjects with narcolepsy with or without cataplexy (NT1 or NT2).

5.1.3 Additional/ Exploratory Objectives--PART A and PART D

[redacted]

[redacted]

[redacted]

5.1.4 Primary Efficacy Objective--PART B and PART C

- To assess the efficacy of TAK-994 on reducing EDS as measured by prolongation of sleep onset in MWT procedure.

5.1.5 Secondary Objective--PART B and PART C

- To assess the efficacy of TAK-994 on WCR and ESS reduction.
- To assess the safety and tolerability of TAK-994 following chronic administration.

5.1.6 Additional/ Exploratory Objectives--PART B and PART C

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoints- PART A and PART D

The primary endpoints assessing safety and tolerability are:

- Number of subjects with at least 1 TEAE during the study.
- Number of subjects with at least 1 markedly abnormal value (MAV) for postdose laboratory values during the study.
- Number of subjects with at least 1 MAV for vital signs during the study.
- Number of subjects with at least 1 MAV for ECGs during the study.

5.2.2 Secondary Endpoint- PART A and PART D

- Day 1: maximum observed concentration [C_{max}], time to reach C_{max} [t_{max}], area under the concentration-time curve [AUC] from time 0 to time of the last quantifiable concentration [AUC_{last}].
- Day 28: C_{max}, t_{max}, AUCτ.

5.2.3 Additional/Exploratory Endpoints-PART A and PART D

[redacted]

[redacted]

5.2.4 Primary Endpoint- PART B and PART C

The primary endpoint assessing efficacy is:

- Change from baseline in average sleep latency from MWT to Week 8.

5.2.5 Secondary Endpoints- PART B and PART C

The secondary endpoints assessing efficacy are:

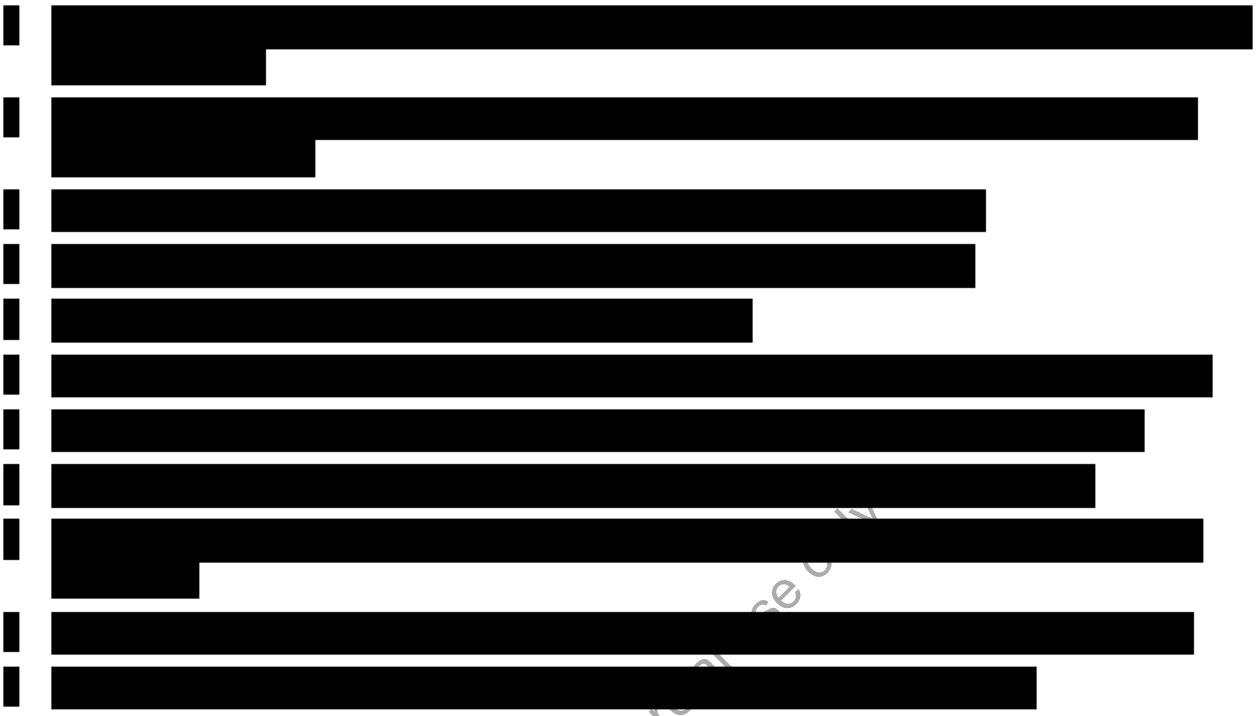
- Change from baseline in the ESS total score to Week 8.
- WCR at Week 8.

The secondary endpoints assessing safety are:

- Number of subjects with at least 1 TEAE during the study.
- Number of subjects with at least 1 MAV for post dose laboratory values during the study.
- Number of subjects with at least 1 MAV for vital signs during the study.
- Number of subjects with at least 1 MAV for ECGs during the study.

5.2.6 Additional/Exploratory Endpoints- PART B and PART C

[redacted]



6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2 randomized, double-blind, placebo-controlled study to assess the safety, tolerability, PK, [redacted] of multiple rising oral doses of TAK-994 administered to subjects with NT1 or NT2. An interactive response technology (IRT) system will be utilized for the randomization of subjects to treatment.

Approximately 202 (male and female) subjects, aged 18 to 65 years (inclusive) who satisfy the inclusion and exclusion criteria will be enrolled in the study in 4 study parts (Table 6.a). The same subjects will not be allowed to be enrolled or randomized into different parts of the study; therefore, these 4 study parts are considered distinct from each other. However, subjects in Part B will have the opportunity to participate in an open-label extension study.

Subjects recruited for the study are expected to be generally healthy, other than having narcolepsy.

For Part B, the randomization will be stratified by baseline WCR (<8 vs ≥8) and regions/countries (ie, North America, Japan, South Korea, and Europe).

For Part C, the randomization will be stratified by baseline WCR (<8 vs ≥8).

For other parts, the randomization will be stratified by regions/countries (North America, Japan, South Korea, and Europe).

Subjects who were in the screening period at the time that coronavirus disease 2019 (COVID-19) related factors resulted in discontinuation may be rescreened with approval (Refer to Section 9.0

for additional details). Subjects will receive BID dosing of TAK-994 or matching placebo for 28 days or 56 days, as applicable).

Table 6.a Planned Study Cohorts and Dose Levels

PART/Cohort Number	Daily Dose Level (mg) [a]	Dosing Regimen [b]	Randomization and design
PART A-Cohort A1a and A1b	240 mg (A1a), TBD (A1b)	Oral, 120 mg twice daily for 28 days (A1a),	Approximately 18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind
PART A-Cohort A2 (optional)	TBD	Oral, twice daily for 28 days	Approximately 9-18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind
PART B	TBD	Oral, twice daily for 56 days	Approximately 112 subjects in a 4-arm parallel group design: TAK-994 Dose 1, Dose 2, and Dose 3 vs Placebo. 28/group with a randomization of 1:1:1:1
PART C (China-specific)	TBD	Oral, twice daily for 56 days	Approximately 12-18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind
PART D, Cohort D1a and D1b	TBD	Oral, twice daily for 28 days	Approximately 18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind
PART D, Cohort D2 (optional)	TBD	Oral, twice daily for 28 days	Approximately 9-18 subjects randomized 2:1 to TAK-994 vs placebo, double-blind

PK: pharmacokinetic; NT1: narcolepsy type 1 (narcolepsy with cataplexy); NT2: narcolepsy type 2 (narcolepsy without cataplexy); TBD: to be determined.

[a] Doses will be determined based on the available and emerging safety/tolerability, PK, [redacted] data from prior study TAK-994-1001 and/or previous cohorts in the current study.

[b] Doses will be administered approximately 5 hours apart.

c. Parts A to C include subjects with NT1 and part D will include subjects with NT2.

Table 6.b Relative Timing for Initiation of Study Parts

Study Part/ Description	Relative Timing of Cohort Initiation and Rationale	
Part A, Cohort A1a (sentinel)	This will start first	The dosing regimen, 120 mg BID, used in Cohort A1a, is supported by the predicted range of pharmacologically active plasma exposure from animal studies, and available clinical safety and PK data from the completed TAK-994-1001 FIH study. See Section 6.2.1 for details.
Part A, Cohort A1b	This will start after 9 sentinel subjects in Cohort A1a are dosed for at least 2 weeks	The dose level for Cohort A1b will be determined based on the available safety, tolerability, PK, [redacted] data from Cohort A1a. See Section 6.2.1 for details.
Part A, Cohort A2 (optional)	This will start after Cohort A1b, if deemed necessary based on A1 data	The totality of Cohort A1 data will be used to determine whether Cohort A2 is needed to further evaluate safety, efficacy, PK, [redacted] in NT1 before initiating Part B. The dose level for Cohort A2 will be determined based on the available Cohort A1 data. See Section 6.2.1 for details.
Part B	After the last cohort in Part A.	Doses in Part B will be determined using all available data from Part A. See Section 6.2.1 for details.
Part C	This will start after Part A	The dose for Part C will be selected based on all available data. See Section 6.2.1 for details.
Part D, Cohort D1	This will begin after Cohort A1	The dose for Cohort D1a will be determined based on the available clinical safety and PK data from the completed TAK-994-1001 FIH study and available safety, tolerability, PK, [redacted] data from Cohort A1. See Section 6.2.1 for details.
Part D, Cohort D2 (optional)	Based on the Cohort D1 data, if additional data are needed	The dose level for Cohort D2 will be determined based on the available safety, tolerability, PK [redacted] from Cohort D1, if the sponsor decides that D2 is needed to further evaluate safety, PK, [redacted] in NT2. See Section 6.2.1 for details.

BID: twice daily; FIH: first-in-human; NT1: narcolepsy type 1 (narcolepsy with cataplexy); NT2: narcolepsy type 2 (narcolepsy without cataplexy); [redacted] PK: pharmacokinetic.

PART A (Cohorts A1 and A2):

Cohort A1: Cohort A1 will enroll 18 subjects with the sentinel 9 subjects to be randomized 2:1 to receive treatment with oral TAK-994 120 mg BID versus placebo in a double-blinded fashion. The starting dose level in the first cohort of subjects, Cohort A1a, is 120 mg BID, which was based on the preliminary safety, tolerability, and PK data from the FIH Study TAK-994-1001 (Section 6.3.2.1), as well as nonclinical data. Sentinel dosing on the first 9 subjects (Cohort A1a) (with randomization ratio of 2:1) will be performed. The second cohort of 9 subjects (Cohort A1b) will be randomized 2:1 to receive treatment with oral TAK-994 versus placebo in a double-blinded fashion.

Optional Cohort A2: Based on the Cohort A1 data, if an additional dosing cohort is needed, Cohort A2 will be enrolled and started with 9 subjects. They will be randomized in a 2:1 ratio to receive TAK-994 or placebo in a double-blinded fashion. Based on the emerging data from these first 9 subjects, 9 additional subjects may be enrolled in this cohort in a 2:1 ratio.

PART B:

Part B will start after Part A is completed. In order to initiate Part B, 3 dose levels of TAK-994 will be selected based on unblinded safety [redacted] data from the previous Part A cohort(s). A total of 112 subjects will be randomized to either placebo or 1 of the 3 selected TAK-994 dose levels in a 1:1:1:1 ratio administered for 56 days. Subjects completing Part B study treatment will be invited to participate in an open-label extension study, if they are eligible. Details of that open-label extension (OLE) study design will be communicated via a separate protocol.

PART C (Cohort C1):

PART C, Cohort C1 is a China-specific cohort and is planned to consist of 12 to 18 subjects who will be randomized 2:1 to receive treatment with oral TAK-994 versus placebo in a double-blinded fashion.

PART D (Cohorts D1 and D2):

Cohort D1 will start with sentinel dosing in a cohort of 9 subjects with NT2 (Cohort D1a) who will receive TAK-994 BID or placebo in a randomization ratio of 2:1. Dosing for the next 9 subjects (Cohort D1b) may be adjusted based on the safety and/or efficacy data from the first 9 subjects. Overall randomization ratio for the 18 subjects in Cohort D1 will remain at 2:1.

Based on the Cohort D1 data, if an additional dosing cohort is needed, optional Cohort D2 will start. Cohort D2 will enroll 9 subjects randomized in a ratio of 2:1 to receive TAK-994 or placebo in a double-blinded fashion. Based on the emerging data from these first 9 subjects, 9 additional subjects may be enrolled in this cohort in a 2:1 ratio.

Subjects who are active in screening in Parts A or B and found to not meet the criteria for NT1, may be considered for Part D, if they are eligible. These subjects will not be assigned a new subject number (in these cases when they have not screen-failed), must sign the Part D ICF and will not be required to undergo another screening visit (in these cases where they are still active in screening within the 45-day screening window).

ALL PARTS:

After the screening visit, eligible subjects will participate in study activities as shown in the overview of the study schedule (Table 6.c and Section 2.0). The full Schedules of Study Procedures are shown in Table 3.a, Table 3.b, Table 3.c, Table 3.d, Table 3.e, Table 3.f, Table 3.g, Table 3.h, Table 3.i, Table 3.j, Table 3.k, Table 3.l, Table 3.m, Table 3.n.

Table 6.c Overview of the Study Schedule

<table>
<tr><th colspan="2" rowspan="2">Screening, Check-In and Baseline</th><th colspan="2">Treatment Period</th><th rowspan="2">Follow-Up Visit</th></tr>
<tr><th>Dose</th><th>Sample Collection</th></tr>
<tr><td rowspan="4">Days -45 to -3</td><td rowspan="4">Day -2 and Day -1</td><td rowspan="2">PART A and PART D: Day 1 to Day 28
Study drug administration twice daily</td><td>Day 1 to Day 30 (See Section 3.1 and Section 3.3)</td><td>Day 35 ±2 days</td></tr>
<tr><td rowspan="2">Day 1 to Day 57
(See Section 3.2)</td><td rowspan="2">PART B and PART C:
Day 63 ±2 days</td></tr>
<tr><td>PART B and PART C: Day 1 to Day 56
Study drug administration twice daily</td></tr>
<tr><td colspan="3">←———— In- and outpatient setting ————→</td><td></td></tr>
</table>

After screening, eligible subjects must discontinue their medication used for treatment of NT1/NT2, including medications used for EDS and cataplexy (valid for NT1 only). Medications that must be discontinued before Day -2 are listed in Section 7.3. Subjects in Parts A, B and C may undergo optional CSF sampling (single time point) for OX assessment during screening. (NOTE: optional CSF testing at a country-level is dependent upon local regulations [either health authority or other government's] and guidelines and site capacity. See Section 9.3.3.2 for details.)

During confinement, study drug will be administered orally twice every day per the schedule of study procedures. For detailed dosing instructions see Section 7.4.1. Study assessments will be obtained per the schedules of study procedures in accordance with the priority specified in Section 6.3.4. Subjects will remain as inpatient from check-in at Day -2 until Day 2; after completion of the scheduled test procedures on Day 2, they will be discharged.

While at home, subjects will take TAK-994 orally BID at approximately the same times each day, with the first dose given in the morning and the second dose approximately 5 hours later and will continue to complete the daily electronic patient-reported outcome (ePRO) diary. See Section 7.4.1 for complete dosing instructions. Subjects will return to the clinic for safety, PK, [redacted] assessments on in-clinic visit days. Subjects will return home on the discharge day after each in-clinic period. A final follow-up is also required approximately a week after the discharge days. See Section 3.0 for details.

