

The Effects of an Orexin Receptor 2-Selective Agonist on Cognition in Adults With Narcolepsy Type 1

A Secondary Analysis of a Phase 2 Randomized Clinical Trial

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This supplement contains the following items:

1. Original protocol, which was unchanged and only one version exists.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

TAKEDA PHARMACEUTICALS
PROTOCOL

A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1)

A Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421 USA		
Study Number:	TAK-861-2001		
Study Phase:	2		
IND Number:	154232	EudraCT/CTIS Number:	2022-001654-38
ClinicalTrials.gov:	Posting planned prior to study start	WHO Universal Trial Number:	U1111-1277-4261
Investigational Product:	TAK-861		
Date:	17 Aug 2022	Version/Amendment Number:	Initial version

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APPROVALS

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- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP).
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES OF THE RESPONSIBLE TAKEDA MEDICAL OFFICER AND OTHER SIGNATORY(IES)

Electronic signatures of the following individuals are provided on the last page of this document.

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED] Clinical Science	[REDACTED] Statistics and Quantitative Sciences

INVESTIGATOR AGREEMENT

I confirm that I have read and understand this protocol, the investigator's brochure (IB), prescribing information, 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, life, dignity, integrity, confidentiality of personal information, safety, privacy, and well-being of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH GCP.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events (SAEs) as defined in this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator as described in this protocol.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a potential participant to obtain their informed consent to participate.

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I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Name and Location of Facility (City, State/Province)

Location of Facility (Country)

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ADMINISTRATIVE INFORMATION

CONTACTS

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in relevant guidelines provided to the site.

Takeda Development Center Americas, Inc.–sponsored investigators will be provided with emergency medical contact information cards to be provided to each study participant and carried by each participant per individual country requirements.

ADDITIONAL INFORMATION

A separate contact information list will be provided to each site.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: +1 224-554-1052 Email: PVSafetyAmericas@tpna.com
24-hour urgent medical contact	North America: +1 888 483 7729 Europe, Middle East and Africa/Asia Pacific: +44 122 337 4240

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1. Protocol Summary

1.1 Synopsis

Name of Sponsor(s): Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington MA 02421 USA		Compound: TAK-861	
Study Number: TAK-861-2001	Phase: 2	IND No.: 154232	EudraCT No.: 2022-001654-38
Title of Protocol: A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1)			
Short Title: A Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 in the Treatment for Narcolepsy With Cataplexy			
Number of participants: A total of approximately 100 participants (20 per arm)			
Investigator(s): Multicenter global study			
Site(s) and Region(s): Up to approximately 70 sites across North America, Europe, and Asia Pacific			
Study Period (planned): Q1 2023 to Q2 2024			
Objectives and Endpoints			
Objectives		Endpoints	
Primary			
<ul style="list-style-type: none"> To assess the effect of TAK-861 on excessive daytime sleepiness (EDS) as measured by sleep latency from the Maintenance of Wakefulness Test (MWT). 		<ul style="list-style-type: none"> Change from baseline to Week 8 in mean sleep latency from the MWT 	
Secondary			
<ul style="list-style-type: none"> To assess the effect of TAK-861 on EDS as measured by the Epworth Sleepiness Scale (ESS) total score. To assess the effect of TAK-861 on cataplexy as assessed by the weekly cataplexy rate (WCR). To evaluate the safety and tolerability of TAK-861. 		<ul style="list-style-type: none"> Change from baseline to Week 8 in ESS total score WCR at Week 8 Occurrence of at least 1 treatment-emergent adverse event (TEAE). 	

	<ul style="list-style-type: none"> • Additional/Exploratory 	
	<ul style="list-style-type: none"> • To evaluate the safety and tolerability of TAK-861. • To assess the effect of discontinuation of TAK-861, as assessed by ESS, WCR, and patient-reported sleep parameters. • To assess the effect of TAK-861 on sustained attention as measured by the psychomotor vigilance test (PVT). • To assess the effect of TAK-861 on overall narcolepsy symptoms measured by the Clinical Global Impression Scale – Global Improvement Scale (CGI-I) and the Patient Global Impression of Improvement (PGI-I) scale. • To assess the effect of TAK-861 on severity of narcolepsy symptoms measured by Narcolepsy Severity Scale for Clinical Trials (NSS-CT). • To assess the effect of TAK-861 on mobility, self-care, usual activities, pain/discomfort and anxiety/depression as assessed by the EuroQol-5 Dimensions 5-Levels (EQ-5D-5L) scale. • To assess the effect of TAK-861 on quality of life of participants, as assessed by the Short Form-36 Survey (SF-36). • To assess the efficacy of TAK-861 on functional impacts of narcolepsy as assessed by the Functional Impacts of Narcolepsy (FIN) scale. 	<ul style="list-style-type: none"> • Occurrence of at least 1 markedly abnormal value (MAV) for postdose laboratory values. • Occurrence of at least 1 MAV for postdose vital signs. • Occurrence of at least 1 MAV for postdose electrocardiogram (ECG) parameters. • Time-matched change in blood pressure (BP) and heart rate (HR) from baseline to specified postdose time points. • Change in ambulatory BP and HR parameters from baseline. • Number (and percent) of participants with at least 1 endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). • Change from baseline in ESS total score, WCR, and sleep parameters reported in the patient-reported sleep electronic diary (e-diary) at the follow-up visit 1 week after drug discontinuation. • Change from baseline in number of lapses on PVT. • PGI-I and CGI-I scores. • Change from baseline in NSS-CT. • Change from baseline in EQ-5D-5L index score. • Change from baseline in quality of life as measured by SF-36 domain scores. • Change from baseline in the FIN domain scores.

	<ul style="list-style-type: none"> To assess the effect of TAK-861 on quality of nocturnal sleep and presence or absence of rapid eye movement sleep-related abnormalities, including hypnagogic/hypnopompic hallucination, sleep paralysis, and nocturnal awakenings from the daily e-diary. To assess the effects of TAK-861 on memory, working memory, and processing speed as measured by the cognitive tests (Continuous Paired Associate Learning [CPAL] test, One Back test [ONB], and international Digit Symbol Substitution Test-symbols [iDSST-s]). To assess the treatment satisfaction with TAK-861 as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM). To assess the effect of TAK-861 on sleep architecture as measured by nocturnal polysomnography (nPSG). To assess the effect of TAK-861 on daily/nighttime activity as measured by actigraphy (accelerometry) and HR (photoplethysmography). To assess steady-state exposures of TAK-861. To assess the pharmacokinetic (PK)/pharmacodynamic (PD) relationship(s) of TAK-861 for selected efficacy or safety measures. 	<ul style="list-style-type: none"> Change from baseline in frequency of refreshing nocturnal sleeps, sleep paralysis, hypnagogic/hypnopompic hallucinations, and nocturnal awakenings reported in the daily e-diary. Change from baseline in CPAL, ONB, and iDSST-s measurements. Treatment satisfaction as measured by the 4 dimensions of the TSQM. Change from baseline in various nPSG measures, including nocturnal awakenings. Change from baseline in daily/nighttime activity metrics derived from continuous actigraphy (accelerometry) and HR (photoplethysmography) from a wrist-worn device. TAK-861 plasma concentrations and selected noncompartmental analysis PK parameters (maximum observed concentration [C_{max}], time of first occurrence of C_{max}, and area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration). 	
<p>Rationale:</p> <p>This study is designed to evaluate the efficacy, safety, and tolerability of multiple oral doses of TAK-861 in participants with narcolepsy type 1 (NT1).</p> <p>Narcolepsy with cataplexy, or NT1, has been defined by International Classification of Sleep Disorders, 3rd Edition (ICSD-3) criteria as having low levels of orexin (OX) in the cerebrospinal fluid (CSF) (≤ 110 pg/mL, or less than one-third of normal levels), resulting from the nearly complete loss of OX-producing neurons. An orexin type-2 receptor (OX2R) agonist is thus the first approach to directly address the loss of OX peptide in the brain in as it may restore OX2R signaling at the postsynaptic receptors and may be more effective than current therapies in treating the entire NT1 pentad, especially EDS and cataplexy. Nonclinical pharmacology studies showed wake-promoting effects and improvement of cataplexy-like syndrome with TAK-861 in a murine narcolepsy model. In human studies, administration of an orexin agonist has been well-tolerated and was associated with marked improvements in sleep latency in patients with NT1. The available nonclinical information and emerging clinical safety, tolerability, and PK profiles of single and multiple doses of TAK-861 in healthy participants in the TAK-861-1001 study support this study, which is designed to evaluate the safety, tolerability, PK, and PD of multiple oral doses of TAK-861 in participants with NT1.</p>			

Study Intervention, Dose, and Mode of Administration:

The following treatments will be administered orally:

- TAK-861 Dose Regimen 1: 0.5 mg twice daily approximately 3 hours apart
- TAK-861 Dose Regimen 2: 2 mg twice daily approximately 3 hours apart
- TAK-861 Dose Regimen 3: 2 mg followed by 5 mg approximately 3 hours apart
- TAK-861 Dose Regimen 4: 7 mg once daily (QD)
- Matching placebo

Dose regimens include QD or twice daily dosing (2 doses approximately 3 hours apart). Study treatment will be administered at approximately 8 am and 11 am. (Participants assigned to a QD dose regimen will receive placebo for the second dose. Participants assigned to placebo will receive placebo for both doses.) Study treatment will be administered for 8 or 12 weeks.

Overall Design and Methodology:

This is a randomized, double-blind, placebo-controlled, multicenter, 8-week parallel group study to evaluate the efficacy, safety, and tolerability of 4 oral dose regimens of TAK-861.

Approximately 100 (male and female) participants with NT1, who satisfy the inclusion and exclusion criteria, will be randomized such that each participant has an equal chance of being assigned to any 1 of 5 arms: 3 TAK-861 twice daily dose regimens, 1 TAK-861 QD dose regimen, or matching placebo. An interim analysis may occur after at least 40 participants have completed the Week 4 visit. If one or more active treatment arms are discontinued after the interim analysis, participants will be randomized with equal probability to the remaining arms. Randomization will be stratified by region. Starting on the morning of Day 1, the study drug will be administered at approximately the same time each day for 8 or 12 weeks. (If the participant wishes to enroll in the long-term extension (LTE) study but the LTE study has not started at the participant's site when the participant completes the Week 8 visit of the current study, the participant will be allowed to continue in the current study for an additional 4 weeks; see below.) Participants who have provided informed consent will complete a screening period of up to 50 days (see protocol body, Section 6.8.1 for different washout periods) to washout any NT1 medication (if applicable). Participants will be asked to complete an e-diary, starting from the initial screening visit, no later than Day -16. To be eligible for the study, participants must fill out self-reported cataplexy questions in the e-diary for at least 11 days of the 14-day period from Day -16 to Day -3 and have ≥ 4 partial and/or complete episodes of cataplexy/week (averaged over Days -16 to -3).

Participants will remain confined overnight at the study site during the following times:

- Days -2 to 1 (1 mandatory overnight at Day -2; 1 optional overnight at Day -1).
- Days 27 to 28 (1 overnight).
- Days 55 to 56 (1 overnight).

After the Week 8 visit, participants will have the option to participate in an LTE study under a separate protocol (assuming protocol is open for enrollment). Participants who enroll in the LTE study will not have follow-up visits in this study.

If a participant plans to enroll in the LTE study but the LTE study is not open for enrollment at the participant's site when the participant completes the Week 8 visit, the participant will be allowed to continue in the current study for an additional 4 weeks of treatment (continuing the same treatment regimen as the previous 8 weeks). This is to avoid a treatment gap for participants willing to roll over from this study to the LTE study.

For participants who do not participate in the LTE study (including any participant who completes the Week 12 visit and for any reason does not enroll in the LTE), every effort should be deployed to have them complete a first follow-up visit approximately 7 days after the final study drug intake and a second follow-up visit (home healthcare visit) approximately 28 days after the final study drug intake. For participants who early terminate the study, every effort should be deployed to have them complete an early termination visit as soon as possible and a follow-up visit (in-clinic visit or home healthcare visit if available) approximately 28 days after the last dose of study drug. Participants not participating in the LTE study can restart their non-exclusionary medications after the first follow-up visit or early termination visit.

Inclusion and Exclusion Criteria:

Note that the site's principal investigator (PI) may determine if there is a need to repeat any screening assessments to ensure participant suitability.

Inclusion Criteria

Informed Consent

1. The participant is willing and able to understand and fully comply with study procedures and requirements (including digital tools and applications), in the opinion of the investigator.
2. The participant has provided informed consent (that is, in writing, documented via a signed and dated informed consent form [ICF] and/or electronic consent) and any required privacy authorization before the initiation of any study procedures.