After the treatment period, a follow-up visit will be done, after which subjects may resume the use of their prior medication for the treatment of narcolepsy.

Sites should see subjects at the study site to conduct the in-clinic study procedures. In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Procedures, contingency measures may be implemented. Restrictions of human activities or institution activities placed by hospitals, local, state and national governments may prevent conduct of study procedures according to the Schedule of Procedures. Alternative approaches to study procedures and data collection for the current study are described in Section 9.1.1.

6.2 Dose Selection and Cohort Progression

6.2.1 Dose Selection Rules

The dose range to be explored in this study is anticipated to bracket the predicted human efficacious concentration range in order to characterize the dose/exposure-response relationship of TAK-994 in subjects with NT1 or NT2. The starting dose of this study (Part A, Cohort A1a) is 120 mg administered BID with the first dose given in the morning and the second dose given approximately 5 hours later. This dose regimen is supported by the predicted range of pharmacologically active plasma exposure associated with wake-promoting effects in humans from animal studies, and available clinical safety and PK data from the completed TAK-994-1001 FIH study. Refer to Section 6.3.2.1 for starting dose rationale and Section 6.3.2.2 for dose decisions.

The 3 doses for Part B will be determined using all available data from Part A.

The dose for Part C will be selected on the basis of the review of all available data before it starts.

Cohort D1 will start when a dose has been chosen based on emerging safety/tolerability, PK, [redacted] data from Cohort A1. Dose levels in subsequent (sub)cohorts in Part D may be higher than, lower than, or the same as the preceding dose level. However, doses in Part D should not exceed 200 mg BID (Section 6.3.2.2).

6.2.2 Data Review and Interim Analysis

Ongoing medical monitoring will occur during the study. Stopping rules are in Sections 6.5 and 7.5.

Part A and Part D have a design of multiple rising dose study, including different dose cohorts as described in the study design. After completion of each cohort, a data review is needed to decide the dose for the next cohort.

An unblinded sponsor's team (internal review committee [IRC]), composed of members who do not have contact with investigators or sites, will perform the unblinded data reviews to select the dose(s) for upcoming (sub)cohort and study parts to make informed dosing recommendations to the blinded team. Unblinded data reviews will be done at the following times:

Unblinded data review for Part A:

1. When the sentinel cohort (first 9 subjects) in Cohort A1 complete at least 14 days of dosing.
2. At the end of Cohort A1.
3. If the optional Cohort A2 is conducted, when the first 9 subjects in Cohort A2 complete at least 14 days of dosing.
4. If the optional Cohort A2 is conducted, at the end of Cohort A2.

Based on all available data in Part A, the doses for Part B will also be selected.

Unblinded data review for Part D:

1. When the sentinel cohort (first 9 subjects) in Cohort D1 complete at least 14 days of dosing.
2. At the end of Cohort D13. If the optional Cohort D2 is conducted, when the first 9 subjects in Cohort D2 complete at least 14 days of dosing.

An IRC charter will be prepared and approved before the first unblinding event. Access to the unblinded analysis results at the end of each part will also be described in the IRC charter.

Planned Interim Analysis:

In addition, there is one preplanned interim analysis (IA) at the end of Cohort A1 in Part A. For details regarding the end-of-part unblinded analyses, see Section 11.2.

6.3 Rationale for Study Design, Dose, and Endpoints

6.3.1 Rationale of Study Design

6.3.1.1 Rationale for Study Population

The subjects included in the study will be subjects with NT1 (Parts A, B and C) or NT2 (Part D) who are otherwise generally healthy. Subjects with NT1 are deficient in OX, and hence, are the first candidates who are likely to benefit from treatment with an OX2R agonist. In nonclinical pharmacology studies, wake-promoting effects as well as improvement of cataplexy-like syndrome by TAK-994 were observed in a murine narcolepsy model; these effects were confirmed after chronic dosing for up to 14 days. The efficacious dose of TAK-994 was approximately 3 times lower in the narcolepsy model than in wild-type mice, suggesting that there may be a difference in sensitivity to TAK-994 between subjects with narcolepsy and healthy subjects. Based on these data, subjects with NT1 are expected to be more sensitive to TAK-994 than healthy subjects, and hence, the starting dose of TAK-994 needed for safety in NT1 are expected to be lower in NT1 patients than those tested in healthy normal subjects.

6.3.1.2 Rationale for Study Design

Several key considerations were taken into account when designing the study, as the information generated will inform the design and dose selection for the further development of TAK-994 as a potential treatment for NT1 and NT2. These considerations are described below.

Since this is the first study of TAK-994 in NT1 and NT2 subjects, Parts A and D of the study are designed to evaluate the safety, tolerability, PK, [redacted] effects of TAK-994 after repeat oral dosing for 1 month in subjects with NT1 and NT2. Cohorts (up to 2 in each population) will be enrolled in a sequential manner after data review at the end of each cohort. In each cohort, 18 subjects will be randomized in a ratio of 2:1 to receive TAK-994 and placebo for 28 days.

Sentinel dosing in the first 9 subjects will also be performed in the first cohorts of NT1 and NT2 subjects, Cohort A1 and Cohort D1, respectively.

Part B is a dose-ranging part designed to fully characterize the clinical efficacy and safety profiles of TAK-994 administered orally to inform late phase development. This part is a 4-arm parallel group design with 3 different dose levels and placebo. This will be performed after Part A is completed and appropriate dose levels are identified.

Part C [China-specific] will enroll 12-18 subjects to explore the safety and efficacy in Chinese subjects with NT1 for future TAK-994 development.

Each of these parts has its own objectives and own set of subjects that are not overlapping to each other. At the end of each part, a data cleaning and database lock will be performed for that part to ensure its integrity.

Study safety assessments have been selected based on data from nonclinical studies with TAK-994 and emerging final clinical data from Study TAK-994-1001 in healthy subjects. In nonclinical studies in monkeys, while increases in BP were observed after TAK-994 acute administration, these BP effects were attenuated on the second day of dosing and not noted on the final day of dosing after daily administration for 7 days. [redacted]

As discussed in Section 4.3, LFTs will be monitored throughout Part A of the study. Results from this part will determine whether similar monitoring will be required in the subsequent parts of the study.

Based on the emerging data in Study TAK-994-1001, GLDH and fluoride levels did not change following TAK-994 treatment, therefore, GLDH and fluoride levels will not be monitored after this amendment.

See Section 7.5 and Section 6.5.3.1 for individual and cohort stopping rules related to LFT changes, and Section 10.2.8.5 for the procedure for reporting abnormal LFTs.

In addition, subjects will be confined to an inpatient or in laboratory sleep center for specified periods throughout the conduct of the study. This confinement ensures adherence to study procedures and permits monitoring of safety and tolerability.

Nonclinical data with TAK-994 have demonstrated rapid onset of wake promoting effects within 14 days and tolerance to safety effects over 7 days. The current study will evaluate safety and efficacy at 28 days and over a longer duration of up to 56 days to better characterize the treatment effect. This longer duration is chosen to be consistent with the likely study duration of pivotal studies in phase 3. Considering the short half-life of TAK-994, the 7-day follow-up period is considered sufficient to monitor safety.

6.3.2 Rationale for Dose

6.3.2.1 Starting Dose

The starting dose of this study (Cohort A1a, sentinel dosing) is 120 mg administered BID (240 mg total daily dose) with the first dose given in the morning and the second dose given approximately 5 hours later.

Single doses of TAK-994 30, 90, 180, 360, and 450 mg and multiple doses of TAK-994 180 mg QD for 7 days, and 120 or 200 mg BID (6-hour dosing interval) for 14 days have been safe and generally well tolerated in healthy subjects in the recently completed TAK-994-1001 FIH study (see Section 4.1.3). None of the TEAEs were considered serious, and all TEAEs were mild or moderate in severity, except for 1 severe AE of syncope reported in the CSF cohort at 180 mg QD, which the investigator considered related to study procedure but not study drug. AEs increased in number with increasing dose. One subject discontinued from the study due to AE after repeat dosing up to 14 days.

The concentration threshold for wake-promoting effect of TAK-994 in humans is predicted to be 253 ng/mL based on nonclinical pharmacology studies. At the proposed starting dose of 120 mg BID, the predicted mean concentration-time profile of TAK-994 at steady state is expected to produce and maintain TAK-994 plasma concentrations above this efficacy threshold for about 6 hours. Preliminary PK results showed approximate dose-proportional increases in C_{max} after single oral doses up to 450 mg in healthy subjects, while some slight deviation from linearity was observed for AUC_{∞} at the highest dose studied. Following 120 mg BID given 6 hours apart, mean C_{max} values were 409/609 and 365/462 ng/mL after the first/second dose on Day 1 and Day 14, respectively. TAK-994 daily systemic exposures (AUC_{24}) were on average 5220 and 4320 h*ng/mL on Days 1 and 14, respectively. Both the higher plasma peak concentrations observed after the second dose and total daily systemic exposures on Day 1 fell well within the range of those observed after single doses of 180 and 360 mg. Of note, all doses and dose regimens studied to date in healthy subjects have resulted in systemic exposures of TAK-994 that are well below the NOAEL exposures of 1000 mg/kg/day in rats (Day 28 mean values for both sexes: C_{max} = 9765 ng/mL and AUC_{24} = 156,500 h*ng/mL).

Taken altogether, 120 mg BID is deemed appropriate as the starting dose for the Cohort A1 sentinel dose group to initiate evaluation of the clinical safety, PK, and efficacy profile of TAK-994 in patients with NT1. The BID dose regimen is supported by the relatively short elimination half-life of TAK-994 and allows for blunted peak concentrations, lower peak-to-trough fluctuations, and sustained wakefulness during daytime. Both doses will be taken approximately 5 hours apart to not interfere with the four 40-min MWT sessions planned at 2, 4, 6, and 8 hours after the morning dose during the confinement periods, to ease management of dosing and meal times while at home, and to minimize sleep disturbances.

6.3.2.2 Maximum Dose/Exposure for This Study

The maximum daily dose will not exceed 200 mg BID (400 mg/day).

In Parts A, B and C, dose decisions and subsequent dose levels will be determined based on a full review of all available safety, tolerability, PK, [redacted] data (see Section 6.2.2). For example, dose selection for Part B will be based on the outcome of Part A-cohort A1 and optional cohort A2. The emerging [redacted] effects and time above the efficacy threshold will also be considered. Subsequent dose levels may be higher than, lower than, or the same as the preceding dose level.

In Part D, dose for Cohort D1 will be selected based on available data from Cohort A1. Doses for the subsequent subcohort or cohort will be determined based on previous data from Part D.

Dosing will continue as long as the following conditions are met:

1. Based on the adverse fluorosis of incisors at 1500 mg/kg/day, the NOAEL of TAK-994 was 150 mg/kg/day for both sexes. The mean C_{max} and AUC24 at 150 mg/kg/day were 6030 ng/mL and 78,900 h*ng/mL and 13,200 ng/mL and 198,000 h*ng/mL in males and females, respectively, on Day 91. The mean AUC and C_{max} of the maximal dose are predicted to not exceed the mean AUC_{24} and C_{max} values in rats (the more conservative species) at the NOAEL of 150 mg/kg/day from the 13-week toxicology study (Day 91 mean values for both sexes: C_{max} = 9600 ng/mL [average of 6030 ng/mL and 13,200 ng/mL] and AUC24 = 139,000 h*ng/mL [average of 78,900 h*ng/mL and 198,000 h*ng/mL]).
2. Adequate safety and tolerability are present.

Specific criteria for cohort and study termination are provided in Section 6.5.5.1.

6.3.3 Rationale for Endpoints

6.3.3.1 Safety Endpoints

Standard safety endpoints (eg, TEAEs, physical examinations, vital signs [BP, pulse rate, respiratory rate], 12-lead ECGs, clinical laboratory evaluations) for early clinical investigation are included in this study.

Ambulatory blood pressure monitoring (ABPM) is also being obtained to assess BP in the outpatient setting in a rigorous manner.

The Columbia Suicide Severity Rating Scale (C-SSRS) will be used as a standard tool for monitoring any signs of suicidal ideation or behavior.

LFTs will include ALT and AST at the minimum.

6.3.3.2 PK Endpoints

Standard noncompartmental PK analyses will provide measures of drug exposure in the plasma following multiple oral dose administration of TAK-994 in subjects. Metabolites may also be evaluated, as deemed appropriate.

6.3.3.3 Efficacy [redacted] Endpoints

To evaluate the effect of TAK-994 on symptoms of narcolepsy after multiple dosing, this study includes well-established objectives and subjective efficacy endpoints for narcolepsy symptom

measures. Major narcolepsy symptoms include daytime sleepiness measured by objective endpoints such as sleep latency from the MWT procedure, and subjective endpoints such as ESS total score. In addition, cataplexy (in subjects with NT1 only) and disturbance in nighttime sleep are also collected from daily diary.

[redacted]

Rationale for these [redacted] endpoints is provided in Section 9.3.2.

6.3.4 Critical Procedures Based on Study Objectives: Timing of Procedures

For this study, assessments should be performed as close to the scheduled time as possible. In the event of conflicts between scheduled procedures, the following rules should be applied:

- BP assessments should be completed first, followed by ECG and PK, [redacted]. MWTs should be done at scheduled times and assessments staggered to occur before or after so as to not interfere with the conduct of the MWT.
- Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

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

Modifications to the protocol 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. The following minor modifications may be permitted based on newly available data:

- [redacted]
- For PK blood draws, the timing of sampling collection may be changed without changing the total number of samples that will be taken.
- The timing of planned procedures for assessment of safety (eg, vital signs, ECG, safety laboratory tests) [redacted] currently outlined in the protocol may be modified during the study based on newly available safety, tolerability, PK, [redacted] 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 a serum chemistry panel that was already drawn).

- Dose adjustments may be made based on the sentinel dosing results, and review of safety, tolerability, and efficacy data as described in Section 6.2.1.

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).

6.5 Study Beginning and End/Completion

6.5.1 Definition of Beginning of the Study

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

6.5.2 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), withdraws from the study, or is lost to follow-up (ie, the investigator is unable to contact the subject).

6.5.3 Definition of Study Completion

For an individual subject, study completion is defined as when the subject is examined after receiving all planned intervention/treatment to collect final data for all primary, secondary, and exploratory endpoints.

6.5.4 Definition of Study Discontinuation

Study discontinuation is defined as cessation of the overall study due to nonsafety or safety reasons.

- For the overall study and individual cohorts, criteria and procedures for premature termination or suspension are described in Section 6.5.5.
- For study sites, criteria and procedures for premature termination or suspension are described in Section 6.5.6.
- For individual subjects, criteria and procedures for discontinuation or withdrawal are described in Section 7.5 and Section 7.6, respectively.