Age and Body Mass Index

3. The participant is aged 18 to 70 years, inclusive, at the time of signing the ICF.
Note: In Japan, participants aged 16 to 70 years, inclusive, may be included.
4. The participant has body mass index within the range 18 to 40 kg/m² (inclusive)

Type of Participant and Disease Characteristics

5. The participant has an ICSD-3 diagnosis of NT1 by polysomnography (PSG)/Multiple Sleep Latency Test (MSLT), performed within the past 10 years and meeting the minimal acceptable criteria for the proper performance of PSG/MSLT as outlined in the ICSD-3.
Note: If there is a potential participant with NT1 for whom a diagnostic nPSG/MSLT was performed more than 10 years ago or is not available, the site may repeat the diagnostic PSG/MSLT before Day -2.
Note: For participants with results from a CSF test indicating an OX/hypocretin-1 concentration of ≤ 110 pg/mL (or less than one-third of the mean values obtained in normal participants within the same standardized assay), the PSG/MSLT requirement may be waived after a discussion with the sponsor or designee.
6. The participant has an ESS score >12 on Day -1.
7. The participant has ≥ 4 partial and/or complete episodes of cataplexy/week (WCR), calculated as the weekly average over 14 days (Days -16 to -3 of the screening period). Before the start of WCR recording, participants must complete washout of anticataplexy medications (see protocol body, Section 6.8.1 for washout requirements for specific medications). Participants must complete self-reported cataplexy questions in the e-diary for at least 11 of 14 days during Days -16 to -3, to be considered compliant. In cases where the e-diary becomes unavailable, the study site may use alternative methods to collect these data with approval from the sponsor or designee.
8. The participant is positive for the HLA genotype HLA-DQB1*06:02 (positive results for either homozygous or heterozygous alleles will be considered "positive" and acceptable) or results from CSF testing indicate the participant's CSF OX/hypocretin-1 concentration is <110 pg/mL (or less than one-third of the mean values obtained in normal participants within the same standardized assay).
Note: Previous HLA results are acceptable if available for review by the PI and provided for inclusion in the electronic case report form.
9. The participant is judged by the investigator to be sufficiently healthy to participate in the study, on the basis of 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.

Note: Screening laboratory assessments may be repeated; the sponsor or designee should be informed.

Contraception

10. The participant agrees to follow the birth control requirements (see protocol body, Section 10.4).

Exclusion Criteria

Medical Conditions

1. The participant has a current medical disorder, other than narcolepsy with cataplexy, associated with EDS.
 - a) This includes restless legs syndrome/periodic limb movement disorder that has a significant impact on daytime sleepiness.
 - b) Participants with clinically significant moderate-to-severe obstructive sleep apnea may be eligible if they are compliant with continuous positive airway pressure (CPAP), defined as having at least 4 hours of CPAP use per night on at least 70% of nights for approximately 1 month before randomization (assessed by machine tracking time) and have apnea hypopnea index (AHI) ≤ 10 with CPAP or other modes of positive airway pressure.
 - c) For all participants, past PSG data demonstrating any of the following is exclusionary: AHI ≥ 15 , apnea index ≥ 10 , or periodic leg movement arousal index of ≥ 15 /hour, unless a more recent PSG and/or clinical evaluation by the investigator indicates a meaningful change in clinical status. All attempts should be made to confirm eligibility based on Day -2 nPSG data.
2. The participant has a current medical condition such as unstable cardiovascular, pulmonary, renal, or gastrointestinal disease, that would preclude enrollment in the view of the investigator.
3. The participant has medically significant hepatic or thyroid disease.
4. The participant 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 participant.
5. The participant has a history of cancer in the past 5 years (does not apply to participants with carcinoma in situ that has been resolved without further treatment or basal cell cancer; these participants may be included after approval by the sponsor or designee).
6. The participant has clinically significant coronary artery disease, a history of myocardial infarction, clinically significant angina, clinically significant cardiac rhythm abnormality, or heart failure.
7. The participant has a clinically significant history of head injury or head trauma.
8. The participant has a history of epilepsy, seizure, or convulsion, or has a family history of inherited disorders associated with seizure (except for a single febrile seizure in childhood).
9. The participant has one or more of the following psychiatric disorders:
 - a) Any current unstable psychiatric disorder.
 - b) Current or history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including schizoaffective disorder, major depression with psychotic features, bipolar depression with psychotic features, obsessive compulsive disorder, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).
 - c) Current diagnosis or history of substance use disorder as defined in the DSM-5.

Note: If the history of substance use disorder is more than 12 months before baseline, the participant may be allowed to enroll in the study after consultation with the sponsor or designee. (Participant must also have negative urine drug screen at the screening and Day -2 visits.)
 - d) Current active major depressive episode (MDE) or who have had an active MDE in the past 6 months.

Note: Neurodevelopmental disorders (eg, attention deficit hyperactivity disease) are not excluded unless severity does not allow termination of prohibited medications (see protocol body, Section 6.8.1 for list of restricted medications).
10. The participant has a history of cerebral ischemia, transient ischemic attack (< 5 years ago), intracranial

aneurysm, or arteriovenous malformation.

11. The participant has a current history of significant multiple or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
12. The participant has a known hypersensitivity to any component of the formulation of TAK-861 or related compounds.
13. The participant had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.

Prior/Concomitant Therapy

14. The participant is unable to refrain from or anticipates using excluded food products (see protocol body, Section 5.3), beginning by Day -7 and continuing until the first follow-up visit, or prohibited medication (as described in protocol body, Section 6.8.1).
15. The participant has participated in another investigational drug study, in which they received the investigational drug, within 60 days (or 6 months if participant may have received an investigational biologic product). The interval window from the previous study will be derived from the date of the last study procedure in the previous study to the screening visit of the current study.
Note: This does not apply to approved drugs, for which rules are laid out in protocol body, Section 6.8.1.
16. The participant has any prior exposure to an oral Takeda OX agonist other than TAK-861.

Diagnostic Assessments

17. The participant has a BP >140 mm Hg (systolic) or >90 mm Hg (diastolic) during screening. BP measures should be obtained after the participant has been resting for a minimum of 5 minutes. If the BP is slightly elevated above these parameters, measurement may be repeated 3 times, and the median of the 3 recordings used.
Note: Participants with a history of hypertension are not excluded if the BP does not meet the above criteria.
18. The participant has a resting HR <40 or >100 beats per minute during screening, confirmed on repeat testing within a maximum of 30 minutes.
19. The participant's screening ECG reveals a QT interval with Fridericia correction method >450 milliseconds (genetically male) or >470 milliseconds (genetically female).
20. The participant has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or HIV antibody/antigen at screening.
21. The participant's renal creatinine clearance (Cockcroft-Gault Equation) is ≤ 50 mL/min at screening.
22. The participant has alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values >1.5 times the upper limit of normal (ULN) at screening or Day -2 (if results available); or the participant has ALT or AST between 1.0 and 1.5 \times ULN at screening with $\geq 15\%$ increase from screening to Day -2.
23. The participant has a positive pregnancy test at screening or Day -2 or is lactating/breastfeeding.
24. The participant has a positive urine screen for drugs of abuse and/or positive alcohol test at screening or Day -2. An exception at screening is made for stimulants or other drugs the participant has been prescribed, but the drug screen must be negative on Day -2. Products containing cannabidiol are allowed throughout the study, at the discretion of the investigator.
Note: Participants testing positive for marijuana at screening may be eligible for participation in the study provided that the investigator's clinical assessment indicates the participant is not a regular user of marijuana, and after discussion with and approval from the sponsor or designee. Under this circumstance, a local urine dipstick drug screen must be performed at the baseline visit and verified to be negative before conducting any other study procedures at this visit.
25. The participant is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the participant has attempted suicide within the past year before screening, or has positive answers on item number 4 or 5 on the C-SSRS (based on the past year) before randomization.

Other Exclusion Criteria

26. The participant is a study site employee or an immediate family member of or in a dependent relationship with a study site employee (eg, spouse, parent, child, sibling) who is involved in the conduct of this study, or may consent under duress.
27. The participant consumes excessive amounts of caffeine, defined as greater than 600 mg per day. (1 cup of coffee is approximately 120 mg.)
28. The participant currently consumes alcohol exceeding 2 standard drinks per day on average (1 standard drink is approximately equivalent to the following: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz] per day).
29. The participant has a nicotine dependence that is likely to have an effect on sleep (eg, a participant who routinely awakens at night to smoke) or an unwillingness to refrain from smoking and nicotine use during the confinement portions of the study.
30. The participant is unwilling to refrain from driving during times of heightened sleepiness or fatigue as well as during times of medication weaning/changes or is unwilling to adhere to local regulations and any PI guidance restricting driving.
31. The participant has a usual bedtime later than 12:00 AM (midnight), an occupation requiring nighttime shift work or variable shift work within the past 6 months, travel with significant jet lag within 14 days before Day -2, or plans for travel with significant jet lag during the study.
32. The participant, in the opinion of the investigator or subinvestigator is unlikely to comply with the protocol or is unsuitable for any other reason.

Participants meeting any of the following criteria will not be eligible for optional CSF collection:

33. The participant has undergone CSF collection within 30 days before the planned optional CSF collection day.
34. The participant 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 participant has significant vertebral deformities (scoliosis or kyphosis) that, in the opinion of the investigator, may interfere with the lumbar puncture procedure.
36. The participant has a history of major back (lumbar) surgery, clinically significant back pain, and/or injury, in the opinion of the investigator.
37. The participant has a local infection at the puncture site.
38. The participant has developed signs of lumbar radiculopathy, including lower extremity pain and paresthesia.
39. The participant has any known focal neurological deficit that might suggest an increase in intracranial pressure.
40. The participant has any abnormal findings on ophthalmological/funduscopy assessment indicative of raised intracranial pressure (ie, optic disc swelling/edema or [uncontrolled] hypertension retinopathy).
41. The participant has a bleeding abnormality or history of bleeding abnormalities. The participant has thrombocytopenia or other suspected bleeding tendencies noted.
42. The participant is taking an anticoagulant (1 tablet/day of low dose aspirin [81 mg] is allowed) or has abnormal coagulation test results (prothrombin time/international normalized ratio, activated partial thromboplastin time) from a sample taken during the screening period. Results must be received and reviewed by the investigator in advance of the CSF sample collection.

Maximum Duration of Participation in the Study:

The total duration of study participation for each participant includes:

- Planned duration of screening period: up to 50 days
- Planned duration of treatment period: 8 or 12 weeks
- Planned duration of follow-up period: 0 or 4 weeks (0 if immediately enrolling in LTE study)

Statistical Analysis:

Safety:

TEAEs will be summarized by treatment group. Observed values and change from baseline in safety clinical laboratory measurements, vital signs, and ECG parameters will be summarized by treatment group. The number and percent of participants meeting the MAV criteria for safety laboratory tests, vital signs, and ECGs will be summarized by treatment group.

Efficacy:

The change from baseline in mean sleep latency will be analyzed using a linear mixed model for repeated measures (MMRM), with visit, treatment, and treatment-by-visit interaction, as the fixed effects. Baseline age and mean sleep latency will be used as covariates. The estimated change from baseline in the mean sleep latency for each treatment and the associated SE and 95% CIs will be extracted from the model, along with all estimated treatment differences from placebo and associated SEs, 95% CIs, and p-values.

The change from baseline in ESS total score will also be evaluated using a linear MMRM with the baseline value as a covariate.

The WCR will be analyzed by generalized estimating equations using a log-link featuring a Poisson distribution. The model will include fixed effects for visit, treatment, and treatment-by-visit interaction. The baseline WCR will be included as a covariate. The estimated incidence rate of weekly cataplexy for each treatment and the associated SE and 95% CIs will be extracted from the model, along with the incidence rate ratio of weekly cataplexy (TAK-861/placebo) for all TAK-861 treatment groups, and the associated SEs, 95% CIs, and p-values.

An interim analysis may occur after at least 40 participants have completed the Week 4 visit. In this case, an Internal Review Committee, composed of members who do not have study-related contact with sites, will review the study data and determine if any active treatment arms or the study will be discontinued.

Sample Size Justification:

Assuming an SD of 11 minutes, a sample size of 16 participants per treatment group completing 8 weeks is enough to achieve >90% power to detect a difference of 14 minutes between a TAK-861 dose and placebo by a 2-sample t-test on the change from baseline to Week 8 in mean sleep latency from 4 MWT sessions at 0.05 2-sided significance level. Assuming a 20% dropout rate, 20 participants per treatment group may be enrolled for a total of up to 100 participants.