6.5.5 Criteria for Premature Termination or Suspension of the Study

6.5.5.1 Criteria for Premature Termination or Suspension

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of a study cohort or the overall study:

- New information or other evaluation regarding the safety or efficacy of the study drug indicates a change in the known risk/benefit profile for the product, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) compromises the ability to achieve the primary study objectives or compromises subject safety.
- A finding (eg, PK, [redacted]) from another nonclinical or clinical study using the study treatment results in the study being stopped for a nonsafety-related reason.
- Data from drug(s) of the same class or methodology(ies) used in this study become available and result in the study being stopped for a nonsafety-related reason.
- The study is stopped because of nonscientific and nonsafety reasons, such as slow enrollment.
- Unanticipated concerns of safety to the study subjects arise from this clinical study or additional nonclinical or clinical studies with TAK-994 or drug(s) of the same class.
- Study-specific stopping criteria are met by any of the following criteria, after unblinded review:
  - BP increase: If 4 or more subjects in the same cohort (Parts A, C, D) or in the same arm (Part B) meet the individual subject stopping criteria for BP increases defined in Section 7.5, then further dosing in the cohort will be stopped. In this case, no human dosing will be performed at this and any higher dose levels in the planned clinical study.
  - Insomnia: If 4 or more subjects in the same cohort (Parts A, C, D) or in the same arm (Part B) meet the individual subject stopping criteria for severe insomnia defined in Section 7.5, then further dosing in the cohort will be stopped. No further dose escalation will occur if the cases are assessed as causally related to the investigational product by the sponsor.
  - LFT: If 3 or more subjects in the same cohort meet (Parts A, C, D) or in the same arm (Part B) the individual subject stopping criteria for abnormalities, as defined in Section 7.5, then further dosing in the cohort will be stopped. No further dose escalation will occur.
  - SAE: If 3 or more subjects in the same cohort (Parts A, C, D) or in the same arm (Part B) meet the individual subject stopping criteria or 3 or more experience a similar SAE that is drug-related in investigator's and sponsor's opinions, then further dosing in the cohort will be stopped. No further dose escalation will occur.
  - For Part B, there will be an unblinded review by the sponsor's unblinded safety physician who will make the final decision to either stop part B or the dosing arm in which the SAE/AE occurred, or continue with further dosing.
- The study will be paused for further evaluation if any of the following criteria are met:
  - ≥10% or 3 subjects, whichever is higher, in the same cohort (Parts A, C, D) or in the same arm (Part B) experience a similar SAE.
  - ≥10% or 3 subjects, whichever is higher, in the same cohort (Parts A, C, D) or in the same arm (Part B) experience a similar severe AE, with the exception of insomnia.

- ≥10% or 3 subjects, whichever is higher, in the same cohort (Parts A, C, D) or in the same arm (Part B) discontinue study for safety reasons.
- ≥1 death determined by the investigator and the sponsor to be related to study medication.

- Subject may be withdrawn from the study at any time, due to disease progression or any other safety reason, if it is in the best interest of the subject.
- The sponsor terminates or suspends the study, or any study cohort, at any time for any other clinical or administrative reasons.

6.5.5.2 Procedures for Premature Termination or Suspension of the Study

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

6.5.6 Criteria for Premature Termination or Suspension of a Site

6.5.6.1 Criteria for Premature Termination or Suspension

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

6.5.6.2 Procedures for Premature Termination or Suspension

If the sponsor, an IRB/IEC, or a regulatory authority elects to terminate or suspend 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 site(s) during the course of termination or study suspension. If the site closure is due to COVID-19, this should be captured on the CRF, end of treatment disposition page.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility will be determined according to the following criteria before administration of the first dose in the study:

1. The subject must be aged 18 to 65 years, inclusive, at the time of informed consent.
2. The subject must understand the study procedures and agree to participate by providing written informed consent.
3. The subject must be willing and able to comply with all study procedures and restrictions.

4. The subject must be judged to be in good health by the investigator to participate in the study, 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 the first dose of study drug or first study assessment.

   Note: Screening labs may be repeated once, after consultation with the Medical Monitor.

5. The subject must have a diagnosis of NT1 (Parts A-C) or NT2 (Part D) by [redacted] MSLT performed within the past 10 years meeting the minimal acceptable criteria for the proper performance of [redacted] MSLT as outlined by the ICSD-3 criteria (Appendix E).

   Note: If there is a potential subject with a diagnosis of NT1 or NT2 whose diagnostic [redacted] MSLT was performed more than 10 years ago or is not available, special exemptions, ie, ability of the site to repeat the diagnostic [redacted] MSLT will be considered on a case-by-case basis after discussions between the investigator and the sponsor or designee.

6. The subject's ESS score must be ≥10 at Day -1.
7. The subject must be willing to discontinue all medications used for the treatment of NT1/NT2.
8. The human leukocyte antigen (HLA) genotype:

   – Part A: The HLA genotype should test positive for HLA-DQB1*06:02 - (positive results for either homozygous or heterozygous alleles will be considered "positive" and acceptable). However, if the HLA test is negative (ie, negative for the heterozygous allele) and the PI feels strongly that the subject has narcolepsy with cataplexy (NT1) then a discussion should be initiated between the PI and the sponsor or designee about the advisability of doing a spinal tap to determine the subject's cerebrospinal fluid (CSF) orexin-1 (OX-1) level. If the CSF result shows the OX-1 concentration is either less than or equal to 110 pg/mL, or less than one-third of mean values obtained in normal subjects with the same standardized assay, then the diagnosis of NT1 is established allowing the subject to be enrolled and randomized, If the CSF OX-1 concentration is >110 pg/mL then the subject will not be allowed to continue in the study. See Section 9.2.11.2.4 for details. Subjects previously excluded in Part A for being HLA negative will not be included in Part B.

     Parts B and C: HLA genotyping will be done for these subjects as well; however, HLA test results are not a study entry criteria. Subjects who present with CSF testing results indicating OX-1 concentration either less than or equal to 110 pg/mL, or less than one-third of mean values obtained in normal subjects with the same standardized assay, may be considered for enrollment into Parts B and C after a discussion with the sponsor or designee. For all subjects in Parts B and C, site staff will complete the cataplexy questionnaire during screening. This questionnaire along with a copy of the most recent [redacted] MSLT report will be submitted to the sponsor for adjudication by a committee of experts in the field of narcolepsy/cataplexy to be chosen by the sponsor. This committee will determine eligibility for the study and the committee's determination will be final for study entry criteria. Additional documentation may be requested by the sponsor.

9. For Parts A, B, and C, during the screening period, the subject must have ≥4 partial or complete episodes of cataplexy/week (WCR), averaged over 2 weeks (14 consecutive days) minimum. WCR recording taken during following period will be considered for study eligibility: after the patient has stopped taking anticataplexy medications for at least 7 days (minimum 7-day washout) and study Day -2. Refer to Section 9.3.2.7 for details.
10. For a male subject who is not sterilized and sexually active with a female partner of childbearing potential, the subject must meet the following birth control requirements:
    - Agrees to use an appropriate method of contraception, including a condom with spermicidal cream or jelly, from the first dose of study drug until 5 half-lives (1 day) 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 post-bilateral 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 non-vasectomized man. Appropriate documentation of surgical procedure should be provided.
    - Agrees to not donate sperm from the first dose of study drug until 5 half-lives plus 90 days after the last dose of study drug.
11. For a female subject of childbearing potential who is sexually active with a male partner who is not sterilized, the subject must agree to use **highly effective methods of contraception** from signing of the informed consent throughout the duration of the study and for 5 half-lives of TAK-994 plus 30 days. Additional guidance for contraception before the study start, definitions and procedures for adequate contraception, pregnancy avoidance, and reporting responsibilities are defined in Appendix D.
12. Subjects who smoke must be willing to abstain from smoking while confined in the inpatient unit.
13. The subject must have a body mass index (BMI) ≥17.0 and ≤40 kg/m^2 at the screening visit.
14. The subject must have BP <140 mmHg (systolic) and <90 mmHg (diastolic). The subject may have a history of hypertension and be on antihypertensive medication treatment as long as the BP meets these criteria. BP measurements should be obtained after the subject has been resting for a minimum of 10 minutes and will be repeated 3 times. The median BP obtained will be used.

7.2 Exclusion Criteria

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

All Subjects

1. The subject has participated in another investigational study within 60 days (or based on local regulations) before the screening visit. The 60-day 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. (Exceptions may be made for observational, natural history, and nonintervention type studies with sponsor or designee approval).

2. The subject is an employee of the sponsor or study site or an immediate family member (eg, spouse, parent, child, sibling) of an employee of the sponsor or study site who is directly involved in the conduct of the study.
3. The subject has a history of cancer (does not apply to subjects with carcinoma in situ that has been resolved without further treatment or basal cell skin cancer; these subjects may be included after approval by the sponsor or designee i.e. medical monitor [MM]).
4. The subject has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-994 or related compounds.
6. The subject has a positive pregnancy test or is a lactating/nursing female subject.
7. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody at the screening visit or has a history of human immunodeficiency virus.

   Note: Subjects with positive hepatitis B virus or hepatitis C virus serology may be enrolled if quantitative polymerase chain reaction for hepatitis B virus or hepatitis C virus ribonucleic acid is negative.
8. The subject had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.
9. The subject is unable to refrain from or anticipates using excluded medications, including food products and grapefruit juice (see Section 7.3), beginning approximately 7 days (14 days for anticataplexy medications) before baseline, throughout the study, and until the follow-up visit.
10. The subject's renal creatinine clearance is ≤50 mL/min.
11. Has LFTs (ALT, AST) higher than 1.5× ULN at screening.
12. The subject has poor peripheral venous access, as assessed by the investigator.
13. The subject has a risk of suicide according to endorsement of Item 4 or 5 of the screening/baseline visit C-SSRS and/or has made a suicide attempt in the previous 12 months.
14. The subject has past or current epilepsy or seizure, except for a single febrile seizure in childhood.
15. The subject has a lifetime history of major psychiatric disorder, such as bipolar disorder or schizophrenia. Subjects who have history of major depressive disorder (MDD) may be included, but subjects who have current active MDD or who have had active MDD in the past 6 months are excluded.

16. The subject has a clinically significant history of head injury or head trauma per the judgment of the investigator.
17. The subject has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation.
18. The subject has known coronary artery disease, a history of myocardial infarction, angina, cardiac rhythm abnormality, or heart failure.
19. The subject has a screening ECG with a QT interval with Fridericia's correction method (QTcF) >450 ms (men) or >470 ms (women).
20. The subject has a resting heart rate outside of the range of 40 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes at screening.
21. The subject has medical condition other than narcolepsy, such as medically significant unstable cardiovascular, pulmonary, hepatic, renal, or gastrointestinal disease, that would preclude enrollment in the view of the investigator.
22. The subject has current or recent (within 6 months) gastrointestinal disease that is expected to influence the absorption of drugs (ie, a history of malabsorption, esophageal reflux, peptic ulcer disease, erosive esophagitis, frequent [more than once per week] occurrence of heartburn, or any surgical intervention). Any history of Roux-en-Y gastric bypass is considered exclusionary and any other surgical intervention that may influence the absorption of drugs should be discussed and approved by the sponsor or designee before enrolling the subject.
23. The subject, in the opinion of the investigator, is unlikely to comply with the protocol or is unsuitable for any other reason.
24. The subject is an excessive (>600 mg/day) caffeine user 1 week before the study screening.
25. Subjects on fluoxetine (any dose) or on ≥300 mg per day of venlafaxine will be excluded due to the drug's long elimination half-life or clinically significant tapering/washout difficulties. See Section 7.3 for a complete list of medications that are not allowed during the treatment period and the guidelines for washout for stimulant, anticataplexy, antidepressant medications and sodium, and/or multisalt oxybate, that must be followed, as applicable.
26. The subject has a medical disorder, other than narcolepsy, associated with EDS. This includes clinically significant moderate to severe obstructive sleep apnea with or without treatment with mandibular advanced device hypoglossal nerve stimulation and/or positive airway pressure (PAP) therapy) and/or restless legs syndrome (RLS)/periodic limb movement disorder that has a significant impact on daytime sleepiness. This is evidenced by a clinical history of sleep apnea syndrome (loud snoring with observed respiratory pauses in the absence [redacted]) and/or RLS causing historical sleep onset/maintenance insomnia with resultant insufficient sleep as evaluated during the clinical interview at screening. Past [redacted] data demonstrating any of the following sleep disturbances: apnea Hypopnea Index ≥15 or apnea index ≥10, an oxygen saturation of ≤80 for ≥10 seconds, periodic leg movement arousal index of ≥15/h) should be considered exclusionary unless, based on a clinical evaluation by the investigator, a

meaningful change in clinical status has occurred that would impact the results. Because [redacted] data is obtained on Day -2, subjects may fail screening if criteria are not met on the Day -2 [redacted].

27. The subject has any other medical condition, such as anxiety, depression, heart disease, or significant hepatic, pulmonary, or renal disease, that requires the subject to take excluded medications (see Section 7.3) or at the time of screening the subject is being treated with nasal /oro-nasal positive airway pressure (PAP) for any reason.
28. The subject is unwilling to abstain from driving and operating dangerous or hazardous machinery during study participation, starting from when narcolepsy medication is discontinued and extending until after the follow-up visit (35 ±2 days or 63 ±2 days).
29. The subject has a positive urine screen for drugs of abuse and/or positive alcohol test at screening and Study Day -2. An exception at screening is made for stimulants or other drugs that the subject has been prescribed, but the drug screen must be negative at Study Day -2.
30. The subject has a history of drug or alcohol abuse within the 12 months before screening (Diagnostic and Statistical Manual of Mental Disorders, Edition 5 criteria).
31. The subject has a nicotine dependence that is likely to have an effect on sleep (eg, a subject who routinely awakens at night to smoke) and/or an unwillingness to discontinue all smoking and nicotine use during the confinement portions of the study.
32. The subject has a usual bedtime later than 2400 (12:00 AM, midnight) or an occupation requiring nighttime shift work or variable shift work within the past 6 months or travel within more than 3 time zones, within 14 days before Study Day -2.

Subjects Undergoing Optional CSF Collection

33. The subject has undergone CSF collection within 30 days before check-in.
34. The subject has a known hypersensitivity to anesthesia/local anesthetics, or its derivatives used during CSF collection or to any medication used to prepare the area of lumbar puncture.
35. The subject has significant vertebral deformities (scoliosis or kyphosis) that, in the opinion of the investigator, may interfere with the lumbar puncture procedure.
36. The subject has a history of major back (lumbar) surgery, clinically significant back pain, and/or injury, in the opinion of the investigator.
37. The subject has a local infection at the puncture site.
38. The subject has developed signs of lumbar radiculopathy, including lower extremity pain and paresthesia.
39. The subject has any known focal neurological deficit that might suggest an increase in intracranial pressure.
40. The subject has any abnormal findings on ophthalmological/funduscopic assessment indicative of raised intracranial pressure (ie, optic disc swelling/edema or [uncontrolled] hypertension retinopathy).

41. The subject has a bleeding abnormality or history of bleeding abnormalities. The subject has thrombocytopenia or other suspected bleeding tendencies noted.
42. The subject is taking an anticoagulant (1 tablet/day of low dose aspirin [81 mg] is allowed) or has abnormal coagulation test results (prothrombin time [PT]/international normalized ratio [INR], activated partial thromboplastin time) from a sample taken during the screening period. Results must be received and reviewed by the investigator in advance of CSF sample collection.

7.3 Excluded Medications, Supplements, and Dietary Products

Excluded medications and dietary products are shown in Table 7.a.

Table 7.a Excluded Medications, Supplements, and Dietary Products

Prohibited Drug Category	Drugs Restricted From 7 Days or 5 Half-Lives [a] Before Dosing (Day 1) Until Follow-Up (Unless Otherwise Specified)
Any investigational drug	<60 days before screening or 5 half-lives – whichever is longer
Psychostimulants	Methylphenidate hydrochloride, modafinil, armodafinil, methamphetamine hydrochloride, solriamfetol, and pitolisant need to be restricted from 7 days or 5 half-lives before Day -2 and through the follow-up visit.
Sodium, and/or multisalt oxybate	Should be discontinued at a minimum of 4 weeks before Day -2; decision to discontinue should be made after consulting with sponsor or designee
Antipsychotic drugs	Not allowed
Antianxiety/sleeping drugs (tranquilizers/sleeping medications)	Including benzodiazepines, non-benzodiazepine drugs and melatoninergic agonists
Antidepressants	1. At screening, those on fluoxetine (any dose) or venlafaxine ≥300 mg/day will be excluded from the study. 2. Stimulant medications must be discontinued for a minimum of 7 days or 5 half-lives before Day -2 check-in 3. Anticataplexy medications (eg, tricyclic antidepressants, SSRI, and SNRI) washout should start at least 21 days before Day -2 to allow for confirmation of cataplexy eligibility criterion. (Parts A, B and C).
Mood stabilizers (such as lithium or valproic acid or other antipsychotic drugs)	Not allowed
Anticonvulsants	Not allowed
Sleeping pills	Including Chinese medicine (*Yokukansan, Yokukansankachinpihange*) used for insomnia
Anti-Parkinson's disease drugs (completely excluded)	Not allowed
Adrenocorticosteroids (excluded except for inhaled and topical)	Systemic administration permissible during the study for purposes of treating an AE only
Interferon, interleukin-formulation (excluded)	Not allowed
Muscle-relaxant drug (eg, baclofen)	Not allowed
Antihistamines	Only centrally acting antihistamines are prohibited. Loratadine is also prohibited. The use of antihistamines and steroids are allowed for the management of severe allergic reactions.
Antitussives with CNS action	Not allowed
Antiemetics with CNS action	Not allowed
Narcotic analgesics and non-narcotic analgesics,	Use of over-the-counter pain medications (acetaminophen; excluding occasional use of ibuprofen, naproxen, and aspirin) is

Table 7.a Excluded Medications, Supplements, and Dietary Products

Prohibited Drug Category	Drugs Restricted From 7 Days or 5 Half-Lives [a] Before Dosing (Day 1) Until Follow-Up (Unless Otherwise Specified)
varenicline (CHANTIX)	prohibited unless otherwise approved by the principal investigator after consultation with the sponsor or designee (i.e. MM)
St. John's Wort, health foods containing melatonin	Not allowed
Known moderate and strong CYP3A inhibitors or inducers are available in and Appendix F.	Not allowed
Known Pgp inhibitors (azithromycin, captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor)	Not allowed
Known CYP3A substrates with narrow therapeutic range including but not limited to ergot alkaloids, fentanyl, pimozide, astemizole, terfenadine, systemic corticosteroids (dose equivalent to ≥10 mg prednisone per day), nisoldipine, lovastatin, simvastatin, midazolam, triazolam, buspirone, almorexant, lemborexant, suvorexant, lurasidone, naloxegol, tilidine, sildenafil, vardenafil, cilostazol, and eletriptan	Not allowed
Known sensitive OATP1B1 substrates including but not limited to pravastatin, rosuvastatin, pitavastatin, atorvastatin, elagolix, repaglinide, valsartan	Not allowed
Sensitive Pgp substrates with narrow TI: digoxin, dabigatran etexilate, fexofenadine	Not allowed
Sensitive BCRP substrates: sulfasalazine	Not allowed
Chinese herbal medicine	Not allowed [b]

AE: adverse event; BCRP: breast cancer resistance protein; CNS: central nervous system; CYP: cytochrome P-450; MM: medical monitor; OATP: organic anion transporting polypeptide; OTC: over-the-counter; Pgp: P-glycoprotein; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

If medications are required to treat an AE, certain medications, including supplements, may be allowed after discussion and agreement between the sponsor or designee and principal investigator, unless the investigator or investigator's designee considers immediate administration necessary.

[a] Whichever is longer.

[b] Topical use is allowed.

7.3.1 Concomitant Medications

Subjects may take any medication that is not prohibited in Section 7.3. The investigators or the sub-investigators will review concomitant medication use at screening and determine the time of discontinuation, keeping in mind that some medications will need to be tapered. The investigator or sub-investigator will consult with the sponsor or designee (i.e. MM) before allowing any concomitant medication during the study. Subjects will also be instructed not to take any medications, including over-the-counter drugs, without prior consultation with the investigator or sub-investigator.

The use of any investigational drug other than TAK-994 is not permitted throughout any study participation period.

7.3.2 Fruit Juice and Fruit

Consumption of all fruit juices and fruit other than grapefruit fruit and grapefruit juice is allowed on all days of the study.

7.3.3 Alcohol

PART A and D (28 Days Treatment Period):

During the screening and study drug dosing period, subjects should refrain from the intake of alcohol.

PART B and C (56 Days Treatment Period):

Prohibited for 7 days before check-in on Day -2 and all site visits. It is also prohibited during confinement at site. Outside of these periods, alcohol consumption is limited to no more than approximately 2 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. Subjects will be asked to record the approximate time and number of beverages containing alcohol consumed each day during the study period.

7.3.4 Caffeine

On days of [redacted] MWT assessments (Section 3.0), caffeine will not be allowed; subjects will follow the [redacted] MWT manual.

At all other times, caffeinated beverages (including caffeinated tea) or xanthine-containing products will be limited to amounts of no more than 600 mg per day.

7.3.5 Smoking

Subjects will follow the [redacted] MWT manual. Subjects may smoke during the study outside the confines of the center but must be willing to abstain during the period of confinement in the inpatient or in-laboratory sleep center.

7.4 Dosing Instructions, and Activity

7.4.1 Dosing Instructions

Each subject in this study will be instructed to take study drug BID: the first dose will be taken in the morning upon awakening, as close to 8 AM as possible (after completion of predose assessments if in the unit) and the second dose will be taken approximately 5 hours later. Both doses should be taken without food. A minimum of 4 hours apart is required between the morning and afternoon doses. The second dose should be taken no later than 2 PM based on the elimination half-life of TAK-994.

During the confinement periods (as indicated in Section 3.0), the first dose of TAK-994/matched placebo will be administered in the morning by mouth (at approximately 8 AM) with 240 mL of water after an overnight fast of at least 8 hours; subjects will then be allowed to have a morning meal approximately one-half to one hour after study drug administration. The second dose of TAK-994/matched placebo will be administered orally approximately 5 hours later at the site. Subjects may consume water ad libitum. Standardized meals (approximately 30% fat content relative to total calories) will be administered at approximately 4 (lunch) and 10 (dinner) hours post the morning dose. On discharge days, lunch or dinner may be taken at home.

On ABPM fitting days (as indicated in Section 3.0), because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device. If the subject is travelling to the site for the ABPM fitting, **they should delay their morning dose of study medication (between 8 AM ±2 hours)** and take their study drug right after the ABPM device begins recording the measurements in the clinic. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts.

While at home, subjects will be instructed to take TAK-994/matched placebo upon arising in the morning as close to 8 AM as possible (± 1 hour) and have breakfast approximately one-half to one hour after study drug intake whenever possible. Subjects will be instructed to take the second dose approximately 5 hours after the morning dose and no later than 2 PM in the afternoon. The second dose should be taken without food on an empty stomach (approximately 1 hour before eating or 2 hours after eating), whenever possible. Subjects are encouraged to take study drug at approximately the same time each day in the morning (first dose) and afternoon (second dose). Breakfast and lunch should be standard meals each containing approximately 30% fat (relative total calories). Subjects will be provided written instructions by the site on how to take study drug (dosing and mealtimes) at home.

Tablets should be taken with a large glass of water (approximately 240 mL total). Subjects should swallow the study medication whole and not chew it or manipulate it in any way before swallowing. Subjects should be instructed to take not more than the prescribed dose at any time. If a subject fails to take the TAK-994/matched placebo dose within the time frame specified, s/he should be instructed to take it at least 30 minutes before the next scheduled meal. Under no circumstance should a subject repeat a dose or double-up doses. If the second dose is missed, that

dose should be skipped and should not be taken again until the next morning. Both doses should never be taken at one time.

Subjects will be instructed to record their intake of TAK-994/matched placebo each day, or any skipped or mistimed doses, in their electronic dosing diary (Section 9.3.2.7). Additional steps may be taken to ensure subjects understand the dosing instructions and that they follow the correct TAK-994 dosing regimen, such as additional site communication with the subject throughout the treatment course, i.e. on-site visits or phone calls.

Subjects will adhere to the medication and dietary restrictions described in Section 7.3.

7.4.2 Activity

During confinement, subjects should remain upright (seated, standing, or ambulatory) for 4 hours as feasible, following dose administration, except as necessitated by the occurrence of an AE or study procedure (eg, obtaining 12-lead ECG). Please follow specific instructions for study assessments (eg. MWT).

Subjects should refrain from strenuous physical activity (eg, weightlifting, running, bicycling) from 72 hours before check-in until check-out for scheduled study visits. Subjects may engage in usual activities at other times with the exception of driving or operating hazardous machinery.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of a subject from the study or study drug should be recorded in the electronic case report form (eCRF). The following criteria for discontinuation or withdrawal of a subject will apply to all parts of the study:

1. Pretreatment event (PTE), SAE, or AE: The subject has experienced a PTE, SAE, 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, SAE, or AE.

    - 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 9.2.11.1), if the following circumstances occur at any time during the study drug treatment:
        - ALT or AST >5 × ULN.
        - ALT or AST >3 × ULN in conjunction with elevated bilirubin >2 × ULN or INR >1.5 .
        - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
        - ALT >3 × ULN twice consecutively at least 24 to 48 hours apart.
    - 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: Study drug should be discontinued immediately if the median of 3 in-clinic BP measurements (at least 10 minutes apart) meets any of the following criteria:
  - Systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg.
  - Neurologic or cardiac findings associated with increases in BP.

  In the event of BP values meeting the criteria above, the subject will be treated for elevated BP according to the best judgment of the investigator and in accordance with good medical practice, and, if needed, further emergency medical evaluation sought. If the drug is discontinued in any subject due to a BP increase, the subject will not be rechallenged with TAK-994.

  Any subject found to have significantly elevated BP as an outpatient should be treated per standard to care in order to obtain BP lowering. The sponsor or designee (i.e. MM) should be notified and consulted.
- Pulse rate increase: Increased from baseline earlier in the day and sustained pulse rate >100 bpm measured during the in-clinic visit will result in stopping treatment.
- Insomnia: Study drug should be discontinued for subjects with sustained severe or serious insomnia as determined by the principal investigator after consultation with the sponsor or designee (i.e. MM).

2. Significant protocol deviation: The discovery post randomization 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 3 attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents. A certified letter can be sent as a last attempt.
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). If a subject chooses to withdraw from study participation due to personal concerns related to the COVID-19 pandemic (other than a COVID-19-related AE), this should be specified as the reason for subject withdrawal in the eCRF.
5. Pregnancy, as described in Appendix D.
6. Other: The reason for discontinuation should be entered into the eCRF including unavoidable circumstances such as the COVID-19 pandemic. Subjects may withdraw from the study at any time at the discretion of the investigator or sponsor for safety reasons which should be entered into the eCRF.

7. Study termination: The sponsor, IRB, IEC, or regulatory agency terminates the study. Criteria for premature cohort and/or study termination are provided in Section 6.5.5.1.

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. The investigator should consult with the sponsor or designee (i.e. MM) before subject discontinuation whenever possible.

7.7 Subject Replacement

If a subject withdraws 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.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Clinical Study Drug

Details regarding the dosage form description and strengths of the active drug and matching placebo can be found in the pharmacy manual. Study drug will be packaged to support enrollment and replacement subjects as required.

Tablet strengths for this study are 10, 30, and 90 mg.

On occasion in unavoidable circumstances such as the COVID-19 pandemic, additional drug supply may be provided to subjects (either at an in-person visit or delivered to subject's residence) to cover extended periods between on-site visits. Any additional re-supply must be reviewed and approved in advance by the sponsor or designee.

8.1.1 Clinical Study Drug Labeling

Study drug containers will be affixed with a clinical label in accordance with local regulatory requirements.

8.1.2 Clinical Study Drug Inventory and Storage

Study drug at the sites must be stored in a secure, limited-access location under the storage conditions specified on the label and remain in the original container until dispensed. The temperature excursion information can be found in the pharmacy manual. Receipt and dispensing of study drug at the study site must be recorded by authorized personnel.

8.1.3 Clinical Study Drug Blinding

This is a double-blind study; the investigator and subjects are blinded to treatment assignment. Treatment identity (name and strength or potency) will be included on the study drug container label; emergency randomization code access will be made available through the IRT system in accordance with the standard operating procedures of the clinical site.

Details on blinded/unblinded data review for determination of study drug doses and cohort initiation are provided in Section 6.2.2.

8.1.4 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule for the IRT system.

For Part B, the randomization will be stratified by baseline WCR (<8 vs ≥8) and regions/countries (ie North America, Asia [Japan, South Korea], Europe).

For other parts, the randomization will be stratified by regions/countries (North America, Asia [China, Japan, South Korea], Europe.

Details are in the IRT system specifications. The pharmacy manual includes instructions for emergency unblinding. Storage conditions are also specified in the pharmacy manual.

8.1.5 Clinical Study Blind Maintenance/Unblinding Procedure

The study drug blind will be maintained through a randomization schedule held by the IRT system. The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. If possible, the sponsor or designee (i.e. MM) should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator is responsible for keeping accurate records of the 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 study drug accountability, return, and destruction. Subjects will be instructed to return any remaining study drug they may have to the site for assessment of compliance

8.2 Ancillary Supplies

All ancillary supplies will be provided by either the study site or the sponsor or designee, based upon availability. The list of ancillary supplies and source information can be found in the pharmacy manual or in the referenced compounding manual when applicable. If provided by the sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the sponsor or designee.

9.0 STUDY PROCEDURES

The following sections describe the study procedures to be performed and data to be collected as indicated in the Schedules of Study Procedures (Section 3.0).

Alternative Approaches to Study Procedures and Data Collection Due to COVID-19 or Other Unavoidable Circumstances

In unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Section 3.0), contingency measures may be implemented. In acknowledgement of study site, hospital, local, state and national restrictions established in response to circumstances like COVID-19, the following measures are being taken for the current study:

- For subjects active in the study, all attempts should be made to perform the assessments with the subject present at the site using the visit windows. Exceptions may be granted for alternative approaches to study procedures and data collection through approval by the sponsor or designee. Such instances must be documented in the study records and may include the following:
  - Sites impacted by COVID-19 Pandemic or similar unavoidable circumstances, must contact the sponsor or designee to discuss individual subject and site circumstances to obtain approval for use of alternative approaches to study procedures and data collection due to COVID-19 or other unavoidable circumstances.
  - Sites may seek approval from the sponsor or designee to continue subjects in the study despite departures from the Schedule of Study Procedures. The principal investigator is expected to evaluate the impact to the safety of the study participants and site personnel for subjects to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the subjects. Subjects must be willing and able to continue taking study medication and remain compliant with the protocol.
  - Other than discharge visits, alternative methods for conducting subject visits (eg, video conferencing, telephone visits, or in-home study visits conducted by study site personnel or designated medical personnel, contingent upon local regulations) may be used per approval by the sponsor or designee:
    - Under these circumstances, collection of certain study assessments may be omitted and visit windows may be extended.
    - When approval is given for a subject to miss an in-person study visit, a study site physician will speak directly with the subject by telephone or other medium (e.g. a computer-based video communication) during each visit window to assess subject safety and overall clinical status.
    - The study site physician or other qualified site personnel should conduct the following assessments within specified-visit window timeframes: AE assessments, documentation of concomitant medication, administration of C-SSRS (at applicable visits), and an assessment of clinical symptoms.