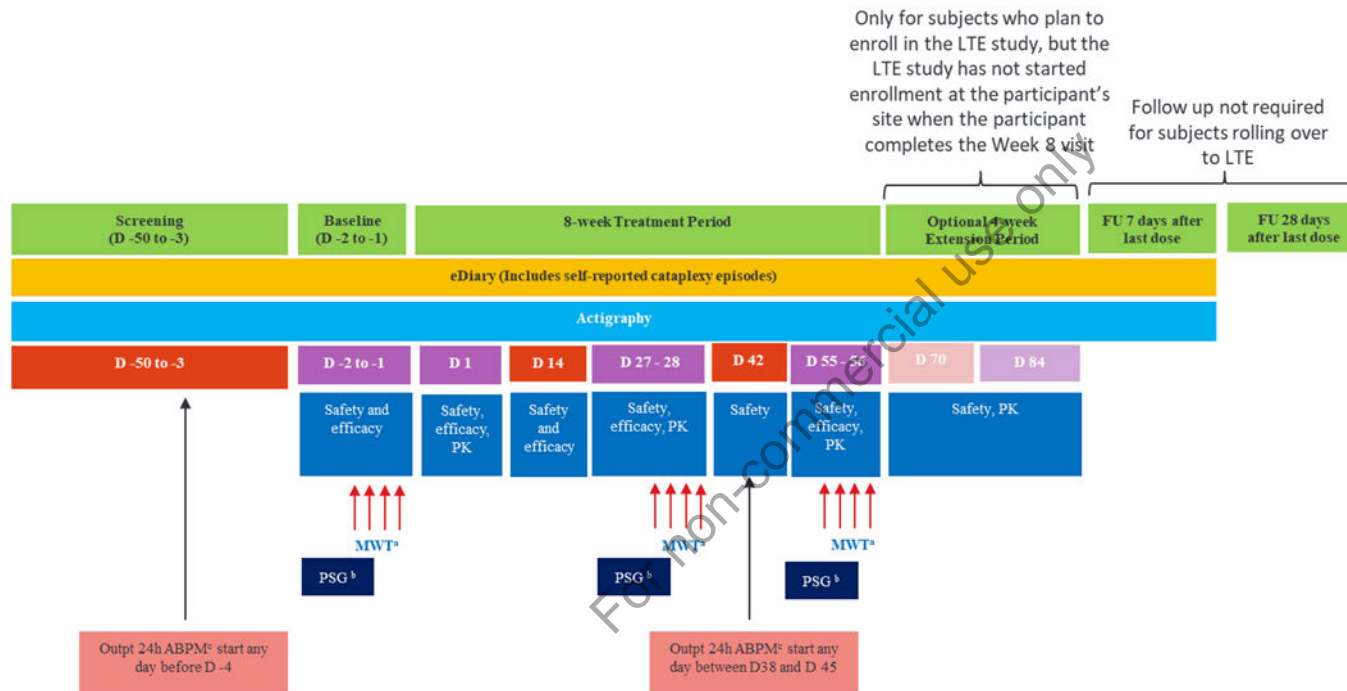
This sample size will also provide 88% power to detect a difference of 8 points between TAK-861 and placebo by a 2-sample t-test on the change from baseline to Week 8 in ESS total scores at 0.05 2-sided significance level, assuming an SD of 7 points.

In addition, this sample size will provide approximately 86% power to detect a 50% reduction in WCR relative to placebo with TAK-861 using a Poisson model at 0.025 1-sided significance level, assuming a baseline WCR of 4, with a placebo effect of 25% reduction from baseline.

Data Monitoring/Other Committee: Yes

1.2 Schema

Figure 1.a Study Schema



ABPM: ambulatory blood pressure monitoring; D: day; ePRO: electronic patient-reported outcome; FU: follow-up; LTE: long-term extension; MWT: Maintenance of Wakefulness Test; nPSG: nocturnal polysomnography; Outpt: outpatient; PK: pharmacokinetic(s).

^a Confinement will start on evening of Days -2, 27, and 55 with MWT done on Days -1, 28, and 56.

^b nPSG will be done on the nights of Days -2, 27, and 55.

^c ABPM readings should be obtained over at least 24.5 hours and participants should not be confined to the clinical site during most of the 245-hour recording period. See Schedule of Activities for additional instructions.

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1.3 Schedule of Activities

Table 1.a Schedule of Activities

Dark grey highlights indicate the visit requires overnight confinement; overnight stay on Day -1 at the clinic is optional. Light grey highlights indicate the visit may be in-clinic or by home healthcare.

	Screening / Baseline ^a			8-Week Treatment Period								Optional 4-Week Extension Before LTE Study ^b		FU 7 Days After Last Dose ^d /ET ^e	FU 28 Days After Last Dose ^{c,d}
				1		14	27	28	42 ^c	Final Visit		70 ^c	84		
	Pre	Post	55	56											
	Day	-50 to -3	-2	-1											
Week					2	4	6	8	10	12					
Visit Window (days) ^f					±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Visit Number	1	2			3	4		5	6		7	8	9/99 ^g	10	
Administrative Procedures															
Informed consent	X														
Inclusion/ exclusion criteria	X	X	X	X											
Demographics, medical history, medication history	X														
Concomitant medications/ procedures	Throughout the study from signing the informed consent onwards														
Pregnancy avoidance counseling	Throughout the study from signing the informed consent onwards														
Medication washout ^h	X														
Medication restart ^h													X		
Clinical Procedures and Assessments															
TAK-861/ placebo administration				X		X	X	X	X	X	X	X	X		
AE assessment	Throughout the study from signing the informed consent onwards														
BP (supine) and HR (supine) ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Respiratory rate and temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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	Screening / Baseline ^a			8-Week Treatment Period							Optional 4-Week Extension Before LTE Study ^b		FU 7 Days After Last Dose ^d /ET ^e	FU 28 Days After Last Dose ^{c,d}	
				1		14	27	28	42 ^c	Final Visit		70 ^c			Final Visit
										Pre	Post				
Day	-50 to -3	-2	-1			2	4	6	8	10	12	±3	±3		
Week															
Visit Window (days) ^f															
Visit Number	1	2			3	4	5	6	7	8	9/99 ^g	10			
ABPM (start before time of first morning dose) ^j	X							X							
ECG	X			X		X			X		X	X			
Height	X														
Body weight	X		X				X			X	X	X			
Physical examination ^k	X		X			X	X			X	X	X			
C-SSRS	X		X			X	X	X		X	X	X	X		
Fundoscopy examination (optional)	X														
CSF sample for OX assessment	X														
Clinical Laboratory Procedures and Assessments															
Pregnancy test ^l	X	X				X	X		X		X	X			
FSH assessment (required for postmenopausal women only)	X														
Hematology ^m	X	X								X	X		X		
Blood chemistry ^m	X	X		X ⁿ	X	X	X	X		X	X	X	X		
Urinalysis	X	X			X	X	X		X		X	X			
Urine drug screening ^o	X	X				X	X		X		X				
Blood samples for HLA genotyping ^p	X														
Blood sample for DNA	X														

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	Screening / Baseline ^a			8-Week Treatment Period								Optional 4-Week Extension Before LTE Study ^b		FU 7 Days After Last Dose ^d /ET ^e	FU 28 Days After Last Dose ^e /d
				1		14	27	28	42 ^c	Final Visit		70 ^c	Final Visit		
	Pre	Post	55							56					
	Day	-50 to	-2	-1			2	4	6	8	10	12			
Week	-3					±3	±3	±3	±3	±3	±3				
Visit Window (days) ^f															
Visit Number	1	2			3	4	5	6	7	8	9/99 ^g	10			
(optional) ^h															
Alcohol screening ^f	X	X				X	X		X		X				
Efficacy Assessments															
e-diary ^g	Throughout the study from signing the informed consent onwards up to first FU or rollover into LTE														
Actigraphy ^f	Throughout the study from signing the informed consent onwards up to first FU or rollover into LTE														
TSQM ^u							X			X					
Cognitive assessments ^v		X	X				X			X					
NSS-CT	X	X					X			X					
SF-36		X					X			X					
nPSG ^w		X					X			X					
MWT ^x			X				X			X					
ESS ^u	X		X			X	X			X	X	X			
CGI-S/PGI-S ^u			X												
CGI-I/PGI-I ^u							X			X					
EQ-5D-5L ^u and FIN ^u			X				X			X					
PK Evaluation															
Plasma sample for TAK-861 PK ^y				X	X		X	X		X	X				
Plasma sample for CYP3A4/5 activity ^z				X				X		X					

ABPM: ambulatory blood pressure monitoring; AE: adverse event; BP: blood pressure; CGI-I: Clinical Global Impression Scale–Global Improvement Scale; CGI-S: Clinical Global Impression Scale–Severity of Illness Scale; CPAL: continuous paired associate learning; CSF: cerebrospinal fluid; C-SSRS: Columbia Suicide Severity Rating Scale; CYP: cytochrome P450; ECG: electrocardiogram; eCRF: electronic case report form; e-diary: electronic diary; EQ-5D-5L: EuroQol-5 Dimensions 5 Levels; ESS: Epworth Sleepiness Scale; ET: early termination; FIN: Functional Impacts on Narcolepsy; FSH: follicle stimulating hormone; FU: follow-up; HR: heart rate; hCG: human chorionic gonadotropin; HLA: human leukocytic antigen; iDSST-s: international Digit Symbol Substitution

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Test-symbols; IEC: independent ethics committee; IRB: institutional review board; LTE long-term extension; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; nPSG: nocturnal polysomnography; NSS-CT: Narcolepsy Severity Scale for Clinical Trials; NT1: narcolepsy type 1; ONB: One Back test; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression– Severity; PI: primary investigator; PK: pharmacokinetic(s); PRO: patient-reported outcome; PSG: polysomnography; PVT: psychomotor vigilance task; SF-36: Short Form-36 Survey; TSQM: Treatment Satisfaction Questionnaire for Medication.

^a The site may contact the sponsor or designee for approval to extend the screening window, eg, in the case of an unexpected schedule change or need to extend the screening window to complete the washout of NT1 medications. The site PI may determine if there is a need to repeat any screening assessments to ensure participant suitability.

^b After the Week 8 visit, participants will have the option to participate in an LTE study under a separate protocol (assuming protocol is open for enrollment). If the LTE study has not started at the participant's site at the time a participant completes the Week 8 visit, the participant will be allowed to continue in the current study for an additional 4 weeks of treatment.

^c The visits on Days 42 and 70, and the FU visit 28 days after the last dose may be in-clinic or by home healthcare.

^d Two FU visits are planned for approximately 7 and 28 days after the final study drug intake (corresponding to Days 63 and 84 for participants whose final study drug intake is on Day 56). The FU visit 7 days after the final study drug intake is an in-clinic visit; the FU visit 28 days after the last dose may be in-clinic or by home healthcare. After the Week 8 visit, participants will have the option to participate in an LTE study. Participants who enroll in the LTE study will not have FU visits in this study.

^e For all participants who withdraw early, except those refuse further contact, every effort should be deployed to have them attend an ET visit as soon as possible. If the ET visit coincides with another scheduled visit and the participant has not yet discontinued study drug, participants should be encouraged to complete all scheduled assessments. Participants who withdraw early will be encouraged to continue completing their daily e-diary until the ET visit. Further, every effort should be deployed to have these participants attend the follow-up visit 28 days after the last dose (the FU visit 7 days after the last dose is not needed in addition to the ET visit).

^f If the date of a participant visit does not conform to the study plan, the timing of subsequent visits should be planned so that the visit schedule relative to the first study drug intake (Day 1) is maintained. For the Week 8 and Week 12 (for participants in the 4-week extension) visits, every effort should be deployed to have participants come in as close to Day 55 or 84 (if applicable) as possible.

^g Visit 9 for 7-day FU; visit 99 for ET.

^h Medication washout should begin at initial screening visit to minimize duration of screening period. See Section 6.8.1 for list of medication restrictions. Medication restart can occur 1 week after the last dose (restart must occur after final visit/ET unless the investigator feels an earlier restart is warranted). Participants who immediately enroll in the LTE study will not restart medications.

ⁱ BP will be checked (single measurement) with the participant resting for a minimum of 5 minutes sitting or lying in a bed with the head of the bed at 30 degrees. BP and HR measurements on the days listed below will be checked at specific time points:

- On days on which nPSG starts (Days -2, 27, and 55) at 1 hour before lights off.
- On Day 1 at 1.5 and 3 hours post 8AM dose and prior to discharge (Note: Measurement at 3 hours post 8AM dose should be obtained prior to administration of second dose.)
- On MWT days (-1, 28, and 56) at pre 8AM dose and 1.5, 3.5, 5.5, and 7.5 hours post 8AM dose.
- On ABPM days (once before Day -3 and once between Days 38 and 45) at pre 8AM dose.

On Days 14, 70, and 84, BP and HR may be checked anytime during the day.

^j The ABPM device will be applied on-site or by home healthcare personnel. ABPM should begin just before the first morning dose of study drug and continue for at least 24.5 hours. **If necessary, participants may delay their first morning dose (8 AM ±2 hours) so that it is taken right after the ABPM device begins recording.** For convenience, site staff may offer to confine participants the evening before ABPM begins. The participants should not be confined to a clinical site for the majority of the 24.5-hour recording period, as real world data collection while wearing the device is critical.