- For this study, home nurses or other qualified clinical personnel may be deployed at the request of the site, when appropriate. Advance approval from the sponsor or designee should be obtained.
- Other study assessments may be collected using an alternative method as feasible, and may involve audio or video recording where allowed by local regulation. This will be documented in the study records.
- Subjects may choose to get COVID-19 vaccine at any time during this study.
- In some instances, sites may need to split visits or sites may only be able to perform a few procedures on site and some procedures may need to be performed remotely. Sites should inform sponsor or designee when this occurs.
- Sites may seek approval to extend a visit window in order to conduct an on-site visit. Assessments that cannot be completed during the protocol-specified window or within the visit window granted by the sponsor or designee will be considered missing data and such departures will be recorded in the study records.
- There will be no interval longer than 2 weeks between successive visits at which clinical laboratory tests are performed and vital signs are measured. Should the period of 2 weeks be met for a particular subject, the site should reach out to the sponsor or designee to discuss withdrawal of the subject.

– Study site personnel may dispense additional IP to subjects at a visit to allow for potentially longer intervals between visits than originally planned per protocol, or IP may be supplied to subjects via delivery by site personnel or by courier.

– Early termination visits should be performed in person. When it is not possible for the subject to come to the study site and the protocol specified visit window cannot be extended further, the preferred alternative for the early termination visit is for qualified study site personnel or designated clinical personnel to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at a subject's residence should comply with applicable local regulations. If neither option is available with sponsor or designee approval, sites may conduct early termination procedures remotely as is feasible.

All subject discontinuations and alternative approaches to study procedures (ie, procedures not conducted per the Schedule of Procedures) due to the COVID-19 pandemic must be documented in the study records. Data collected using alternative methods may be handled differently in the final data analyses. This will be documented in the Statistical Analysis Plan.

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 (and e-consent, if applicable, as per local regulations) are described in Appendix B.

9.1.1.1 Assignment of Subject Numbers

All consented subjects will be given a unique subject number (site number plus a unique sequential number) through an IRT system that will be used to identify the subject for all procedures that occur during the study. Each subject will be assigned only 1 subject number except in the event of rescreens authorized by the sponsor. Subject numbers must not be reused for different subjects.

Rescreening may be allowed up to, but not more than, once for any one subject. Additional rescreening may be allowed for COVID-19 related factors. Subjects who were found to not meet criteria for NT1, may be re-screened to participate in Part D. Such subjects may enter screening an additional time with sponsor or designee approval. Rescreening of any subject must be reviewed with the sponsor or designee. Any subject who is screened more than once will be assigned a new subject number for each screening event.

9.1.1.2 Study Drug Assignment

On Day 1, subjects will be assigned a randomization number through the IRT system at the clinical site. The randomization number encodes the subject treatment assignment according to the randomization schedule generated before the study. The randomization number will be recorded on the CRF. Each subject will be dispensed blinded study drug assigned by the IRT system 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.

9.1.2.1 The Cataplexy Questionnaire

The cataplexy questionnaire is designed to ascertain the frequency and triggers of cataplexy events. It is designed to help differentiate cataplectic events, which are part of the NT1 clinical definition from pseudo-cataplexy which would be exclusionary from the NT1 portion of our study.

For all subjects in Parts B and C, site staff will complete the cataplexy questionnaire. This questionnaire along with a copy of the most recent [redacted] MSLT report will be submitted to the sponsor for adjudication by a committee of experts in the field of narcolepsy/cataplexy to be chosen by the sponsor, to determine eligibility for the study. The committee's determination will be final for study entry criteria. Additional documentation may be requested by the sponsor.

9.1.3 Medical History/Demography

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, along with subject demographics (eg, date of birth, sex, race [reported by the subject], height, weight, caffeine consumption, alcohol consumption, smoking status). Information on the primary disease (narcolepsy) will also be collected including age of onset and year of diagnosis. Any prior CSF testing results will also be collected.

9.1.4 Concomitant Medications

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

Subjects will be asked whether they have taken any medications other than the study drug (during a period from the signing of informed consent through the end of the study), and all medications used by a subject must be recorded in each subject's eCRF. The nonproprietary name, route of administration, dates of initial and final administrations, and reasons for use must also be recorded.

9.2 Clinical Procedures and Assessments

9.2.1 Physical Examination

Qualified site personnel will conduct full physical examinations (including neurological examination) at screening and final visit (final discharge)/early termination. On all other time points, an abbreviated PE will be done.

Subjects undergoing optional CSF sampling during screening will undergo ophthalmological assessment of the retina (fundoscopy), a nondilated ophthalmoscopy exam to evaluate for any evidence of increased intracranial pressure. If needed, a dilated exam for fundoscopy may be performed by a trained person (optometrist, ophthalmologist, or neurologist) after dilatation of the pupil in both eyes by administration of tropicamide 0.5% eye drops. After pupil dilatation, subjects will be advised to wear sunglasses for the next 4 to 6 hours and avoid operating a car.

9.2.2 Height and Weight

Body weight and height will be obtained with the subject's shoes off and jacket or coat removed at the times indicated in the Schedule of Study Procedures (Section 3.0).

9.2.3 BMI

BMI is defined as a subject's weight (in kilograms) divided by height (in meters) squared (BMI = kg/m^2). BMI will be calculated at the times indicated in the Schedules of Study Procedures (Section 3.0).

9.2.4 Vital Signs

Vital signs, including pulse rate, systolic and diastolic BP, respiratory rate, and body temperature, will be obtained at the times indicated in the Schedule of Study Procedures (Section 3.0).

When assessed in the clinic, BP will be checked (single measurement) with the subject lying in a bed resting for a minimum of 5 minutes with the head of the bed at 30 degrees. In the event of conflicts between scheduled BP assessment and PK blood draw times, BP assessments should be taken first.

For screening Days -45 (or the first screening visit, as applicable) and Day -2, blood pressure measurement may be checked up to 3 times and the median value should be used to assess eligibility. For all other visits a single measurement should be taken.

Outpatient vital signs monitoring is described in Section 9.2.6.

9.2.5 12-Lead ECGs

ECG monitoring will be obtained according to the Schedule of Study Procedures (Section 3.0).

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 and will remain in that position until ECG is completed. The principal investigator should arrange to have a study cardiologist available as needed to review ECG tracings with abnormalities.

If a subject demonstrates an increase in QTcF interval ≥40 milliseconds compared with a 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 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.

9.2.6 Wearable Devices (ABPM [redacted])

9.2.6.1 ABPM

ABPM readings should be obtained over an approximately 24-hour period and subjects should not be confined to the clinical site during most of the 24-hour recording period. Because it is a requirement that the ABPM devices begin recording in the morning before the morning dose, site staff may opt to confine subjects in the evening before fitting subjects with the APBM monitoring device. If the subject is travelling to the site for the ABPM fitting, they should delay their morning dose of study medication (between 8 AM ±2 hours) and take their study drug right after the ABPM device begins recording the measurements in the clinic. Subjects who are confined the evening prior should also take their study drug right after the ABPM recording starts. Subject will need to return to the clinic the next day to have the device removed and data downloaded.

Sites should ensure that all readings meet the minimum threshold of acceptability. If a reading does not meet this threshold the site should collect a new reading within the protocol-specified timeframe (avoiding nights immediately before [redacted] or MWT).

ABPM will be performed for 24 hours on the days specified in the Schedule of Study Procedures (Section 3.0). Subjects will be trained on the use of the device.

9.2.6.2 [redacted]

[redacted]

9.2.7 Study Drug Administration

Study drug (TAK-994 at the subject's specified dose or placebo) will be administered as described in Section 7.4.1 and the Schedule of Study Procedures (Section 3.0).

9.2.8 C-SSRS

Suicidal ideation will be assessed using the C-SSRS at the times stipulated in the Schedule of Study Procedures (Section 3.0). Two versions of the C-SSRS will be used in this study: the C-SSRS Lifetime at screening and the Since-Last-Visit C-SSRS for all other visits. Any suicidal ideation or suicidal behavior during the study periods detected by the C-SSRS will be recorded as an AE. The investigator will ensure that any suicidal ideation or behavior is medically addressed, including assessment and treatment by qualified medical personnel.

9.2.9 [redacted]

[redacted]

9.2.10 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 collection procedures is provided in Section 10.0.

9.2.11 Laboratory Procedures and Assessments

Laboratory samples will be collected in accordance with acceptable laboratory procedures. A discussion between the investigator and the sponsor or designee will take place to consider additional lab assessments or rescreening.

9.2.11.1 Safety Clinical Laboratory Tests

Samples for assessment of hematology, chemistry, and urinalysis will be taken as indicated in the Schedule of Study Procedures (Section 3.0).

9.2.11.1.1 Hematology

Hematology will consist of the following tests:

Erythrocytes (red blood cell count)	PT/INR [b], aPTT [a]
Hematocrit	Leukocytes (white blood cell count) with absolute differential
Hemoglobin	Platelets

aPTT: activated partial thromboplastin time; CSF: cerebrospinal fluid; INR: international normalized ratio; PT: prothrombin time.
[a] For subjects undergoing CSF collection only.
[b] If ALT or AST >3 times the ULN and for subjects undergoing optional CSF collection.

9.2.11.1.2 Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Chloride
Alkaline phosphatase	Creatinine
ALT	γ-glutamyltransferase
AST	Glucose
Bilirubin (total), if above ULN total bilirubin will be fractionated	FSH [a]
Blood urea nitrogen	
Calcium	Potassium
Carbon dioxide	Protein (total)
Triglycerides	Sodium
Lipid panel (HDL, LDL, total cholesterol)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; HDL: high density lipoproteins; LDL: low density lipoproteins; ULN: upper limit of normal.
[a] Optional; for postmenopausal women.

If subjects experience ALT, or AST >3 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyltransferase, and INR) should be performed within 24 to 48 hours after the abnormality is noted.

As detailed in Section 7.5, subjects with 2 consecutive ALT elevation >3x ULN should be withdrawn from the study. For subjects with ALT or AST elevated >3 × ULN at any occasion, the investigator must contact the sponsor or designee 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 10.2.8.5 for guidance on reporting abnormal LFTs.

9.2.11.1.3 Urinalysis

Urinalysis will consist of the following tests:

Blood	Nitrite
Glucose	Protein
Urine specific gravity	

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

9.2.11.2 Diagnostic Screening

Samples for serum screening, alcohol screening, urine drug screening, HLA genotyping, and pregnancy testing (if applicable) will be taken as indicated in the Schedule of Study Procedures (Section 3.0).

9.2.11.2.1 Serum

The serum diagnostic screening assessment will include the following tests:

HIV	Hepatitis screen (hepatitis B surface antigen, hepatitis C virus)

HIV: human immunodeficiency virus

9.2.11.2.2 Alcohol Screen

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

9.2.11.2.3 Urine Drug Screen

The urine drug screening assessment will include the following tests:

Amphetamines	MDMA (3,4-methylenedioxy-methamphetamine)
Barbiturates	Methadone/metabolite
Benzodiazepines	Opiates
Buprenorphine/metabolite[a]	Oxycodone/oxymorphone
Cannabinoids	Phencyclidine
Cocaine/metabolites	
Confirmatory UDS	

UDS: Confirmatory urine drug testing will be done where available for all study parts except PART A. See clinical laboratory reference document for details. Confirmatory UDS will be done at PI discretion.

[a] In some regions testing for this substance may not be available.

*9.2.11.2.4 HLA-DQB1*06:02 Genotyping*

Many patients with NT1 who experience cataplectic attacks have this HLA-DQB1*06:02 genotype (heterozygous or homozygous expression), and it has been found to correlate with low OX concentrations in the CSF. The HLA genotype will be determined only at screening.

Pre-screening for HLA is allowed per the protocol and will require a separate informed consent. Dependent upon local regulations, informed consent for HLA testing may be administered through e-consent or be administered over-the-phone for participants who may not live close to the site. In these cases, home nurses or other qualified clinical personnel may be deployed by the site to the subject's residence to collect pre-screening HLA sample (as per local regulations).

Part A

The human leukocyte antigen (HLA) genotype should test positive for HLA-DQB1*06:02 - (positive results for either homozygous or heterozygous alleles will be considered "positive" and

acceptable). However, if the HLA test is negative (i.e. negative for the heterozygous allele) and the PI feels strongly that the subject has narcolepsy with cataplexy (NT1) then a discussion should be initiated between the PI and the sponsor or designee about the advisability of doing a spinal tap to determine the subject's cerebrospinal fluid (CSF) orexin-1 (OX-1) level. If the CSF result shows the OX-1 concentration is either less than or equal to 110 pg/mL, or less than one-third of mean values obtained in normal subjects with the same standardized assay, then the diagnosis of NT1 is established allowing the subject to be enrolled and randomized. If the CSF OX-1 concentration is >110 pg/mL then the subject will not be allowed to enroll in the study.

Part B-C

All subjects will be tested for HLA-DQB1*06:02 at screening, however, HLA test results are not a study entry criteria for these subjects. CSF testing can be considered to confirm NT1 diagnosis based on results indicating hypocretin-1 (OX-1) concentration (measured by immunoreactivity) of either less than or equal to 110 pg/mL, or less than one-third of mean values obtained in normal subjects with the same standardized assay.

9.2.11.2.5 Pregnancy Testing

Women of childbearing potential will undergo urine or serum pregnancy testing on the days indicated in the Schedules of Study Procedures (Section 3.0 for details).

9.3 PK, [redacted] Measurements

Samples for PK, [redacted] analysis will be collected as specified in the Schedules of Study Procedures (Section 3.0). Please refer to the Central Laboratory Reference Document for information on the collection, processing, and shipment of samples.

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
Plasma sample for TAK-994 PK	Plasma	N/A	Plasma sample for PK TAK-994 analysis	Mandatory
Plasma sample for CYP3A4/5 activity	Plasma	N/A	Plasma sample for 4β-hydroxycholesterol/cholesterol ratio	Mandatory
CSF sample for OX assessment [b]	CSF	N/A	CSF sample for OX assessment	Optional
[redacted]				

CSF: cerebrospinal fluid; CYP: cytochrome P-450; HLA: human leukocyte antigen; N/A: not applicable; OX: orexin; PK: pharmacokinetic(s).
[a] This testing is separate from HLA genotyping (see Section 9.3.3.3).
[b] Sample collection dependent upon local guidelines and regulations (including feasibility of sample export) as well as IRB/EC approval.

9.3.1 PK Measurements

The PK parameters of TAK-994 for each treatment group or cohort will be determined from plasma concentrations on study days with serial PK sampling timepoints, as data permit (See Table 3.b, Table 3.d, Table 3.f, Table 3.h, Table 3.j, Table 3.l, Table 3.n) using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

Symbol/Term	Definition
Plasma	
AUC_{τ}	Area under the concentration-time curve during a dosing interval, where τ is the length of the dosing interval
AUC_{last}	Area under the concentration-time curve from time 0 to time of the last quantifiable concentration
$C_{av,ss}$	Average plasma concentration during a dosing interval, at steady state, calculated as AUC_{τ}/τ
C_{max}	Maximum observed concentration
$C_{max, ss}$	Maximum observed concentration during a dosing interval, at steady state
C_{trough}	Trough plasma concentration at steady state (observed concentration at the end of a dosing interval measured directly before the next study drug administration)
t_{max}	Time to reach C_{max}

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

9.3.1.1 Plasma for PK Measurements

Blood samples (one sample per scheduled time) for plasma TAK-994 concentration will be collected according to the schedules of study procedures (Section 3.0). Additional blood samples will be collected predose on the days specified in the Schedules of Study Procedures (Section 3.0) for measurement of the 4β-hydroxycholesterol/cholesterol ratio to assess CYP3A4/5 activity.