ABPM recording during screening period may start any day up to Day -4 (ending no later than Day -3). If recording quality is not satisfactory, ABPM may be repeated starting any day up to Day -4. During screening the ABPM timing should account for potential repeat of the recording before Day -4. ABPM recording during the treatment period will start any day between Days 38 and 45, inclusive. If this treatment period ABPM recording quality is not satisfactory, ABPM may be repeated as long as the recording ends no later than 1 day before check-in for the Week 8 visit.

^k Full physical examination will be performed at screening and at first FU visit (or ET visit). On all other time points, an abbreviated physical examination may be performed.

^l Pregnancy test is required for participants of childbearing potential only. Serum pregnancy test will be done at screening. At all other time points, urine hCG testing may be done. Pregnancy testing can be repeated at any time at the investigator's discretion.

^m Hematology and blood chemistry procedures should occur pre 8AM dose, after at least 8 hours of fasting, except for Day -2 and Day 1 (blood chemistry only). If the participant is arriving to the site on the morning of the procedure, the participant may delay their first morning dose of study medication (8 AM \pm 2 hours). The second (if a sample was taken pre 8AM dose, see footnote “n”) Day 1 blood chemistry sample should be drawn just before discharge.

ⁿ Blood chemistry test pre 8AM dose on Day 1 is only required if the participant opted not to stay overnight at the clinic on Day -1.

^o Urine drug screen: may be repeated any time at the investigator’s discretion. Confirmatory urine drug tests will be performed in study in regions where available at the investigator’s discretion.

^p Previous HLA results are acceptable if available for review by the PI and provided for inclusion in the eCRF.

^q One blood sample for DNA analysis may be collected at any visit before the initiation of study drug administration. Country-level participation to be determined by local regulations and IRB/IEC approval.

^r At the screening visit, alcohol screening will be done initially with a breathalyzer, and, if positive, a serum ethanol level will be obtained. For other time points, a breathalyzer will be done at check-in.

^s e-diary measures, including self-reported assessments of cataplexy, will be obtained starting after the successful initial screening visit and continuing until the first FU visit. e-diary dosing questions will begin on Day 1 and end on last day of dosing. In cases where the e-diary becomes unavailable, the site may use alternative methods to collect these data with approval from the sponsor or designee. In case a participant did not complete cataplexy questions 11 of 14 days (ie, is not compliant) during Days -16 to -3, the screening period can be extended at the discretion of the investigator to allow the participant to improve compliance.

^t Actigraphy (accelerometry) device will be worn continuously (as much as possible throughout the day and night) from screening (after signed consent) to first follow-up visit or rollover into the LTE.

^u Administration of PROs (ESS, PGI-S/I, EQ-5D-5L, FIN, and TSQM) on MWT days -1, 28, and 56 should begin after first MWT session. If additional time is needed, completion can continue when convenient during the remainder of the day.

^v On Day -2, participants will be administered a practice assessment once to familiarize the participants with the task. On Days -1, 28, and 56 the cognitive assessments PVT, CPAL, ONB, and iDSST-s will be administered at approximately 1 hour post 8AM dose (at equivalent time on Day -1) and the PVT will be administered a second time at 7 hours post 8AM dose (at equivalent time on Day -1).

^w nPSG consisting of 8-hour nighttime polysomnography will be obtained. In the rare event that PSG exclusion criteria cannot be assessed by Day -1, dosing may be delayed until the issue is resolved. Site investigator may opt to repeat baseline nPSG/MWT before randomization. The sponsor or designee should be consulted for any such situation.

Note: Per the inclusion criteria, if there is a potential participant with NT1 for whom a diagnostic nPSG/MSLT was performed more than 10 years ago or is not available, diagnostic nPSG/MSLT may be performed before Day -2.

^x An MWT will be obtained at 2, 4, 6, and 8 hours after the 8AM dose on Days 28, and 56. MWT session will also be performed on Days -1 at the same clock time as planned for Day 28.

^y Blood samples for the determination of the TAK-861 concentration will be collected as follows:

- On Day 1 at pre 8AM dose and 1.5 and 3 hours post 8AM dose (Note: blood sample at 3 hours post 8AM dose should be obtained prior to administration of second dose.)
- On days on which nPSG starts (Days 27 and 55) at 1 hour before to lights off
- On MWT days (28, and 56) at pre 8AM dose and 1.5, 3.5, 5.5, and 7.5 hours post 8AM dose.

^z Blood samples for the measurement of 4 β -hydroxycholesterol/cholesterol ratio to assess CYP3A4/5 activity will be collected pre 8AM dose on Days 1, 28, and 56.

Table 1.b Efficacy, Safety, and PK Assessments with Time Requirements

Day Procedure	Screening/ baseline			8-Week Treatment Period								Optional 4-Week Extension Before LTE Study	
	-50 to -3	-2	-1	1		14	27	28	42	55	56	70	84
				Pre	Post								
Primary Specimens													
Hematology	Fasted	X									Fasted; pre 8AM dose		Fasted; pre 8AM dose
Blood chemistry	Fasted	X		Fasted; pre 8AM dose ^a	At discharge	Fasted; pre 8AM dose		Fasted; pre 8AM dose	Fasted; pre 8AM dose		Fasted; pre 8AM dose	Fasted; pre 8AM dose	Fasted; pre 8AM dose
Plasma sample for TAK-861 PK				Pre 8AM dose	1.5 and 3 h post 8AM dose (3h sample prior to second dose)		1 h before nPSG lights off	Pre and 1.5, 3.5, 5.5, and 7.5h post 8AM dose		1 h before nPSG lights off	Pre and 1.5, 3.5, 5.5, and 7.5 h post 8AM dose		
Blood sample for CYP3A4/5 activity				Pre 8AM dose				Pre 8AM dose			Pre 8AM dose		
Vital Signs													
BP (supine) and HR (supine)	X	1 h before nPSG lights off	Same times as planned for Day 28	Pre 8AM dose	1.5 and 3 h post 8AM dose and at discharge (3h measureme nt prior to second dose)	Pre 8AM dose	1 h before nPSG lights off	Pre and 1.5, 3.5, 5.5, and 7.5h post 8AM dose	Pre 8AM dose	1 h before nPSG lights off	Pre and 1.5, 3.5, 5.5, and 7.5 h post 8AM dose	Pre 8AM dose	Pre 8AM dose
ABPM	Start 24.5h recording any day up to Day -4								Start 24.5h recording any day from Day 38 to 45				

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Table 1.b Efficacy, Safety, and PK Assessments with Time Requirements

Day Procedure	Screening/ baseline			8-Week Treatment Period								Optional 4-Week Extension Before LTE Study	
	-50 to -3	-2	-1	1		14	27	28	42	55	56	70	84
				Pre	Post								
Efficacy Evaluations													
nPSG		Overnight					Overnight			Overnight			
MWT (4 sessions)			Same clock time as planned for Day 28					2, 4, 6, and 8 h post 8AM dose			2, 4, 6, and 8 h post 8AM dose		
PVT		Practice session, no specified time	Same times as planned for Day 28					1 and 7 h post 8AM dose			1 and 7 h post 8AM dose		
CPAL, ONB, iDSST-s		Practice session, no specified time	Same times as planned for Day 28					1 h post 8AM dose			1 h post 8AM dose		
ESS, PGI-S/I, EQ-5D-5L, FIN, and TSQM	X (ESS only)		After first MWT session			X (ESS only)		After first MWT session			After first MWT session		X (ESS only)

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; CPAL: continuous paired associate learning; CYP: cytochrome P450; EQ-5D-5L: EuroQol-5 Dimension 5-level questionnaire; ESS: Epworth Sleepiness Scale; FIN: Functional Impacts on Narcolepsy; HR: heart rate; iDSST-s: international Digit Symbol Substitution Test-symbols; LTE: long-term extension; MWT: Maintenance of Wakefulness Test; nPSG: nocturnal polysomnography; ONB: One Back test; PGI-I: Patient Global Impression of Improvement; PGI-S: Patient Global Impression- Severity; PK: pharmacokinetic(s); pre: pre-8am-dose; PVT: psychomotor vigilance task; TSQM: Treatment Satisfaction Questionnaire for Medication.

*Blood chemistry test only to be performed in case the participant opted not to stay overnight at the clinic on Day -1.

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2. Introduction

2.1 Study Rationale

Narcolepsy with cataplexy, or narcolepsy type 1 (NT1), has been defined by International Classification of Sleep Disorders, 3rd Edition (ICSD-3) criteria as having low levels of orexin (OX) in the cerebrospinal fluid (CSF) (≤ 110 pg/mL, or less than one-third of normal levels), resulting from the nearly complete loss of OX-producing neurons. An OX2R agonist is thus the first approach to directly address the loss of OX peptide in the brain in as it may restore OX2R signaling at the postsynaptic receptors and may be more effective than current therapies in treating the entire NT1 pentad, especially excessive daytime sleepiness (EDS) and cataplexy. Nonclinical pharmacology studies showed wake-promoting effects and improvement of cataplexy-like syndrome with TAK-861 in a murine narcolepsy model. In human studies, administration of an OX agonist has been well-tolerated and was associated with marked improvements in sleep latency in patients with NT1 (Evans et al, Orexin 2 receptor-selective agonist danavorexton improves narcolepsy phenotype in a mouse model and in human patients, in preparation; 27 Jun 2022). The available nonclinical information and emerging clinical safety, tolerability, and pharmacokinetic (PK) profiles of single and multiple doses of TAK-861 in healthy participants in the TAK-861-1001 study support this study, which is designed to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of multiple oral doses of TAK-861 in subjects with NT1.

Additional rationale relating to the study design, TAK-861 dose administered, and study endpoints is provided in Section 4.2.

2.2 Background

The orexinergic system is a major wake-promoting system of the brain. It is comprised of 2 types of wake-promoting OX (also known as hypocretin) neurons, localized in a specific region of the lateral and posterior hypothalamus and have excitatory projections to wide areas of the central nervous system including the basal forebrain and brainstem nuclei involved in maintaining wakefulness (ie, cholinergic neurons of the reticular activating system, 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.

OX is a neuropeptide, and the orexinergic system is a major wake-promoting system of the brain. Two orexinergic neuropeptides, OX-A and OX-B, have been identified to date. The OXs exert effects via 2 types of receptors, the OX1R and the OX2R. OX-A has a high affinity for the OX1R and OX2R, and OX-B has a high affinity for the OX2R. These 2 OX receptors 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 (Ohno et al., 1997).

The pathological loss of orexinergic neurons is associated with the development of NT1 (Scammell and Winrow, 2011). As mentioned above, NT1, has been defined by ICSD-3 criteria (American Academy of Sleep Medicine, 2014) as having low levels of OX in the CSF (≤ 110 pg/mL, or less than one-third of normal levels), resulting from the nearly complete loss of OX-producing neurons. In contrast, narcolepsy type 2 (NT2) is characterized by the absence of cataplexy. The pathophysiology of NT1 has a presumed, although unproven, autoimmune basis in individuals with a specific genetic predisposition, the most common of which is the human leukocyte antigen (HLA) DQB1*06:02 (Krahn et al., 2002, De la Herran-Arita and Garcia-Garcia, 2014). Narcolepsy is a rare, acquired, chronic neurologic disorder that alters sleep-state stability. The cardinal symptom of narcolepsy is EDS, described as a sudden overpowering need to sleep during the day's normal periods of alertness. Intrusion of REM sleep phenomena into wakefulness 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 uncinat 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.

Because 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.

2.2.1. Summary of Nonclinical Data

Nonclinical information is provided in the TAK-861 investigator's brochure (IB).

2.2.2. Summary of Effects in Humans

Two phase 1 studies (TAK-861-1001 and TAK-861-1003) are ongoing to evaluate the safety, tolerability, mass balance, and PK of single- and multiple-rising oral doses of TAK-861 in healthy non-Japanese and Japanese adult participants, healthy elderly participants, and participants with NT1. One phase 1 study, TAK-861-1002, is clinically complete and the clinical study report is in preparation. A total of 146 participants have been enrolled, 108 of whom have received active treatment based on actual exposure and enrollment data as of 22 April 2022 (safety data cutoff date for the IB).

The first-in-human study TAK-861-1001 is an ongoing study designed to evaluate the safety, tolerability, and PK of single- and multiple-rising oral doses of TAK-861 in healthy non-Japanese and Japanese adult participants, healthy elderly participants, and participants with

NT1. This study also assessed the effect of food on the PK of a single dose of the tablet formulation of TAK-861.

The study consists of 7 parts, 3 of which have PK and safety data (Parts A, B, and E) and 1 has preliminary PK and blinded safety data (Part C). Part A (completed) was a randomized, double-blind, placebo-controlled, single-rising dose part to assess the safety, tolerability, and PK of TAK-861 administered as a suspension or tablet to healthy Japanese participants. Part B (ongoing) is a randomized, double-blind, placebo-controlled, multiple-rising dose and multiple dose part to assess the safety, tolerability, and PK of TAK-861 administered to healthy Japanese participants. Part E (completed) was a randomized, double-blind, placebo-controlled, single and multiple-rising dose, and multiple dose part to assess the safety, tolerability, and PK of TAK-861 administered to healthy non-Japanese participants. Part C is a randomized, double-blind, placebo-controlled, multiple dose (ongoing) part to assess the safety, tolerability, and PK of TAK-861 administered to healthy elderly (aged ≥ 65 years) Japanese subjects.

Following single- and repeated oral administrations of TAK-861 to healthy participants under fasted conditions, TAK-861 was readily absorbed into the systemic circulation. Mean TAK-861 exposures (based on maximum observed concentration [C_{max}] and area under the plasma concentration-time curves [AUCs]) increased approximately dose-proportionally after single dosing (range 1 to 75 mg) and multiple once daily (QD) dosing (range 5 to 30 mg QD). TAK-861 displayed a biexponential disposition phase with an estimated mean terminal elimination half-life ranging from approximately 16 to 24 hours after single and multiple doses, respectively. Additionally, there were no apparent concentration- or time-dependent changes in TAK-861 clearance across all dosing groups and study parts. Ingesting a high-fat, high-calorie meal immediately before administering TAK-861 increases mean TAK-861 peak concentration by 46% and mean total exposures by 37%. Overall, the clinical PK profiles of TAK-861 after single and repeat dosing appeared to be similar between Japanese and non-Japanese participants. Healthy elderly Japanese participants receiving TAK-861 5 mg QD exhibited similar mean TAK-861 exposures (based on C_{max} and AUCs) to that of healthy younger Japanese participants at the same dose level in study Part B.

The safety data showed that the majority of participants reported mild treatment-emergent adverse events (TEAEs); 2 participants reported 3 moderate TEAEs (micturition urgency, pollakiuria, and upper respiratory tract infection). No deaths or serious adverse events (SAEs) were reported in any treatment group of Parts A, B, and E. Three participants discontinued study drug due to mild TEAEs: 1 participant from Part B (TAK-861 30 mg treatment group) and 2 participants from Part E (1 subject from the TAK-861 5 mg treatment group and 1 participant from the TAK-861 30 mg treatment group). Only one of these discontinuations (from Part B) was considered drug related. Considering all 3 study parts together, the most frequently reported adverse events (AEs) were blood pressure (BP) increased, insomnia, micturition urgency, dizziness, hyperhidrosis, euphoric mood, and pollakiuria. Insomnia was observed only in single doses of 50 mg (1 of 6 participants in Part A) and 75 mg (4 of 6 participants in Part A) and multiple doses of 20 mg QD (2 of 6 participants in Part A) and 30 mg QD (4 of 6 participants in Part B, and 2 of 7 participants in Part E). Increased overall mean systolic and diastolic BP were

observed after single doses of 20 mg or greater in Parts A, B, and E, with estimated increases ranging from 5 to 15 mm Hg. After 14 days of repeated dosing, no overall mean change in diastolic BP was observed and mean systolic BP was not consistently increased (increased in the 20 mg cohort in Part B, but not in the 30 mg cohorts in Parts B or E). No notable trends were observed with HR changes. Based on blinded safety data in healthy elderly Japanese participants, 5 of 8 participants (62.5%) reported TEAEs that were mild to moderate in intensity. The most frequently reported TEAEs were micturition urgency and pollakiuria, and no TEAEs led to study drug discontinuation or death.

The phase 1 study TAK-861-1002 is a clinically complete, randomized, double-blind, placebo-controlled, 3-period crossover study designed to evaluate the safety, tolerability, and PK of TAK-861 during an acute sleep phase delay paradigm in healthy adults. The study consisted of 3 treatment periods, in which 11 healthy adult male participants (aged 18-40 years) received the following 3 regimens (1 per treatment period): TAK-861 high-dose regimen (total dose of 40 mg), TAK-861 low-dose regimen (total dose of 15 mg), and placebo in 1 of 3 possible treatment sequences.

Single doses of TAK-861 40 mg and 15 mg demonstrated a significant improvement in the objective and subjective measures of wakefulness assessed in an acute sleep-delayed paradigm model in healthy adults. On the Maintenance of Wakefulness Test (MWT), which has a maximum duration of 40 minutes, the least square (LS) mean sleep onset latencies for placebo, 15 mg TAK-861, and 40 mg TAK-861 were 19.74, 37.57, and 38.84 minutes, respectively. The LS mean placebo-adjusted changes in sleep onset latency were 17.84 minutes ($p < 0.0001$) for 15 mg TAK-861 and 19.10 minutes ($p < 0.0001$) for 40 mg TAK-861. The LS mean Karolinska Sleepiness Scale scores were 8.27 for placebo, 5.67 for TAK-861 15 mg and 4.38 for TAK-861 40 mg. The LS mean placebo-adjusted changes from predose in Karolinska Sleepiness Scale were -2.65 ($p = 0.009$) for 15 mg TAK-861 and -4.40 ($p < 0.0001$) for 40 mg TAK-861.

The safety data showed that the majority of participants reported mild TEAE; only 1 participant reported a moderate TEAE. No deaths or SAEs were reported in any treatment group in this study. All TEAEs related to study drug were mild and occurred in the 40 mg dose period (total of 6 mild TEAEs reported in 5 participants). The most frequently reported TEAE was micturition urgency.

In summary, TAK-861 demonstrated significant improvement in the objective and subjective measures of wakefulness assessed in an acute sleep-delayed paradigm model in healthy adults. TAK-861 was generally safe and well tolerated up to 75 mg single dose and 30 mg QD for 14 days in healthy participants. The safety data showed that the majority of participants reported mild TEAEs; no severe TEAEs were reported. There were no deaths or SAEs in any treatment group for any of the studies detailed the IB.

For additional information, refer to the TAK-861 IB.

2.3 Benefit-Risk Assessment

This phase 2, randomized, double-blind, placebo-controlled, parallel group study includes efficacy, safety, and tolerability evaluations in participants with NT1 receiving repeated oral doses of TAK-861.

2.3.1. Potential Benefits

An OX2R agonist is the first approach to directly address the loss of OX peptide in the brain in NT1 ([Thannickal et al., 2000](#)). An OX2R agonist may restore OX2R signaling at the postsynaptic receptors and may be more effective than current therapies in treating the entire NT1 pentad, especially EDS and cataplexy. NT2 may have partial although less severe OX deficiency. As such, the use of an OX2R agonist would likely be efficacious in supplementing the intrinsic activity of the OX system.

2.3.2. Potential Risks

Based on nonclinical data and clinical results for TAK-861, clinical data of other compounds with the same mechanism of action, literature information on the association between OX2R agonism and cardiovascular effects, as well as effects on wakefulness in nonclinical models ([Huang et al., 2010](#)), potential risks for this product are:

- Increases in BP and HR.
- Insomnia.
- Bladder events (eg, micturition urgency, pollakiuria).

The principal mitigation strategy for risks related to BP increase, HR increase, insomnia, and bladder events includes appropriate selection of the study population; use of the inpatient clinical research unit setting, which permits close monitoring and rapid institution of appropriate care as needed; appropriate specified monitoring procedures; and use of experienced staff trained in study procedures. To mitigate cardiovascular risks, BP and HR will be measured frequently in this study; cardiovascular effects will be evaluated by using BP and HR assessments and electrocardiographic (ECG) assessments. Stopping rules for individual participants and the overall study have been established and are noted in Section 7.

In addition, liver toxicity was observed with firazorexton (another OX2R agonist) in its phase 2 clinical studies. The structure of TAK-861 is closely related to firazorexton; however, TAK-861 is considered to be a more potent OX2R agonist. Total daily doses of 0.5 to 7.0 mg will be investigated to determine TAK-861 clinical safety, tolerability and efficacy profiles in NT1. At the highest planned total daily dose of 7.0 mg, its covalent binding burden is also projected to be lower than the previous OX2R agonist. The relative risk of clinical hepatotoxicity for TAK-861 is believed to be significantly lower than for this OX2R agonist compound on the basis of its predicted low therapeutic dose.

As of 22 April 2022 (IB Edition 2 cutoff date), no cases of DILI were reported for TAK-861 and there were no clinically significant elevation of liver function test (LFT) values reported in any

of the ongoing studies. Additionally, appropriate mitigation measures were put in place in the protocols of the clinical studies to detect any liver enzyme elevations in a timely manner.

LFTs (alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ -glutamyl transferase [GGT], and total bilirubin) will be closely monitored in this study. Stopping criteria for individual participants and the overall study, based on abnormal LFTs have been established and are noted in Section 7. Section 10.5 provides additional guidance on monitoring and follow-up of abnormal liver-associated test results.

Finally, there is minimal risk associated with the noninvasive procedures planned for this study. Potential risks related to noninvasive study procedures include the following:

- Acute hypersensitivity and/or anaphylactic reactions to new chemical entities are always a possible risk in any clinical study. Appropriate procedures will be used to manage such possible risks.
- Study procedure-specific risks include issues related to blood collection for safety and PK assessments (eg, venipuncture may cause bruising).

Review of available nonclinical and clinical data, including the nonserious, mild TEAEs reported in ongoing Study TAK-861-1001, supports a favorable benefit-risk ratio for this study with TAK-861. Refer to the latest version of the TAK-861 IB for the overall benefit/risk assessment and the most current information regarding drug metabolism, PK, efficacy, and safety of TAK-861.

3. Objectives, Endpoints

3.1 Objectives and Endpoints

The following are the objectives and endpoints of this study:

Objectives	Endpoints
Primary	
<ul style="list-style-type: none">• To assess the effect of TAK-861 on EDS as measured by sleep latency from the MWT.	<ul style="list-style-type: none">• Change from baseline to Week 8 in mean sleep latency from the MWT.
Secondary	
<ul style="list-style-type: none">• To assess the effect of TAK-861 on EDS as measured by the Epworth Sleepiness Scale (ESS) total score.• To assess the effect of TAK-861 on cataplexy as assessed by the weekly cataplexy rate (WCR).• To evaluate the safety and tolerability of TAK-861.	<ul style="list-style-type: none">• Change from baseline to Week 8 in ESS total score.• WCR at Week 8.• Occurrence of at least 1 TEAE.
Additional/Exploratory	
<ul style="list-style-type: none">• To evaluate the safety and tolerability of TAK-861.	<ul style="list-style-type: none">• Occurrence of at least 1 markedly abnormal value (MAV) for postdose laboratory values.• Occurrence of at least 1 MAV for postdose vital signs.

Objectives	Endpoints
<ul style="list-style-type: none"> To assess the effect of discontinuation of TAK-861, as assessed by ESS, WCR, and patient-reported sleep parameters. To assess the effect of TAK-861 on sustained attention as measured by the psychomotor vigilance test (PVT). To assess the effect of TAK-861 on overall narcolepsy symptoms measured by the Clinical Global Impression Scale – Global Improvement Scale (CGI-I) and the Patient Global Impression of Improvement (PGI-I) scale. To assess the effect of TAK-861 on severity of narcolepsy symptoms measured by Narcolepsy Severity Scale for Clinical Trials (NSS-CT). To assess the effect of TAK-861 on mobility, self-care, usual activities, pain/discomfort and anxiety/depression as assessed by the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) scale. To assess the effect of TAK-861 on quality of life of participants, as assessed by the Short Form-36 Survey (SF-36). To assess the efficacy of TAK-861 on functional impacts of narcolepsy as assessed by the Functional Impacts of Narcolepsy (FIN) scale. To assess the effects of TAK-861 on memory, working memory, and processing speed as measured by the cognitive tests (Continuous Paired Associate Learning [CPAL] test, One Back test [ONB], and international Digit Symbol Substitution Test-symbols [iDSST-s]). To assess the treatment satisfaction with TAK-861 as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM). To assess the effect of TAK-861 on sleep architecture as measured by nocturnal polysomnography (nPSG). 	<ul style="list-style-type: none"> Occurrence of at least 1 MAV for postdose ECG parameters. Time-matched change in BP and HR from baseline to specified postdose time points. Change in ambulatory BP and HR parameters from baseline. Number (and percent) of participants with at least 1 endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS). Change from baseline in ESS total score, WCR, and sleep parameters reported in the patient-reported sleep electronic diary (e-diary) at the follow-up visit 1 week after drug discontinuation. Change from baseline in number of lapses on PVT. PGI-I and CGI-I scores. Change from baseline in NSS-CT. Change from baseline in EQ-5D-5L index score. Change from baseline in quality of life as measured by SF-36 domain scores. Change from baseline in the FIN domain scores. Change from baseline in CPAL, ONB, and iDSST-s measurements. Treatment satisfaction as measured by the 4 dimensions of the TSQM. Change from baseline in various nPSG measures, including nocturnal awakenings.

Objectives	Endpoints
<ul style="list-style-type: none"> To assess the effect of TAK-861 on daily/nighttime activity as measured by actigraphy (accelerometry) and HR (photoplethysmography). To assess steady-state exposures of TAK-861. To assess the PK/PD relationship(s) of TAK-861 for selected efficacy or safety measures. 	<ul style="list-style-type: none"> Change from baseline in daily/nighttime activity metrics derived from continuous actigraphy (accelerometry) and HR (photoplethysmography) from a wrist-worn device. TAK-861 plasma concentrations and selected noncompartmental analysis PK parameters (C_{max}, of time of first occurrence of C_{max} [t_{max}], and area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration [AUC_{last}]).