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 Central Laboratory Reference Document.

9.3.1.2 PK Sample Analysis

Plasma concentrations of TAK-994 and plasma concentrations of 4β-hydroxycholesterol/cholesterol will be measured by validated high-performance liquid chromatography with tandem mass spectrometry assays. Part of the archival plasma samples may be used for potential analysis of unknown metabolite characterization, if appropriate.

9.3.2 [redacted] Efficacy Measurements

[redacted] efficacy assessments will be performed according to the Schedule of Study Procedures as described in Section 3.0. [redacted]

9.3.2.1 [redacted]

[redacted]

9.3.2.2 ESS

The ESS is a subjective, self-administered scale that has been validated and used extensively as a key endpoint in studies in patients with narcolepsy to measure EDS. The ESS provides individuals with 8 different situations of daily life and asks them how likely they are to fall asleep in those situations (scored 0 to 3) over the past 5 to 7 days and to try to imagine their likelihood of dozing even if they have not actually been in the identical situation; the scores are summed to give an overall score of 0 to 24. Higher scores indicate stronger subjective daytime sleepiness, and scores below 10 are considered to be within the normal range.

In this study, the ESS will be administered to assess sleep propensity on selected days after TAK-994 administration. Subjects will be asked to evaluate their subjective sleepiness based on recalling their most recent daily life experiences. The change in the ESS score from baseline will be evaluated at specified times as a [redacted] secondary endpoint for Parts B and C.

9.3.2.3 [redacted]

[redacted]

[redacted]

9.3.2.4 [redacted]

[redacted]

9.3.2.5 MWT

The MWT is a validated, objective measure that is used to measure EDS in clinical studies. It has been used as a primary outcome measure for EDS. The MWT evaluates a person's ability to remain awake under soporific conditions for a defined period of time. Because there is no biological measure of wakefulness, wakefulness in this study will be measured indirectly by time to fall asleep using the MWT. In this study, four 40-minute (1 session) MWT assessments will be administered at the days and times specified in Section 3.0.

During each MWT, subjects will be instructed to sit or remain in bed with the head positioned 45 to 90 degrees relative to the legs, quietly and remain awake for as long as possible in a dimly lit room (a 7.5 W light is positioned slightly behind the subject's head so that it is just out of the subject's field of vision). Sleep latency in each session will be recorded. Subjects will be required to stay awake in between MWT assessments.

Sleep onset in the MWT is defined as the first epoch of greater than 15 seconds of cumulative sleep in a 30-second epoch. Sessions 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. Specific instructions are located in the study procedure manual.

9.3.2.6 [redacted]

[redacted]

[redacted]

9.3.2.7 ePRO Measures

Subjects with narcolepsy will complete a daily ePRO diary to record self-reported narcolepsy symptoms as indicated in the schedule of assessments, Section 3.0. In cases where the ePRO diary becomes unavailable, the site may employ alternative methods to collect these data with approval from the sponsor or designee.

Subjects in parts A, B, and C (NT1) will record partial or complete episodes of cataplexy, including the time of occurrence, severity (including body location), and other aspects, in the electronic diary. Subjects may begin recording partial and complete episodes at any time after the screening visit at the investigator's discretion. Cataplexy events recorded for 14 consecutive days, starting after a 7-day washout of anticataplexy medications and completed before Day -2, will be considered for WCR study entry criterion. The total number of events/week will be calculated based on the number of cataplexy episodes as averaged over 2 weeks (14 consecutive days) minimum. Subjects must fill out self-reported cataplexy questions in the electronic diary for at least 11 out of 14 days, to be considered compliance. The eligibility criteria pertaining to WCR must be met prior to check in on Day -2.

All subjects in Parts B, C, and D will record alcohol consumption in the ePRO diary.

[redacted]

9.3.2.8 [redacted]

[redacted]

9.3.2.9 [redacted]

[redacted]

9.3.2.10 [redacted]

[redacted]

9.3.3 Biomarker Measurements

Biomarker samples will be collected according to the Schedule of Study Procedures (Section 3.0).

9.3.3.1 [redacted]

[redacted]

9.3.3.2 CSF Orexin Measurements (FOR Subjects with NT1 only)

In addition, subjects with NT1 may separately undergo optional CSF sampling for OX assessment during screening (single time point) requiring a separate consent form. Samples will be collected by trained personnel at the clinical site per their standard operating procedure. OX levels will be measured in the CSF samples using a validated assay. Instructions for collecting, processing, and shipping of CSF samples are provided in the Central Laboratory Reference Document.

Prescreening CSF testing may be permissible and will require a signing of a separate ICF. The optional CSF sampling substudy, may not be available in every region.

Sample collection is dependent upon local laboratory guidelines and regulations (including feasibility of sample export) as well as IRB/IEC approval.

9.3.3.3 [redacted]

9.3.3.4 [redacted]

9.4 Confinement

Subjects will report to the clinical site at check-in and on the days specified in the schedules of study procedures (Section 3.0). Subjects will be discharged after completion of all study-related procedures as described in the Schedules of Study Procedures.

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

9.5 Childbearing Status and Methods of Contraception

9.5.1 Women of Childbearing Potential

9.5.1.1 Definition of Women of Childbearing Potential

A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal, unless permanently sterile.

9.5.1.2 Acceptable Methods of Contraception for Women of Childbearing Potential

Refer to Appendix D.

9.5.2 Women of Nonchildbearing Potential

9.5.2.1 Definition of Women of Nonchildbearing Potential

A female subject of nonchildbearing potential is defined as satisfying at least 1 of the following criteria:

- Postmenopausal (defined as 12 months of spontaneous amenorrhea in females aged >45 years or 6 months of spontaneous amenorrhea in females aged >45 years with serum follicle-stimulating hormone (FSH) levels >40 mIU/mL).
- Surgically sterile by hysterectomy and/or bilateral oophorectomy with appropriate documentation of surgical procedure.
- Had a tubal ligation with appropriate documentation of surgical procedure.
- Has a congenital condition resulting in no uterus.

9.5.2.2 Contraception for Women of Nonchildbearing Potential

No contraception is required for women of nonchildbearing potential.

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 pre-existing 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 retest 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) 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 than 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 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, in order to capture this important safety information consistently in the

database. AEs associated with an overdose will be documented on AE eCRF(s) 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.
   - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
	Acute liver failure
Torsade de pointes/ventricular fibrillation/ ventricular tachycardia	Anaphylactic shock
	Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizures	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/ Stevens-Johnson syndrome	Neuroleptic malignant syndrome/malignant hyperthermia
	Spontaneous abortion/stillbirth and fetal death

AE: adverse event.

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).

10.1.2 Special Interest AEs

Special interest AEs have not been defined for this study.

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 study procedure 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 or study procedure 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 that 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).
- 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 one 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; or 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; the AE is an irreversible congenital anomaly; or 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, Special Interest AEs, and abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until approximately 30 days or 5.5 half-lives, whichever is longer, 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 (eg, "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.

In addition, additional information regarding following AEs may be collected on CRF:

- Increased urinary urgency and frequency (daily urinary frequency), urinary incontinence

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:

SAEs should be reported via SAE eCRF in Rave EDC, which is the preferred method of reporting. 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.

If access to Rave EDC is not feasible within 24 hours of receiving the event, the paper SAE form should be submitted via fax. The SAE form should be completed within 24 hours of first onset or notification of the event, signed by the investigator, and transmitted via fax or email to the attention of the contact listed in Section 14.1.1. In case of fax, site personnel need to confirm successful transmission of all pages and include an email address on the fax cover sheet so that an acknowledgment of receipt can be returned via email within 1 business day.

Email submission of SAE forms (to the appropriate email address listed below) with a PDF attachment should only be used in the case where fax is not possible and access to Rave EDC is not feasible within 24 hours of receiving the event. In case of email, site personnel need to confirm successful transmission by awaiting an acknowledgment of the receipt via e mail within 1 business day.

- United States and Canada: PVSafetyAmericas@tpna.com.
- Rest of World: eupv@tgrd.com.

If SAEs are reported via fax or by email, Rave EDC must be updated as soon as possible with the appropriate information.

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

10.2.8.3.1 SAE Follow-Up

If information not available at the time of the first report becomes available at a later date, the investigator should update SAE eCRF in Rave EDC or 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 Special Interest AEs

No special interest AEs have been defined for this study.

10.2.8.5 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, and the subject should be withdrawn from the study. 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 sponsor or designee 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 9.2.11 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 (SUSARs) 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, SUSARs 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 investigational medicinal product administration or in the overall conduct of the study. The investigational site will also 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 (SAP) will be prepared and finalized before the unblinded data review for the first 9 subjects in Cohort A1 (Cohort A1a). This document will provide further details

regarding the definition of analysis variables and analysis methodology to address all study objectives.

Blinded data reviews will be conducted for each part of the study before the database lock for the specific part. This review will assess the accuracy and completeness of the database, subject evaluability, and appropriateness of the planned statistical methods for the study part of interest.

Primary analyses of endpoints will be performed on each study part separately. Additional analyses may be performed on pooled data across the study parts of the same dose level and populations as follows:

Group 1 (NT1): All NT1 subjects.

Group 2 (NT1- Japan): All NT1 subjects from sites in Japan.

Group 3 (NT1-Asia): NT1 subjects from China, Japan and other Asian countries/places.

Group 4 (NT1-HLA positive) and Group 5 (NT1-HLA negative): Baseline HLA test positive and HLA test negative NT1 subjects, respectively. Subjects may come from Parts A, B and Part C.

Group 6 (NT1- low baseline WCR): Subjects with baseline WCR≤8.

Group 7 (NT1- high baseline WCR): Subjects with baseline WCR>8.

The planned analyses for Parts A, B, C, D, and Groups 1 to 7 are described below. Details will be described in the SAP. Summaries and analyses for other groups will be described in the SAP.

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. In summaries and analysis using the Safety Set, subjects will be analyzed by the treatment to which they were received.

11.1.1.2 PK Set

The PK analysis set will consist of all subjects who received at least 1 dose of TAK-994 and have at least 1 measurable plasma concentration.

11.1.1.3 [redacted]

[redacted]

11.1.1.4 Full Analysis Set (Part B)

A full analysis set will be used for the analysis of the primary efficacy endpoint. It consists of subjects who were randomized to Part B and received at least 1 dose of double-blind study drug

after randomization. In full analysis set efficacy summaries and analysis, subjects will be analyzed by the treatment to which they were randomized.

11.1.2 Analysis of Demography and Other Baseline Characteristics

Demography and other baseline characteristics will be summarized by treatment groups and will be listed. Data from subjects receiving placebo will be pooled as appropriate for each part/study group. Descriptive statistics will be used to summarize data for continuous variables like age and weight (number of subjects [N], mean, median, SD, minimum, and maximum) and for categorical variables like sex, ethnicity, race, HLA positive/negative, and baseline WCR (≤8 vs. >8) (number and percentage of subjects within each category). Medical history and medication history will be listed by subject.

11.1.3 PK Analysis

Individual plasma concentrations of TAK-994 in subjects with NT1 or NT2 will be presented in a data listing and summarized by day, and nominal sampling time point using descriptive statistics for each treatment (arithmetic mean, SD, coefficient of variation, median, minimum, maximum, and geometric mean). Individual plasma noncompartmental analysis PK parameters obtained in NT1 and in NT2 will be tabulated and summarized descriptively by day for each treatment. As data permit, the 4β-hydroxycholesterol/cholesterol ratio, measured predose throughout the treatment period, will also be summarized descriptively for each treatment to assess CYP3A4/5 activity over time.

TAK-994 plasma concentration-time data collected in this study will be combined with other clinical study data to develop a population PK model of TAK-994 in subjects with NT1 or NT2. The objectives and details of this modeling approach will be described in a separate analysis plan, and the results of this analysis will be reported separately.

There will be no imputation of incomplete or missing PK concentration data.

11.1.4 Efficacy [redacted] Analysis

For each study part/subject group, observed MWT, ESS, WCR, and [redacted], and change from baseline (or shift tables) will be summarized by treatment and overall.

The efficacy analyses include the linear mixed effect models for repeated measures on change from baseline in the mean sleep latency from the MWT and ESS scores. In these models, baseline will be included as a covariate; treatment, day, and treatment by day interaction will be included as fixed factors. CSF orexin levels may be included as a covariate in the model. Bayesian models will also be used on the change from baseline in the sleep latency and change from baseline in the ESS score to evaluate the posterior probability of the true TAK-994 effect in delaying the sleep onset to >8, 14, and 20 minutes and reducing the ESS (>4 points and >8 points reduction). In addition, p-values and 95% CIs for pairwise comparisons between each TAK-994 dose group to placebo will be generated.

For WCR, a Poisson model will be used to evaluate the effect of TAK-994 on cataplexy. The model will include baseline WCR as a covariate, treatment, day, and treatment by day interaction will be included as fixed factors. CSF orexin levels may be included as a covariate in the model. P-values and 95% CIs for pairwise comparisons between each TAK-994 dose group to placebo will be generated.

For Part B, the full analysis set will be used for the primary efficacy analysis. P-values from the above statistical models on the primary efficacy endpoints and key secondary endpoints will be used to perform a fixed-sequence hypothesis testing procedure. The following hierarchical testing order will be applied for the primary and key secondary efficacy endpoints: sleep latency from MWT, ESS, and WCR across 3 TAK-994 treatment arms (TAK-994 high, middle, and low dose levels). The testing order in comparison with placebo will be of change from baseline to Week 8 (Day 56) in: sleep latency at the high dose, sleep latency at the middle dose, ESS at the high dose, ESS at the middle dose, WCR at the high dose, and WCR at the middle dose. If the p-value from the last comparison, WCR between the middle dose and placebo is <0.05, then the test will continue to sleep latency at the low dose, ESS at the low dose, and WCR at the low dose. The 2-sided statistical significance level for each test will be 0.05. This means, only when the p-value, rounded to 3 decimal points, for a test is below 0.05, the test will be considered statistically significant, and the testing procedure will move to the next hypothesis on the list. The testing procedure will stop at the first p-value >0.05 and all hypotheses after that step will not be tested.

The above efficacy analysis will also be performed in subgroups based on baseline WCR (<8/week vs ≥8/week), if the number of subjects in each subgroup is deemed sufficient. Other subgroup analyses will be described in the SAP.

Similar efficacy analyses will be performed for Group 1 subjects who were randomized and received at least 1 dose of study drug. Details will be included in the SAP.

[redacted]

Details will be included in the SAP. [redacted]

As data permit, the 4β-hydroxycholesterol/cholesterol ratio, measured predose throughout the treatment period, will also be summarized descriptively by treatment to assess CYP3A4/5 activity over time.

In addition to above statistical analysis, the MCP-MOD approach will be implemented for dose selection in Phase 3. Details will be described in the SAP.

The impact of missing data will be evaluated through sensitivity analyses. Details regarding missing data imputation sensitivity analyses will be specified in SAP.