3.2 Estimands

Not applicable

4. Study Design

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, 8-week parallel group study to evaluate the efficacy, safety, and tolerability of 4 oral dose regimens of TAK-861.

Approximately 100 (male and female) participants with NT1, who satisfy the inclusion and exclusion criteria, will be randomized such that each participant has an equal chance of being assigned to any 1 of 5 treatment arms: 3 TAK-861 twice daily dose regimens, 1 TAK-861 QD dose regimen, or matching placebo. Randomization will be stratified by region. Starting on the morning of Day 1, the study drug will be administered at approximately the same time each day for 8 or 12 weeks. (If the participant wishes to enroll in the long-term extension [LTE] study but the LTE study has not started at the participant's site when the participant completes the Week 8 visit of the current study, the participant will be allowed to continue in the current study for an additional 4 weeks; see below.)

Participants who have provided informed consent will complete a screening period of up to 50 days (see Section 6.8.1 for different washout periods) to washout any NT1 medication (if applicable). Participants will be asked to complete an e-diary, starting from the initial screening visit, no later than Day -16. To be eligible for the study, participants must fill out self-reported cataplexy questions in the e-diary for at least 11 days of the 14-day period from Day -16 to Day -3 and have ≥ 4 partial and/or complete episodes of cataplexy/week (averaged over Days -16 to -3).

Participants will remain confined overnight at the study site during the following times:

- Days -2 to 1 (1 mandatory overnight at Day -2; 1 optional overnight at Day -1).
- Days 27 to 28 (1 overnight).
- Days 55 to 56 (1 overnight).

Information on the timing of the assessments is provided in the schedule of activities (SOA) (Table 1.a).

After the Week 8 visit, participants will have the option to participate in an LTE study under a separate protocol (assuming protocol is open for enrollment). Participants who enroll in the LTE study will not have follow-up visits in this study.

If a participant plans to enroll in the LTE study but the LTE study is not open for enrollment at the participant's site when the participant completes the Week 8 visit, the participant will be allowed to continue in the current study for an additional 4 weeks of treatment (continuing the same treatment regimen as the previous 8 weeks). This is to avoid a treatment gap for participants willing to roll over from this study to the LTE study.

For participants who do not participate in the LTE study (including any participant who completes the Week 12 visit and for any reason does not enroll in the LTE), every effort should be deployed to have them complete a first follow-up visit approximately 7 days after the final study drug intake and a second follow-up visit (home healthcare visit) approximately 28 days after the final study drug intake. For participants who early terminate the study, every effort should be deployed to have them complete an early termination visit as soon as possible and a follow-up visit (in-clinic visit or home healthcare, if available) approximately 28 days after the last dose of study drug. Participants not participating in the LTE study can restart their non-exclusionary medications after the first follow-up visit or early termination visit.

For a schematic of the study design, see Section 1.2. For the SOA, see Section 1.3.

4.2 Scientific Rationale for Study Design

4.2.1. Rationale for Study Population

The participants included in the study will be participants with NT1 who are otherwise generally healthy.

A general rationale for the inclusion of participants with NT1 is provided in Section 2.1.

4.2.2. Rationale for Study Design

This study is a randomized, double-blind, placebo-controlled study investigating the efficacy, safety, and tolerability of TAK-861 in participants with NT1. Approximately 100 participants with NT1 will be randomized with equal probability to 1 of 5 arms: 3 TAK-861 twice daily (approximately 3 hours apart) dose regimens, 1 QD dose regimen, or matching placebo (dose rationale in Section 4.3). This dose-ranging study was designed to inform dose selection and further development of TAK-861 as a potential treatment for NT1.

The duration of the dosing in the study (56 days; optionally 84 days) was chosen to allow enough time to evaluate all study endpoints and provide insight into TAK-861 efficacy and safety in participants with NT1 in conjunction with an acceptable duration of treatment with placebo. Considering the half-life of TAK-861, the 56-day (or 84-day) treatment and 28-day follow-up period are of sufficient duration to collect data about potential effects.

Participants will be confined to an inpatient facility for specified periods throughout the conduct of the study. This confinement ensures adherence to study procedures and permits monitoring of safety and tolerability.

4.2.3. Rationale for Endpoints

4.2.3.1. Safety Endpoints

Standard safety endpoints (eg, TEAEs, physical examination findings, vital signs, 12-lead ECG measures, clinical laboratory results) for early clinical investigation are included.

Further, because cardiovascular effects have been noted in nonclinical models with TAK-861 and OX2R agonists in general and these effects are thought to be on-target effects, close monitoring of cardiovascular parameters, including time-matched BP measurements before and after dosing to detect any changes and potential tolerance in BP after the administration of repeat doses to participants with NT1 will be included (see Section 2.3). Ambulatory blood pressure monitoring (ABPM) is also being obtained to assess BP in the outpatient setting in a rigorous manner.

In addition, because LFT elevation cases have been observed in another OX2R agonist with structural similarity (see Section 2.3), LFTs (ALT, AST, GGT, and total bilirubin) will be closely monitored. Sections 7.1 and 10.5 provide additional guidance on monitoring and follow-up of abnormal liver-associated test results.

Finally, adequate measures have been taken regarding the methodology of this study to assess suicide risk. The selection criteria exclude the participation of participants at significant risk for suicide. Throughout the study, signs of suicide risk will be assessed both by rating scale assessment and by investigator's clinical judgment. Participants will be withdrawn from the study in case of such risk. Furthermore, participants will be screened for the history of suicidal behavior to enter the study and then regularly screened during the study for suicidal behavior and thinking via the C-SSRS to continue to accurately and systematically assess the potential relationship between investigational agents and suicidality. The C-SSRS will be administered every 2 weeks, and during the follow-up visits in this study (if applicable) as indicated in the SOA (Table 1.a) (Posner et al., 2007b, Posner et al., 2007a).

4.2.3.2. Efficacy Endpoints

To evaluate the effect of TAK-861 on symptoms of narcolepsy after multiple dosing, this study includes well-established objective and subjective primary and secondary efficacy endpoints for narcolepsy symptom measures. Major narcolepsy symptoms include EDS measured by objective endpoints such as sleep latency from the MWT assessment, and subjective endpoints such as the ESS total score.

Further, several efficacy endpoints including parameters from nPSG, actigraphy, and cognitive assessments will be evaluated. In addition, cataplexy and disturbance in nighttime sleep are also collected from the e-diary.

4.2.4. Participant Input into Design

Takeda consults patients and patient organizations throughout the development of TAK-861.

4.3 Justification for Dose

In the TAK-861-1001 study, single doses up to 75 mg and multiple doses up to 30 mg QD, 10 mg BID and 7 mg TID have been administered safely in healthy volunteers (HV). In addition to HV cohorts, TAK-861 is currently being explored in participants with NT1 (Part D is currently ongoing), where total daily doses from 0.5 mg to 8 mg, given once or twice daily for a maximum of 28 days are being evaluated.

Previously developed systems pharmacology and population PK/PD models were used to leverage dose/exposure-response relationships from prior OX2R agonists in humans. Based on these, a TAK-861 total daily dose range of 1 to 7 mg per day is expected to achieve OX2R target engagement like that observed with prior OX2R agonists. The planned highest daily dose does not exceed the highest daily dose being evaluated in Part D. This will further allow to fully characterize the dose-response relationships for key efficacy and safety endpoints and support dose selection for future pivotal studies.

Twice daily dosing of TAK-861 in selected arms of this study will further evaluate maintenance of wakefulness during daytime by maintaining drug exposures throughout the day. Both doses will be taken approximately 3 hours apart to not interfere with the four 40-min MWT sessions planned at 2, 4, 6, and 8 hours after the 8AM dose during the confinement periods, to ease management of dosing and mealtimes while at home, and to minimize sleep disturbances.

4.4 End of Study/Study Completion Definition

The end of study is defined as the final date on which data were or are expected to be collected, ie, the last visit of the last participant in the study.

The participant's maximum duration of participation is expected to be up to 23 weeks (including a screening period of up to 50 days, a 8- or 12-week treatment period and 4-week follow-up period). Participants immediately rolling over to the LTE study will not have a follow-up period.

5. Study Population

Investigators must account for all individuals who sign informed consent forms (ICFs), regardless of the outcome of the screening, by completing the required electronic case report forms (eCRFs).

Rescreening will be allowed under circumstances described in Section 5.4.

5.1 Inclusion Criteria

Participants must meet *all* of the following criteria to be eligible for inclusion in the study:

Informed Consent

1. The participant is willing and able to understand and fully comply with study procedures and requirements (including digital tools and applications), in the opinion of the investigator.

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2. The participant has provided informed consent (that is, in writing, documented via a signed and dated ICF and/or electronic consent [eConsent]) and any required privacy authorization before the initiation of any study procedures.

Age and Body Mass Index

3. The participant is aged 18 to 70 years, inclusive, at the time of signing the ICF.
Note: In Japan, participants aged 16 to 70 years, inclusive, may be included.
4. The participant has body mass index (BMI) within the range 18 to 40 kg/m² (inclusive)

Type of Participant and Disease Characteristics

5. The participant has an ICSD-3 diagnosis of NT1 by polysomnography (PSG)/Multiple Sleep Latency Test (MSLT), performed within the past 10 years and meeting the minimal acceptable criteria for the proper performance of PSG/MSLT as outlined in the ICSD-3.

Note: If there is a potential participant with NT1 for whom a diagnostic nPSG/MSLT was performed more than 10 years ago or is not available, the site may repeat the diagnostic PSG/MSLT before Day -2.

Note: For participants with results from a CSF test indicating an OX/hypocretin-1 concentration of ≤ 110 pg/mL (or less than one-third of the mean values obtained in normal participants within the same standardized assay), the PSG/MSLT requirement may be waived after a discussion with the sponsor or designee.

6. The participant has an ESS score >12 on Day -1.
7. The participant has ≥ 4 partial and/or complete episodes of cataplexy/week (WCR), calculated as the weekly average over 14 days (Days -16 to -3 of the screening period). Before the start of WCR recording, participants must complete washout of anticataplexy medications (see Section 6.8.1 for washout requirements for specific medications). Participants must complete self-reported cataplexy questions in the e-diary for at least 11 of 14 days during Days -16 to -3, to be considered compliant. In cases where the e-diary becomes unavailable, the study site may use alternative methods to collect these data with approval from the sponsor or designee.
8. The participant is positive for the HLA genotype HLA-DQB1*06:02 (positive results for either homozygous or heterozygous alleles will be considered “positive” and acceptable) or results from CSF testing indicate the participant’s CSF OX/hypocretin-1 concentration is <110 pg/mL (or less than one-third of the mean values obtained in normal participants within the same standardized assay).

Note: Previous HLA results are acceptable if available for review by the principal investigator (PI) and provided for inclusion in the electronic case report form (eCRF).

9. The participant is judged by the investigator to be sufficiently healthy to participate in the study, on the basis of 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.

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Note: Screening laboratory assessments may be repeated; the sponsor or designee should be informed.

Contraception

10. The participant agrees to follow the birth control requirements detailed in Section 10.4.

5.2 Exclusion Criteria

The participant will be excluded from the study if *any* of the following exclusion criteria are met:

Medical Conditions

1. The participant has a current medical disorder, other than narcolepsy with cataplexy, associated with EDS.
 - a) This includes restless legs syndrome/periodic limb movement disorder that has a significant impact on daytime sleepiness.
 - b) Participants with clinically significant moderate-to-severe obstructive sleep apnea may be eligible if they are compliant with continuous positive airway pressure (CPAP), defined as having at least 4 hours of CPAP use per night on at least 70% of nights for approximately 1 month before randomization (assessed by machine tracking time) and have apnea hypopnea index (AHI) ≤ 10 with CPAP or other modes of positive airway pressure.
 - c) For all participants, past PSG data demonstrating any of the following is exclusionary: AHI ≥ 15 , apnea index ≥ 10 , or periodic leg movement arousal index of ≥ 15 /hour, unless a more recent PSG and/or clinical evaluation by the investigator indicates a meaningful change in clinical status. All attempts should be made to confirm eligibility based on Day -2 nPSG data.
2. The participant has a current medical condition such as unstable cardiovascular, pulmonary, renal, or gastrointestinal disease, that would preclude enrollment in the view of the investigator.
3. The participant has medically significant hepatic or thyroid disease.
4. The participant 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 participant.
5. The participant has a history of cancer in the past 5 years (does not apply to participants with carcinoma in situ that has been resolved without further treatment or basal cell cancer; these participants may be included after approval by the sponsor or designee).

6. The participant has clinically significant coronary artery disease, a history of myocardial infarction, clinically significant angina, clinically significant cardiac rhythm abnormality, or heart failure.
7. The participant has a clinically significant history of head injury or head trauma.
8. The participant has history of epilepsy, seizure, or convulsion, or has a family history of inherited disorders associated with seizure (except for a single febrile seizure in childhood).
9. The participant has one or more of the following psychiatric disorders:
 - a) Any current unstable psychiatric disorder.
 - b) Current or history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including schizoaffective disorder, major depression with psychotic features, bipolar depression with psychotic features, obsessive compulsive disorder, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5).
 - c) Current diagnosis or history of substance use disorder as defined in the DSM-5.

Note: If the history of substance use disorder is more than 12 months before baseline, the participant may be allowed to enroll in the study after consultation with the sponsor or designee. (Participant must also have negative urine drug screen at the screening and Day -2 visits.)
 - d) Current active major depressive episode (MDE) or who have had an active MDE in the past 6 months.

Note: Neurodevelopmental disorders (eg, attention deficit hyperactivity disease) are not excluded unless severity does not allow termination of prohibited medications (see Section 6.8.1 for list of restricted medications).
10. The participant has a history of cerebral ischemia, transient ischemic attack (<5 years ago), intracranial aneurysm, or arteriovenous malformation.
11. The participant has a current history of significant multiple or severe allergies (eg, food, drug, latex allergy) or has had an anaphylactic reaction or significant intolerance to prescription or nonprescription drugs or food.
12. The participant has a known hypersensitivity to any component of the formulation of TAK-861 or related compounds.
13. The participant had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.

Prior/Concomitant Therapy

14. The participant is unable to refrain from or anticipates using excluded food products (see Section 5.3) beginning by Day -7 and continuing until the first follow-up visit, or prohibited medication (as described in Section 6.8.1).
15. The participant has participated in another investigational drug study, in which they received the investigational drug, within 60 days (or 6 months if participant may have received an investigational biologic product). The interval window from the previous study will be derived from the date of the last study procedure in the previous study to the screening visit of the current study.

Note: This does not apply to approved drugs, for which rules are laid out in Section 6.8.1.

16. The participant has any prior exposure to an oral Takeda OX agonist other than TAK-861.

Diagnostic Assessments

17. The participant has a BP >140 mm Hg (systolic) or >90 mm Hg (diastolic) during screening. BP measures should be obtained after the participant has been resting for a minimum of 5 minutes. If the BP is slightly elevated above these parameters, measurement may be repeated 3 times, and the median of the 3 recordings used.

Note: Participants with a history of hypertension are not excluded if the BP does not meet the above criteria.

18. The participant has a resting HR <40 or >100 beats per minute during screening, confirmed on repeat testing within a maximum of 30 minutes.
19. The participant's screening ECG reveals a QT interval with Fridericia correction method (QTcF) >450 milliseconds (genetically male) or >470 milliseconds (genetically female).
20. The participant has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or HIV antibody/antigen at screening.
21. The participant's renal creatinine clearance (Cockcroft-Gault Equation) is ≤ 50 mL/min at screening.
22. The participant has ALT or AST values >1.5 times the upper limit of normal (ULN) at screening or Day -2 (if results available); or the participant has ALT or AST between 1.0 and $1.5 \times$ ULN at screening with $\geq 15\%$ increase from screening to Day -2.
23. The participant has a positive pregnancy test at screening or Day -2 or is lactating/breastfeeding.
24. The participant has a positive urine screen for drugs of abuse and/or positive alcohol test at screening or Day -2. An exception at screening is made for stimulants or other drugs the participant has been prescribed, but the drug screen must be negative on Day -2. Products containing cannabidiol are allowed throughout the study, at the discretion of the investigator.

Note: Participants testing positive for marijuana at screening may be eligible for participation in the study provided that the investigator's clinical assessment indicates the participant is not a regular user of marijuana, and after discussion with and approval from the sponsor or designee. Under this circumstance, a local urine dipstick drug screen must be performed at the baseline visit and verified to be negative before conducting any other study procedures at this visit.

25. The participant is considered by the investigator to be at imminent risk of suicide or injury to self, others, or property, or the participant has attempted suicide within the past year before screening, or has positive answers on item number 4 or 5 on the C-SSRS (based on the past year) before randomization.

Other Exclusion Criteria

26. The participant is a study site employee or an immediate family member of or in a dependent relationship with a study site employee (eg, spouse, parent, child, sibling) who is involved in the conduct of this study, or may consent under duress.
27. The participant consumes excessive amounts of caffeine, defined as greater than 600 mg per day (1 cup of coffee is approximately 120 mg.).
28. The participant currently consumes alcohol exceeding 2 standard drinks per day on average (1 standard drink is approximately equivalent to the following: beer [354 mL/12 oz], wine [118 mL/4 oz], or distilled spirits [29.5 mL/1 oz] per day).
29. The participant has a nicotine dependence that is likely to have an effect on sleep (eg, a participant who routinely awakens at night to smoke) or an unwillingness to refrain from smoking and nicotine use during the confinement portions of the study.
30. The participant is unwilling to refrain from driving during times of heightened sleepiness or fatigue as well as during times of medication weaning/changes or is unwilling to adhere to local regulations and any PI guidance restricting driving.
31. The participant has a usual bedtime later than 12:00 AM (midnight), an occupation requiring nighttime shift work or variable shift work within the past 6 months, travel with significant jet lag within 14 days before Day -2, or plans for travel with significant jet lag during the study.
32. The participant, in the opinion of the investigator or subinvestigator is unlikely to comply with the protocol or is unsuitable for any other reason.

Participants meeting any of the following criteria will not be eligible for optional CSF collection:

33. The participant has undergone CSF collection within 30 days before the planned optional CSF collection day.
34. The participant 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 participant has significant vertebral deformities (scoliosis or kyphosis) that, in the opinion of the investigator, may interfere with the lumbar puncture procedure.
36. The participant has a history of major back (lumbar) surgery, clinically significant back pain, and/or injury, in the opinion of the investigator.
37. The participant has a local infection at the puncture site.
38. The participant has developed signs of lumbar radiculopathy, including lower extremity pain and paresthesia.
39. The participant has any known focal neurological deficit that might suggest an increase in intracranial pressure.
40. The participant has any abnormal findings on ophthalmological/funduscopy assessment indicative of raised intracranial pressure (ie, optic disc swelling/edema or [uncontrolled] hypertension retinopathy).
41. The participant has a bleeding abnormality or history of bleeding abnormalities. The participant has thrombocytopenia or other suspected bleeding tendencies noted.
42. The participant is taking an anticoagulant (1 tablet/day of low dose aspirin [81 mg] is allowed) or has abnormal coagulation test results (prothrombin time/international normalized ratio [INR], activated partial thromboplastin time) from a sample taken during the screening period. Results of coagulation tests must be received and reviewed by the investigator in advance of the CSF sample collection.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Consumption of grapefruit and grapefruit juice is prohibited from Day -7 until the first follow-up visit 7 days after the last dose.

Alcohol use will be restricted from 3 days before any check-in or site visit. During other 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.

On days of nPSG and MWT assessments ([Table 1.a](#)), participants will follow the nPSG/MWT manual. Caffeine will not be allowed on these days. 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.

Participants 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.

For a comprehensive list of prohibited medications and procedures, see Section [6.8.1](#) and [Table 6.b](#).

Information on when to take the study drug in relation to meal times is provided in Section [6.2.4](#).

5.3.2. Activity

During confinement, participants should remain upright (seated, standing, or ambulatory) for 4 hours after dose administration, except as necessitated by the occurrence of an adverse event (AE) or study procedure (eg, obtaining 12-lead ECG).

Participants will abstain from strenuous exercise (eg, weightlifting, running, bicycling) from 72 hours before check-in until checkout for scheduled study visits (including outpatient visits). Participants may engage in usual activities at other times with the exception of driving during times of heightened sleepiness or fatigue and during times of medication weaning/changes. Participants must adhere to local regulations and PI guidance restricting driving.

5.3.3. Contraception for Participants of Childbearing Potential or Capable of Producing Viable Sperm

Participants who are of childbearing potential (that is, capable of producing viable ova and/or becoming pregnant) or capable of producing viable sperm must use highly effective contraception as agreed to in Inclusion Criterion 10. Section 10.4 lists acceptable methods of contraception.

5.4 Screening

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The site PI may determine if there is a need to repeat any screening assessments to ensure participant suitability.

5.4.1. Screen Failures

An individual who has provided informed consent to participate in the study may be categorized as a screen failure for any of the following reasons:

- screen failure (did not meet entrance criteria).
- AE.
- Lost to follow-up.
- Pregnancy.
- Withdrawal by participant.
- Met eligibility criteria but not needed.
- Study terminated by sponsor.
- Other (specify).

Participants are **not** considered screen failures if they were randomized but not treated. See Section 7.2.

Information about screen failures should be collected via the eCRFs, including participant identification, screening disposition (including the reason for screen failure), demography,

inclusion/exclusion criteria, and AEs (if applicable). If a potential participant experiences an SAE during screening, all of the participant's screening eCRFs must be available for collection.

The interactive response technology (IRT) should be contacted as a notification of screen failure.

Participant identification numbers assigned to participants who fail screening should not be reused.

An individual who has been designated a screen failure may be rescreened.

5.5 Criteria for Temporarily Delaying Randomization

Randomization may be delayed for any of the following reasons:

- Screening extension to repeat screening assessments or if additional washout time of specific medications is needed based on judgement of PI.
- Additional time needed to confirm eligibility based on PSG (eg, additional time is needed to resolve queries regarding PSG interpretation).
- Coronavirus disease 2019 (COVID-19) infection.
- Self-quarantine requirement.
- Site closure.
- Pretreatment AE before randomization/treatment.

For participants who were randomized, but not treated, the reason(s) should be captured on the eCRF.

5.6 Enrollment

A participant is defined as enrolled when the participant has been randomized.

6. Study Intervention(s) and Concomitant Therapy

6.1 Study Interventions Administered

In this study, the interventions includes:

- TAK-861 Dose Regimen 1: 0.5 mg twice daily approximately 3 hours apart.
- TAK-861 Dose Regimen 2: 2 mg twice daily approximately 3 hours apart.
- TAK-861 Dose Regimen 3: 2 mg followed by 5 mg approximately 3 hours apart.
- TAK-861 Dose Regimen 4: 7 mg once daily (QD).
- Other products required for the study: Matching placebo.

Dose regimens include QD or twice daily (approximately 3 hours apart) dosing. Study treatment will be administered at approximately 8 AM and 11 AM. (Participants assigned to a QD dose regimen will receive placebo for the second dose. Participants assigned to placebo will receive placebo for both doses.)

Table 6.a describes the interventions administered in all arms of this study.

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation, of the active drug and placebo, can be found in the IB. Study drug will be packaged to support the enrollment of participants as required.

Table 6.a Study Intervention(s) Administered: Drug

Intervention Label	TAK-861	Placebo
Intervention Name	TAK-861	Placebo
Former Name(s) or Alias(es)	NA	NA
Intervention Description	Information provided in the IB	Information provided in the IB
Excipients	Information provided in the IB	Information provided in the IB
Type	Drug	Placebo
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	Information provided in the IB	Information provided in the IB
Dosage Level(s)	See Section 4.3	See Section 4.3
Route of Administration	Oral	Oral
Use	Experimental	Placebo
Classification	Investigational medicinal product	NA
Authorization Status	Not authorized in any region	NA
Sourcing	Provided centrally by the sponsor or designee	Provided centrally by the sponsor or designee
Packaging and Labeling	Information provided in pharmacy manual	Information provided in pharmacy manual

IB: investigator's brochure; NA: not applicable.

6.2 Preparation, Handling, Storage, and Accountability

For preparation, handling, and storage of the sponsor-supplied study product, refer to the pharmacy manual.

6.2.1 Accountability Throughout the Study

The investigator or designee must ensure that the sponsor-supplied study product is used in accordance with the protocol and is only dispensed to/used for participants enrolled in the study.

To document appropriate use of sponsor-supplied study product (Section 6.1), the investigator or designee must maintain 100% accountability for all sponsor-supplied study interventions that the site receives and dispenses during their entire participation in the study.

Proper drug accountability includes, but is not limited to:

- The investigator or designee must maintain records of all sponsor-supplied study interventions delivery to the site, current site inventory, dispensing for use by each participant, and return to the sponsor or designee.
- The investigator or designee must record this inventory on a sponsor (or designee)-approved drug accountability log.
- Based on entries in the log, it must be possible to reconcile study products delivered with those used and returned.
- All study products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.
- If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

6.2.2. Receiving Product at the Site

Investigators will be provided with sufficient amounts of the study intervention to carry out this protocol for the agreed number of participants.

On receipt of sponsor-supplied study drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition.

Refer to the pharmacy manual for details related to the receipt of study drug.

6.2.3. Labeling

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

6.2.4. Dispensing/Administration

6.2.4.1. Dispensing

Participants will be assigned to receive their treatment according to the randomization schedule.