11.1.5 [redacted]

[redacted]

[redacted]

11.1.6 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 performed by treatments for observed values and change from baseline if deemed appropriate. Data from subjects receiving placebo will be pooled across cohorts. Shift tables may be provided for appropriate safety assessment.

11.1.6.1 Adverse Events

All AEs will be coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be summarized by treatment group for TAK-994 overall, and overall.

11.1.6.2 Clinical Laboratory Evaluation

Safety clinical laboratory evaluation data will be summarized by treatment group, and for TAK-994 overall.

Subjects meeting markedly abnormal criteria for safety clinical laboratory assessments will be listed and summarized. The MAV criteria will be defined in the SAP.

11.1.6.3 Vital Signs and ECGs

Where appropriate, BP and safety ECG parameters will be summarized (N, mean, SD, median, minimum, and maximum) for baseline, postdose, and change from baseline (or change from time-matched baseline to postdose, if appropriate) by treatment. Linear mixed-effect models for the repeated measures will be performed to evaluate the drug effect on BP using data from inpatient and ambulatory BP monitoring. In these analyses, change from time-matched baseline will be the response and baseline, treatment, time point, and the treatment by time-point interaction will be the fixed effects.

Twenty-four-hour ABPM mean profiles will be plotted at baseline and post dose days by treatment groups. ABPM parameters will be derived from 24-hour ABPM monitoring at baseline and post dose days, such as mean 24-hour BP, day, and nighttime mean BP. Observed values and change from baseline in these parameters will be summarized by treatment groups. Change from baseline in these parameters to post dose days will be analyzed using analysis of covariance or linear mixed effect models for repeated measures, as appropriate (details will be described in the SAP). Effect of TAK-994 on these ABPM parameters will be evaluated through estimates of difference between TAK-994 treatment groups and placebo and 95% CIs.

The relationships between TAK-994 exposure and selected safety measures (such as change from baseline in systolic and diastolic BP and heart rate) will be explored graphically, as data permit. Details will be described in the SAP.

All other vital signs will be summarized for baseline (predose on Day 1), postdose, and change from baseline by treatment and time, if deemed appropriate. Subjects meeting the MAV criteria for vital signs will be summarized and listed.

11.1.6.4 Other Safety Parameters

Physical examination findings and C-SSRS data will be presented in the data listings.

[redacted]

11.2 IA

At the end of Part A Cohort A1, an IA will be performed. The purpose of this IA is to have an early look of TAK-994 efficacy and safety.

The four parts in this study are independent of each other. They are included in 1 protocol for administrative purposes. With this in mind, data cleaning and database lock will be performed for each of these 4 parts. Unblinded analyses described below may be performed thereafter.

- End-of-Part A: At the end of Part A, a final unblinded analyses will be performed to evaluate the safety and efficacy of TAK-994 for Part A only.
- End-of-Part B: Final unblinded analyses will be performed after Part B completes to evaluate the safety, [redacted], and efficacy of TAK-994 for subjects with NT1 in Part B only, [redacted].
- End-of-Part D: The final unblinded analyses for NT2 may be performed to evaluate the safety, PK, and efficacy at the end of Part D using subjects in Part D only.
- End-of-Part C: the final unblinded analysis for sites in China may be performed at the end of Part C using subjects in Part C only.

Details of these IAs will be described in the SAP.

11.3 Determination of Sample Size

PARTs A, C and D:

In Part A (Cohorts A1 and A2), Part C and Part D (Cohorts D1 and D2), the number of subjects planned are not based on statistical hypothesis testing consideration. They are considered sufficient for dose selection under a typical multiple dose rising design.

PART B:

In Part B, change from baseline in the mean sleep latency, change from baseline in the total ESS score and postdose WCR will be used to evaluate the true TAK-994 effect on delaying the sleep onset (>14 minutes prolongation over placebo), reducing ESS (>8 points reduction over placebo) and reducing WCR (>50% reduction over placebo) at a dose level.

A sample size of 21 in each group will have 98% power to detect a 14-minute difference in means of change from baseline between a TAK-994 dose group and placebo in sleep latency using a 2-sample t-test with a 5% 2-sided significance level. The power to detect an 8-point reduction in means of change from baseline between a TAK-994 dose group and placebo in the total ESS score is estimated to be approximately 95% using a 2-sample t-test with a 5% 2-sided significance level. The power to detect a 50% reduction in WCR from that of placebo group is estimated to be approximately 93% using a 2-incidence-rate ratio test using Poisson model with a 5% 2-sided significance level.

A fixed sequence of tests with MWT at high and middle doses first followed by ESS at high and middle doses and WCR at high and middle doses will be applied. The overall power for the entire testing procedure is approximately 75% (the square of the product of the power of each individual test, 98%, 95%, and 93% respectively) under the assumption that these 3 endpoints are independent at all dose levels. The overall power may be higher or lower than 75% depending on the assumed correlation structure of these 3 endpoints. There is no known reliable data to support any particular assumption on the correlation structure.

To allow for a 25% dropout rate, 28 subjects per group will be enrolled for Part B. The enrollment can be stopped once the number of evaluable 21 subjects is reached. A blinded sample size re-estimation will be performed before Part B starts. The change in the sample size of Part B after the re-evaluation, along with justification, will be documented in the clinical study report.

The SD for the change from baseline in the sleep latency is assumed to be 11 minutes. The SD for the change from baseline in the ESS score is assumed to be 7 points. The incidence rate of WCR at baseline is assumed to be 3.

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 (clinical 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 (such as the

COVID-19 pandemic), 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 FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency [PMDA] 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 Council on Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use 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". 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 Americas sites unwilling to provide names and titles of all members due to 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 IB, 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 the 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.

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 the 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, as well as 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. When applicable, study participation consent may be obtained by e-consent.

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.

The subject 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 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 at the time of consent and before the subject entering into the study. The subject 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 form (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 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 blood 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, FDA, MHRA, PMDA), 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 Study 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 Study Registration

In order to ensure that information on clinical studies 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 studies 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 the 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 study information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study 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 Study Results Disclosure

Takeda will post the results of clinical studies 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 Clinical 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

Contact Type/Role	Contact
SAE and pregnancy reporting	Pharmacovigilance United States and Canada: PVSafetyAmericas@tpna.com. Rest of World: eupv@tgrd.com.
TAKEDA Clinical Science Study Physician	Name: [redacted] MD, FAAN, FAASM Telephone/office: [redacted] Mobile: [redacted] e-mail: [redacted]
24-hour Urgent Medical Contact:	US TMA: [redacted] Toll-Free: [redacted] Cell phone: [redacted]
	EU TMA: [redacted] M: [redacted]
	China TMA: [redacted] Toll-Free: [redacted] Cell phone: [redacted]
	JAPAN TMA: [redacted] Toll-Free: [redacted] Cell phone: [redacted]
	IQVIA 24 hr Medical Emergency Contact Center US numbers: +**1 973-659-6677** or **+1 512 652 0191** Eu number: **+33186990019**

SAE: serious adverse event.

14.1.2 Investigator Agreement

I confirm that I have read and that I understand this protocol, the IB, 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 Council 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 SAEs 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
ABPM	ambulatory blood pressure monitoring
AHI	Apnea-Hypopnea Index
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUCτ	area under the concentration-time curve during a dosing interval
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
C_{max}	maximum observed concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
[redacted]	[redacted]
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P-450
ECG	electrocardiogram
eCRF	electronic case report form
EDS	excessive daytime sleepiness
ePRO	electronic patient-reported outcome
[redacted]	[redacted]
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
hERG	human ether-à-go-go-related gene
HLA	human leukocyte antigen
IA	interim analysis
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentrations
ICH	International Council on Harmonisation

ICSD-3	International Classification of Sleep Disorders, 3rd edition
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
LFT	liver function test
MATE	multidrug and toxin extrusion transporter
MAV	markedly abnormal value
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MM	medical monitor
MRD	multiple-rising dose
MSLT	multiple sleep latency test
MWT	Maintenance of Wakefulness Test
NOAEL	no-observed-adverse-effect level
[redacted]	[redacted]
NT1	narcolepsy type 1 (narcolepsy with cataplexy)
NT2	narcolepsy type 2 (narcolepsy without cataplexy)
[redacted]	[redacted]
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OX	orexin
OX-1	orexin 1
OX1R	orexin type-1 receptor
OX2R	orexin type-2 receptor
[redacted]	[redacted]
Penh	enhanced pause
Pgp	P-glycoprotein
[redacted]	[redacted]
[redacted]	[redacted]
PK	pharmacokinetic(s)
PLMS	Periodic Limb Movements of Sleep
PMDA	Pharmaceuticals and Medical Devices Agency
[redacted]	[redacted]
PROMIS	Patient-Reported Outcomes Measurement Information System
[redacted]	[redacted]
PT	prothrombin time
PTE	pretreatment event

[redacted]	[redacted]
QD	once daily
[redacted]	[redacted]
QTcF	QT interval with Fridericia's correction method
REM	rapid eye movement
RLS	restless leg syndrome
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SOREMP	sleep onset REM period
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2z}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
Tg	transgenic
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
VAS	visual analog scale
WCR	weekly cataplexy rate

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 form.

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, new information, identification of the person making the correction, date the correction was made, and 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, identification log of all participating subjects, medical records, temporary media (eg, 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 trail), 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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Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH guidelines of 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 study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-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.
10. Prepare and maintain adequate case histories of all persons entered into the study, including ePROs, 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 a 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 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 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 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 DNA 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.
    e) That the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active **must use highly effective contraception** (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 5 half-lives plus 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. 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.
27. A statement that clinical study 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, United States, 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.

The 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 the 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 study registries, databases, and websites.

The 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.

The 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

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 spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception shown in the list of highly effective contraception below.

Female Subjects and Their Male Partners

From the signing of the informed consent throughout the duration of the study, and for 5 half-lives PLUS 30 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use:

Two highly effective methods of contraception (from the list below).

In addition, they must not donate ova during this period.

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 postmenopausal 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 FSH level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a postmenopausal state in younger women (eg, those aged <45 years) 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 post-bilateral 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, the only acceptable methods of contraception are as follows:

    - Nonhormonal 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).

- Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound or concomitant medications, which may reduce the efficacy of the contraception method. Therefore, study subjects using hormonal contraception must also use an additional barrier method (male condom, female condom, or diaphragm) throughout the duration of the study, and for 5 half-lives PLUS 30 days after last dose of study drug.
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation. Contraception must be initiated at least 3 months before the first dose of study drug. If female subjects have been taking progestogen-only hormonal contraception for less than 3 months before the first dose of study drug, female subjects must also (or partners of male subjects are advised to) employ a barrier method (male condom, female condom or diaphragm) until she has been on contraceptive for 3 months. The options below are included in the category of progestogen-only hormonal contraception
    - Oral†.
    - Intravaginal† (eg, ring).
    - Transdermal†.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation. Important: Progestogen-only hormonal contraception must be initiated at least 3 months before the first dose of study drug. If female subjects have been taking progestogen-only hormonal contraception for less than 3 months before the first dose of study drug, female subjects must also (or partners of male subjects are advised to) employ a barrier method (male condom, female condom or diaphragm) until she has been on contraceptive for 3 months. The options below are included in the category of progestogen-only hormonal contraception:
    - Oral†.
    - Injectable.
    - Implantable.

2. Unacceptable methods of contraception are as follows:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.

- Declared sexual abstinence is NOT an acceptable method of contraception (unless approved by the investigator).

3. 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 not to donate ova or sperm during the course of the study.
4. During the course of the study, regular hCG pregnancy tests will be performed only for women of childbearing potential, and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and ova donation and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
5. In addition to a negative hCG pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses). Subjects must also have a negative hCG pregnancy test within 24 hours before receiving the first dose of investigational drug as close as possible and before the first dose of investigational drug, preferably on the same day.

General Guidance With Respect to the Avoidance of Pregnancy

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?
   iii. Are your menses late (even in women with irregular or infrequent menstrual cycles, a pregnancy test must be performed if the answer is "yes").
   iv. Is there a chance you (or your partner) could be pregnant? It is recommended that a pregnancy test be performed if a pregnancy is suspected.

Pregnancy/Suspected Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drugs should be immediately discontinued. In addition, any pregnancies in the 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 the right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject and/or 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 subject/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 subject received (blinded or unblinded, as applicable).

All pregnancies in subjects, including female partners of male subjects, on active study drug will be followed up to the 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 ICSD-3 Diagnostic Criteria for Narcolepsy

The criteria for NT1 (narcolepsy with cataplexy) are as follows: Criteria a) and b) must be met.

a) The subject has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

b) The presence of 1 and 2 or 3 of the following:

1. Cataplexy (as defined under essential features).
2. A mean sleep latency of ≤8 minutes and 2 or more sleep onset REM periods (SOREMPs) on a MSLT performed according to standard techniques. A SOREMP (defined as the appearance of REM sleep within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT.
3. The cerebrospinal fluid hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or <1/3 of the mean values obtained in normal subjects with the same standardized assay.

The criteria for NT2 (narcolepsy without cataplexy) are as follows: (Criteria A-E must all be met)

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.

B. A mean sleep latency of ≤8 minutes and 2 or more SOREMPs are found on a MSLT performed according to standard techniques. A SOREMP (REM sleep appearing within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace 1 of the SOREMPs on the MSLT.

C. Cataplexy is absent.

D. Either CSF orexin-1 concentration has not been measured or CSF orexin-1 concentration measured by immunoreactivity is either >110 pg/mL or >1/3 of mean values obtained in normal subjects with the same standardized assay.

E. The hypersomnolence and/or MSLT finding are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder or the effect of medication or substances or their withdrawal.

Appendix F List of Inhibitors and Inducers of CYP3A

Known moderate and strong CYP3A inhibitors or inducers and listed below:

Strong CYP3A inhibitors: clarithromycin, troleandomycin, cobicistat, conivaptan, boceprevir, danoprevir, ritonavir, elevitegravir, indinavir, saquinavir, idelalisib, itraconazole, ketoconazole, voriconazole, posaconazole, lopinavir, nefazodone, nelfinavir, paritaprevir, ombitasvir, dasabuvir, telaprevir, tipranavir.

Moderate CYP3A inhibitors: amprenavir, aprepitant, atazanavir, casopitant, cimetidine,ciprofloxacin, clotrimazole, crizatinib, cyclosporin, diltiazem, dronadarone, erythromycin, fluconazole, fosamprenavir, fluvoxamine, miconazole, imatinib, istradefylline, tofisopam, verapamil.

Strong CYP3A inducers: carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin.

Moderate CYP3A inducers: bosentan, efavivenz, etravirine, modafinil.

Appendix G Criteria for Identification of Markedly Abnormal Laboratory Values-Hematology and Serum Chemistry

Hematology—Criteria for Markedly Abnormal Values

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

LLN: lower limit of normal; RBC: red blood cell; ULN: upper limit of normal: WBC: white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

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

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; GGT: γ-glutamyl transferase; LLN: lower limit of normal; ULN: upper limit of normal.

Appendix H Criteria for Identification of Markedly Abnormal Laboratory Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<40	>115
Systolic blood pressure	mm Hg	<90	≥ 160
Diastolic blood pressure	mm Hg	<50	≥100
Systolic blood pressure change	mm Hg		>20, >30
Diastolic blood pressure change	mm Hg		>20, >30
Body temperature	^{o}C		>38.5
Respiratory Rate	Breath/min		>21

Appendix I Criteria for Identification of Markedly Abnormal Laboratory Values for ECGs

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

Appendix J Protocol History

Date	Amendment Number	Region
15 January 2021	Amendment 3	Global
05 June 2020	Amendment 02	Global
13 March 2020	Amendment 01	Global
26 November 2019	Initial version	Global

Rationale for Amendment 02:

This document describes the changes to the protocol incorporating Amendment 02.

In addition to the overview of changes provided below, in this amendment minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

The primary reason for amending this study design is that the information generated will inform the design and dose selection for the further development of TAK-994 as a potential treatment for narcolepsy with cataplexy (NT1) and narcolepsy without cataplexy (NT2) and to further the phase 3 program development. Changes have also been made also to address the Food and Drug Administration (FDA) feedback (on liver enzyme testing criteria for study inclusion and pharmacokinetics [PK]) on the prior Amendment 01.

These considerations are described below.

Since this is the first study of TAK-994 in NT1 and NT2 subjects, Parts A and D of the study have a multiple-rising dose (MRD) design to evaluate the safety, tolerability, PK, [redacted] effects of TAK-994 after repeated oral, twice daily (BID) dosing in subjects with NT1 and NT2.

Part B is a dose ranging design that characterizes the efficacy and safety of 8-week treatment of TAK-994 in 3 different dose levels or placebo, a total of 4 parallel arms. This will be performed after the MRD Part A in NT1 subjects is completed and appropriate dose levels are identified.

Another major reason for this amendment is to describe management of study procedures (eg, alternative strategies for collecting data, conducting study visits and distributing investigational product) during unexpected, unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) such as the coronavirus disease 2019 (COVID-19) pandemic.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
1. Organization address has been updated.	To document a legal change in the sponsor address.	Title page
2. Overall study description changed due to the study design. Overall number of subjects to be enrolled has increased. Schematics for different parts of the study have been updated according to the updated design. Additional schedule of assessment tables have been added for clarification purposes.	Previous cohort #3 (Amendment 01) has now been changed to a 4-arm parallel group dose ranging part (Part B) to evaluate 3 dose levels of TAK-994 versus placebo. Part B evaluates efficacy as the primary endpoint. Duration of dosing in Part B has also been increased to 56 days to support the longer duration of treatment in future Phase 3 studies. The number of subjects per arm is hence increased to allow for higher drop rate because of a longer treatment duration while maintaining the original power of the study. Doses to be evaluated in this part will be selected based on the emerging safety, tolerability [redacted] data in Part A. Because of these changes, the study phase has been changed to Phase 2. The increase in the treatment duration also necessitated inclusion of additional schematics and additions to the schedule of assessments. The study has now been divided in to 4 parts: Parts A – D to make it easier for the investigators to understand differences between parts because the study includes NT1 and NT2 subjects; dosing duration of 28 and 56 days; and a Chinese cohort.	Section 1.0: STUDY SUMMARY Section 2.0: STUDY SCHEMATICS Section 3.0: SCHEDULE OF STUDY PROCEDURES Section 6.1: Study Design Section 6.3: Rationale for Study Design, Dose, and Endpoints Section 11.0: Statistical Methods

Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
3. Inclusion criterion related to body mass index (BMI) has been revised to align with study population: Acceptable upper range of BMI for study inclusion criterion has been revised to be ≤40 kg/m2. to allow patient participation. Other editorial changes have been made for consistency and clarity.	BMI criteria was updated to in acknowledgment of the comorbidity of obesity in this patient population.	Section 1.0: STUDY SUMMARY Section 7.1: Inclusion Criteria
4. Exclusion criterion related to liver function tests (LFTs) has been revised as follows: Has LFTs (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) higher than 1.0 times the upper limit of normal (ULN) at screening. At the baseline visit, any increase in LFT by more than 50% of the screening value as well as exceeding ULN will prevent randomization. If there is sufficient time in the screening window, ALT assessment may be repeated; if the second ALT value reduces to less than the 50% increase seen at baseline, the subject may be randomized. The timeline for follow-up for abnormal LFTs was changed to "within 24 to 48 hours from "within 7 days"	Based on recent FDA feedback and sponsor decision, subjects will be excluded if the upper limit of transaminase (ALT and/or AST) values is >1.0× ULN (instead of the previous cut-off of >1.5× ULN) and the timeline for follow-up of abnormal LFTs was changed to "within 24 to 48 hours from "within 7 days".	Section 1.0: STUDY SUMMARY Section 7.2: Exclusion Criteria Section 9.2.10.1: Safety Clinical Laboratory Tests
5. Exclusion criteria for patient who is a relative or family members of a study related personnel has been revised to allow patient participation. Other editorial changes have been made for consistency and clarity.	In acknowledgement that some sites may be large research facilities or associated with academic research facilities, this exclusion language was updated to clarify that relatives of site staff or site staff directly involved with the study are to be excluded due to potential conflict of interest and also to protect vulnerable subject populations.	Section 1.0: STUDY SUMMARY Section 7.2: Exclusion Criteria

Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
6. Study objectives and endpoints have been revised to align with the revised design. Other editorial changes have been made for consistency and clarity.	These changes reflect the changes in study design.	Section 1.0: STUDY SUMMARY Section 5.1: Study Objectives Section 5.2: Study Endpoints Section 11.0: Statistical Methods
[redacted]	[redacted]	Section 1.0: STUDY SUMMARY Section 3.0: SCHEDULE OF STUDY PROCEDURES Section 5.1: Study Objectives Section 5.2: Study Endpoints Section 9.3.2.6: Cognitive Assessments
8. Additional information have been added for COVID-19 related flexibility in the study conduct, including home visit, when applicable.	In acknowledgement of outbreaks of COVID 19 or other unexpected circumstances that may disrupt the sites ability to carry out the study as planned, contingency measures for executing certain study activities have been included in this amendment.	Section 6.5.6.2: Procedure for Premature Termination or Suspension Section 9.1.1.1: Assignment of Subject Numbers Section 12.2: Protocol Deviation

Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
9. Provision of e-consent has been added.	In acknowledgement of outbreaks of COVID 19 or other unexpected circumstances that may disrupt the sites ability to carry out the study as planned, contingency measures for executing certain study activities have been included in this amendment.	Section 3.0: SCHEDULE OF STUDY PROCEDURES Section 9.1.1: Informed Consent Procedure Section 13.2: Subject Information, Informed Consent, and Subject Authorization
10. Clinical information has been updated based on emerging data from the study TAK-994-1001, including the blinded safety and preliminary PK data.	To include the most recent available clinical information.	Section 4.1.3: Clinical Study Experience
11. Nonclinical section has been updated based on recently available data including the 13-week repeat dose Good Laboratory Practice toxicity studies in rats and monkeys.	To include the most recent nonclinical information to support the longer treatment period proposed in this amendment.	Section 4.1.2: Summary of Non-clinical Data Section 4.3: Benefit/Risk Profile
12. Instructions related to excluded medications have been revised to accommodate revised study population.	Based on emerging nonclinical data on transporter substrates and inhibitor studies, the excluded medication list is being revised.	Section 7.3: Excluded Medications, Supplements, and Dietary Products
13. Instruction for allowable limit for alcohol consumption has been revised for subjects in Parts B and C.	Based on the longer treatment duration in PARTs B and C, the instruction for abstaining for alcohol during the treatment period has been removed. Instructions for moderation of alcohol intake has been provided instead.	Section 7.3.3 Alcohol
14. Text has been revised for criteria for discontinuation or withdrawal of a subject.	Some changes have been made according to FDA feedback, and also to clarify that the criteria for each part of the study. Instructions has been added to address how study discontinuation related or unrelated to COVID-19 should be handled.	Section 7.5: Criteria for Discontinuation or Withdrawal of a Subject

Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Description of Each Change and Rationale		**Section(s) Affected by Change**
Description	***Rationale***	***Location(s)***
15. Text has been revised for study drug supply, randomization, blinding and storage.	Instructions have been added to address how drug supply should be accessible to the patients to cover extended periods between on-site visits due to COVID-19 or other unavoidable circumstances.	Section 8.1: Clinical Study Drug
16. Alternative approaches for study procedure and data collection guidelines have been included	Instructions have been added to address how, in unavoidable circumstances (eg, a widespread disease outbreak or natural disaster) that impact the study site's ability to conduct study procedures according to the Schedule of Study Procedures (Section 3.0), contingency measures may be implemented.	Section 9.9: STUDY PROCEDURES
17. Physical examination	Clarification regarding full versus abbreviated physical examinations have been added.	Section 9.2.1: Physical Examination Section 3.0: SCHEDULE OF STUDY PROCEDURES Tables 3a-3n
18. Changes in the safety section	Based on the emerging clinical data from study TAK-994-1001, additional data regarding urinary AEs being collected in the electronic case report form.	Section 10.2.8: Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs
19. Changes in Appendix D- Contraception	Guideline for male contraception has been changed based on regulatory feedback.	Appendix D: Pregnancy and Contraception
20. New Appendix F has been added	New appendix F has been added to list of inhibitors and inducers of cytochrome p-450(CYP)3A and P- glycoprotein.	Section 7.3: Excluded Medications, Supplements, and Dietary Products Appendix F: List of Inhibitors and Inducers of CYP3A and PgP
21. Editorial changes	For better flow and clarification	Throughout the protocol.

Rationale for Amendment 01

This document describes the changes to the protocol incorporating Amendment 01.

In addition to the overview of changes provided below, in this amendment minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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

Changes in Amendment

The following is a summary of changes made in the amendment:

1. The title of the study was updated to include both subjects with narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2).
2. The EudraCT number and study phase were added to the protocol title page.
3. The number of participating sites was updated.
4. The baseline period was added to the study duration overview.
5. Separate study schematics, outlining key study assessments, were added for Cohorts 4 and Cohorts 5 and 6.
6. Separate schedules of study procedures, outlining all study assessments, were added for Cohorts 4 and Cohorts 5 and 6.
7. It was clarified in the schedule of study procedures (screening through Day 15) that Day 1 included both planned predose and postdose assessments.
8. [redacted]
9. It was clarified in the schedule of study procedures that serum fluoride testing was not only planned at baseline and Day 28 but at all planned clinical laboratory assessments.
10. It was clarified in the schedule of study procedures that human chorionic gonadotropin (hCG) testing will be performed on Day -1 rather than Day -2.
11. It was clarified in the footnotes of the schedule of study procedures that additional details on urinalysis are available in the Central Laboratory Reference Document instead of the training manual.
12. It was clarified in the footnotes of the schedule of study procedures that the additional blood samples for cytochrome P-450 (CYP) 3A4 were taken predose.
13. The plasma sample for pharmacokinetics (PK) as well as blood pressure (BP) and pulse rate measurements 14 hours postdose on Day 14 were removed.
14. A collection window of 10 minutes was added for the 5-hour PK sampling/assessments on Days 1, 14, and 28.

15. It was clarified in the schedule of study procedures that the electrocardiogram (ECG) taken on Day 29 was not predose.
16. The information on disease background was updated.
17. The statement saying the information on the 4-week repeat-dose toxicity study was not yet included in the investigator's brochure (IB) was deleted.
18. Data from ongoing Study TAK-994-1001 were updated.
19. "other exploratory objectives" were removed.
20. Three additional cohorts were included, 1 consisting of 12 to 18 Chinese subjects with NT1 (Cohort 4) and 2, each consisting of 18 subjects with NT2 (Cohorts 5 and 6).
21. Dose selection rules were clarified.
22. The type of confinement facility that will be used was clarified.
23. In the inclusion criteria, it was specified that screening labs may be repeated once.
24. In the inclusion criteria, glutamate dehydrogenase (GLDH) was removed as a selection criterion. In the same criterion, a note was added to clarify that rescreening for labs may be repeated once.
25. In the inclusion criteria and Appendix E, the diagnosis for subject selection was updated and the acceptability criteria clarified.
26. In the inclusion criteria, it was clarified that subjects' Epworth Sleepiness Scale (ESS) score should be ≥10 at Day -1.
27. In the inclusion criteria, it was clarified that in order to be eligible for study participation, subjects need to have a human leukocyte antigen (HLA) DQB1*06:02 genotype (Cohorts 1-4).
28. In the inclusion criteria, the separate weight criterion was removed.
29. In the inclusion criteria, it was clarified that the subject must have ≥4 partial or complete episodes of cataplexy/week by history when off of anticataplexy medications and ≥4 partial or complete episodes of cataplexy/week during the screening period when off of anticataplexy medications, averaged over 2 weeks minimum, with a ≥80% compliance rate in completion of the self-reported electronic diary for cataplexy episodes (Cohorts 1-4).
30. In the exclusion criteria, it was clarified that subjects with basal cell skin cancer were eligible for study participation.
31. In the exclusion criteria, it was clarified that in order to be eligible for study participation, subjects could have had 1 single febrile seizure in childhood.
32. In the exclusion criteria, the criterion related to medical disorders in general was clarified.
33. In the exclusion criteria, the period subjects need to abstain from driving and operating dangerous or hazardous machinery was clarified.

34. In the exclusion criteria, the usual bedtime for subjects was changed from 0100 to no later than 2400 (12:00 AM, midnight).
35. In the exclusion criteria, it was clarified that for subjects undergoing optional cerebrospinal fluid (CSF) collection (Cohorts 1-3 and 5-6) that subjects could not have a known hypersensitivity to anesthesia as well as local anesthetics.
36. In the exclusion criteria, redundant criteria were removed.
37. In the exclusion criteria, it was clarified that for subjects undergoing optional CSF collection (Cohorts 1-3 and 5-6), signs of lumbar rather than spinal radiculopathy are exclusionary.
38. In the exclusion criteria, it was clarified that for subjects undergoing optional CSF collection (Cohorts 1-3 and 5-6), the use of aspirin (low dose [81 mg]; 1 tablet per day) was not exclusionary.
39. The instructions on prior and concomitant medication use (including discontinuing sodium oxybate at least 4 weeks prior to baseline) were updated.
40. The instructions related to caffeine use were updated.
41. The BP and heart rate limits leading to discontinuation of subjects were updated.
42. The attempts to contact the subject in case he/she is lost to follow-up were clarified.
43. The procedures around study drug blinding were corrected.
44. The procedures around randomization code creation and storage were corrected.
45. [redacted]
46. The instructions related to HLA genotyping performed before the study were updated.
47. The number of blood samples for measurement of the 4β-hydroxycholesterol/cholesterol ratio to assess CYP3A4/5 activity was corrected.
48. Instructions given to subjects related to the ESS were clarified.
49. A strong recommendation for the same clinician to administer the [redacted] at every visit was added.
50. Instructions of body position and lighting during the Maintenance of Wakefulness Test (MWT) were added.
51. [redacted]
52. It was clarified that biomarker measurements, [redacted] CSF orexin measurements, [redacted] are not planned in Cohort 4 (China-specific).
53. It was clarified that a separate informed consent form was needed for the optional CSF measurement.

54. It was added to the protocol that for adverse events (AEs), the causality to the study procedure should be determined.
55. [redacted]
56. The procedure on collecting and reporting of serious adverse events (SAEs) was clarified.
57. The analysis methods for Cohorts 1 to 6 were updated.
58. The description of the planned interim analyses was updated.
59. The determination of sample size was updated enumerating the range of subjects and randomization ratio (study drug: placebo) in Cohorts 4 (China-specific), 5, and 6.
60. The instructions related to pregnancy and contraception were updated.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Pharmacology Approval	19-Jan-2021 03:46 UTC
[redacted]	Clinical Science Approval	19-Jan-2021 14:36 UTC
[redacted]	Biostatistics Approval	19-Jan-2021 16:11 UTC