Information on study drug dispensing is provided in the pharmacy manual.

6.2.4.2. Administration

Each participant in this study will be instructed to take study drug twice daily: the first dose will be taken in the morning upon awakening, as close to 8:00 AM as possible (after completion of pre 8AM dose assessments if in the clinic) and the second dose will be taken approximately 3 hours later, as close to 11:00 AM as possible. Participants assigned to a QD dose regimen will receive placebo for the second dose. Participants assigned to placebo will receive placebo for both doses.

During the confinement periods (as indicated in [Table 1.a](#)), the first dose of TAK-861 or matched placebo will be administered in the morning by mouth (as close to 8:00 AM as possible)

with 240 mL of water after an overnight fast of at least 8 hours; participants will then be allowed to have a morning meal approximately 0.5 to 1 hour after study drug administration. Participants may consume water ad libitum. Participants will be instructed to take the second dose approximately 3 hours after the first morning dose. Standardized meals (approximately 30% fat content relative to total calories) will be administered for lunch (approximately 4-6 hours post 8AM dose) and dinner (approximately 9-13 hours post 8AM dose). On discharge days, lunch or dinner may be taken at home.

On ABPM fitting days (as indicated in [Table 1.a](#)), participants should take their study drug right after the ABPM device begins recording (8:00 AM \pm 2 hours). The ABPM device will be applied on-site or by home healthcare personnel. If the ABPM device will be applied on-site and because it is a requirement that the ABPM devices begin recording in the morning before the first morning dose, site staff may opt to confine participants the evening before fitting participants with the ABPM monitoring device. If the participant is travelling to the site for the ABPM fitting or waiting for the arrival of home health personnel, **they may delay their first morning dose of study drug (between 8:00 AM \pm 2 hours) if needed.** Participants who are confined the evening prior should also take their study drug right after the ABPM recording starts.

While at home, participants will be instructed to take the first dose of TAK-861/matched placebo upon arising in the morning as close to 8:00 AM as possible (\pm 1 hour) with a large glass of water (approximately 240 mL total) and have breakfast approximately 0.5 to 1 hour after study drug intake whenever possible. Participants will be instructed to take the second dose approximately 3 hours (11:00 AM \pm 1 hour) after the first morning dose. Lunch should be taken approximately 0.5 to 1 hour after the second dose whenever possible. Participants are encouraged to take study drug at approximately the same time each day in the morning. Participants will be provided written instructions by the site on how to take study drug at home.

Participants should swallow the study drug whole and not chew it or manipulate it in any way before swallowing. Participants should be instructed not to take more than the prescribed dose at any time. If a dose window is missed, the dose should be skipped and no drug should be taken until the next scheduled dose. Under no circumstance should a participant repeat a dose or double-up doses.

Participants will be instructed to record their intake of TAK-861/matched placebo each day in their e-diary (Section [8.2.2.3.9](#)). Additional steps may be taken to ensure participants understand the dosing instructions and that they follow the correct TAK-861 dosing regimen, such as additional site communication with the participant throughout the treatment course, ie, on-site visits or phone calls.

Participants will adhere to the dietary and medication restrictions described in Sections [5.3](#) and [6.8](#).

Within the source documents, site personnel should document instruction of and understanding by the participant of the safe, responsible storage and administration of study intervention to the study participant.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization

Randomization personnel of the sponsor or designee will generate the randomization schedule for the IRT system. Randomization will be stratified by region. Details are in the IRT system specifications.

6.3.2. Blinding the Treatment Assignment

This is a double-blind study; the investigator and participants are blinded to treatment assignment. Blinded study drug supply will be provided, and the standard operating procedures of the study site for maintaining the double-blind will be followed.

6.3.3. Unblinding

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 participant. If possible, the sponsor or designee (eg, medical monitor) should be contacted before the blind is broken. Unblinding will be performed per the standard operating procedures of the study site.

6.4 Study Drug Compliance

When participants are dosed at the site, they will receive study intervention under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and dosing e-diary. The study participant identification will follow the standard operating procedure of the site and the pharmacy manual.

When participants take the study drug at home, they should record the time of the dose in their dosing e-diary (a component of the e-diary).

Participants must be instructed how and where to return unused study intervention and empty/used study intervention packaging for drug accountability.

6.5 Dose Modification

Not applicable.

6.6 Continued Access to Study Intervention after the End of the Study

After the completion of the current study, participants will have the option to participate in an LTE study under a separate protocol (assuming the protocol is open for enrollment).

6.7 Treatment of Overdose

In this study, an overdose is defined as a known deliberate or accidental administration of the study intervention, either to or by a study participant, at a dose above that assigned to that individual participant.

In the event of a drug overdose, the participant should be treated symptomatically.

All cases of overdose or medication error must be documented on the eCRF. Because these events are not, in and of themselves, AEs, they should be reported regardless of whether any

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manifested signs or symptoms are considered AEs. If there are signs and symptoms meeting the criteria for reporting as AEs or SAEs, they should also be reported, as described in Section 10.3.

6.8 Concomitant Therapy

6.8.1. Excluded Treatments

Restricted medications and supplements are shown in Table 6.b. Restricted medications may be discontinued earlier than, but not later than, the required start of the restriction period. For example, the PI may decide to have participant restrict medications for a longer period before baseline to ensure the participant's narcolepsy symptoms have returned to baseline.

Administration of any drugs used for the treatment of narcolepsy with cataplexy (NT1) must be discontinued. The investigator will determine the schedule for tapering of antidepressants and stimulants. Hormonal contraceptives are not excluded.

Participants may receive the COVID-19 vaccination; however, vaccinations within 48 hours before checkin at any visit will not be allowed. Sites should document the vaccination dosing on the concomitant medication page.

Meals and dietary restrictions are discussed in Section 5.3.1.

Table 6.b Prohibited Concomitant Medications and Therapies

Prohibited Drug Category	Beginning of Restriction Period (Medications can be restarted after first follow-up visit.)
Any investigational drug (restriction does not apply to TAK-861 administration described in this protocol or to any approved drugs)	Excluded from 60 days (or 6 months if participant received an investigational biologic product) before the screening visit
Oxybate (multisalt or sodium)	Excluded from Day -37
Antidepressants with anticataplexy effect including tricyclic antidepressants, SSRIs, SNRIs	Excluded from Day -23 except for the following: <ul style="list-style-type: none"> Venlafaxine ≤ 150 mg/d: Day -30 Venlafaxine > 150 mg/d: Day -44 Fluoxetine: Day -44
Psychostimulants including methylphenidate hydrochloride, modafinil, armodafinil, methamphetamine hydrochloride, and solriamfetol	Excluded from Day -16 or from 5 half-lives before Day -2, whichever is longer
Pitolisant	Excluded from Day -30
Antipsychotic drugs	All other drug categories listed are excluded from 7 days or 5 half-lives (whichever is longer) before Day 1
Antianxiety medications/tranquilizers/sleeping medications including benzodiazepines, nonbenzodiazepine drugs, melatonergic agonists, and <i>Yokukansan</i> , <i>Yokukansankachinpihange</i> used for insomnia	

Table 6.b Prohibited Concomitant Medications and Therapies

Prohibited Drug Category	Beginning of Restriction Period (Medications can be restarted after first follow-up visit.)
St. John's wort, health foods containing melatonin	<div>For non-commercial use only</div>
Herbal medicine (topical use is not restricted)	
Mood stabilizers (such as lithium or valproic acid or other antipsychotic drugs)	
Anticonvulsants	
Anti-Parkinson disease drugs	
Adrenocorticosteroids (excluded except for inhaled and topical; systemic administration would only occur during the study to treat an AE)	
Interferon, interleukin-formulation	
Muscle-relaxant drug (eg, baclofen)	
Cannabis products containing THC (Products containing CBD, but not THC, are allowed throughout the study, at the discretion of the investigator.)	
Centrally-acting antihistamines including loratadine, OTC drugs and pharmaceutical adjuvants	
Antitussives with CNS action	
Antiemetics with CNS action	
Narcotic analgesics, varenicline (Chantix)	
Nonnarcotic analgesics, other than occasional use of ibuprofen, naproxen, or aspirin (use of nonnarcotic analgesics may be approved by the principal investigator after consultation with the sponsor or designee [eg, Medical Monitor].)	
Medications associated with liver enzyme elevations (see list in Appendix 2)	
Known moderate and strong CYP3A inhibitors or inducers ^a and Known CYP3A substrates with narrow therapeutic range ^a (This restriction may be modified on the basis of emerging data from other studies of TAK-861.)	
Known sensitive OATP1B1 substrates ^a .	

Table 6.b Prohibited Concomitant Medications and Therapies

Prohibited Drug Category	Beginning of Restriction Period (Medications can be restarted after first follow-up visit.)
(This restriction may be modified on the basis of emerging data from other studies of TAK-861.)	

AE: adverse event; CBD: cannabidiol; CNS: central nervous system; CYP: cytochrome P450; OATP: organic anion transporting polypeptide; OTC: over-the-counter; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; THC: tetrahydrocannabinol.

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 A list of inhibitors/inducers of CYP3A and substrates of CYP3A and OATP1B1 and medications associated with liver enzyme elevations is provided in [Appendix 1](#).

6.8.2. Permitted Concomitant Medications

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 PI, unless the investigator or investigator's designee considers immediate administration necessary.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

This section describes the circumstances under which individual participants would withdraw or be discontinued from the study intervention or from the study itself.

Section [10.1](#) describes circumstances in which specific sites or the study itself would be discontinued.

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. For participants who early terminate the study, every effort should be deployed to have them complete an early termination visit as soon as possible and a follow-up visit (in-clinic visit or home healthcare visit if available) approximately 28 days after the last dose of study drug (see [Table 1.a](#)).

The primary reason for discontinuation or withdrawal of the participant from the study or study drug should be recorded in the eCRF using the following categories.

- **AE.** An AE may require a participant to discontinue the study drug if continued participation would impose an unacceptable risk to the participant's health or the participant is unwilling to continue because of the AE.
 - LFT abnormalities: Study drug should be discontinued with appropriate clinical follow-up, including repeat laboratory tests until a participant's laboratory profile has returned to

their normal or baseline status, if the following circumstances occur at any time during study drug treatment:

- ALT or AST $>5 \times$ ULN.
- ALT or AST $>3 \times$ ULN twice in measurements at least 24 hours apart with no intervening measurements $\leq 3 \times$ ULN.
- (Collection of sample for repeat laboratory measurements is to be done no more than 72 hours after the initial elevation in ALT or AST $> \times$ ULN is noted.)
- ALT or AST $>3 \times$ ULN in conjunction with elevated bilirubin $>2 \times$ ULN or INR >1.5 .
- ALT or AST $>3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).
- See Section 10.5 for further information on LFT abnormalities.
- Suicidality: Study drug should be discontinued for participants at imminent risk of suicide per the C-SSRS (endorsement of Item 4 with the investigator's clinical judgement or Item 5) or per the investigator's clinical judgment. Once discontinued, the participants should be followed up as described in Section 8.3.8.3.
- BP increase: Study drug should be discontinued if in-clinic BP measurement meets either of the following criteria: sustained systolic BP >160 mm Hg or sustained diastolic BP >100 mm Hg. *Sustained* is defined as 2 readings separated by approximately 15 minutes.

Note: In the event of BP values meeting the criteria above, the participant 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.
- HR (or pulse rate) increase: sustained HR >100 beats per minute measured during an in-clinic visit will result in stopping treatment per the investigator's clinical judgment.

- **Death.**
- **Protocol deviation.** The discovery after randomization that the participant did not meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the participant's health.
- **Lost to follow-up.** The participant did not attend visits and 3 attempts to contact the participant were unsuccessful. Attempts to contact the participant must be documented in the participant's source documents. A certified letter can be sent as a last attempt.
- **Withdrawal by participant.** The participant 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 (for example, withdrawal due to an AE should not be recorded in the “voluntary withdrawal” category). Similarly, lack of efficacy should not be recorded in the “voluntary withdrawal” category.

- **Study terminated by sponsor.**

The sponsor, institutional review board (IRB), or independent ethics committee (IEC), or regulatory agency terminates the study.

- **Other (specify).**

Note: The specific reasons should be recorded in the “specify” field of the eCRF, including unavoidable circumstances such as the COVID-19 pandemic

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution, or may be withdrawn at any time at the discretion of the investigator or sponsor (eg, in the interest of participant safety). The investigator is encouraged to discuss withdrawal of a participant with the medical monitor when possible.

The investigator may discontinue a participant’s study participation at any time during the study when the participant meets the study termination criteria described in Section 7.1.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SOA (see Table 1.a). The primary criterion for termination must be recorded by the investigator. See SOA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Participants who discontinue or withdraw may be replaced.

7.3 Lost to Follow-up

The participant may be lost to follow-up as defined in Section 7.1.

8. Study Assessments and Procedures

Written or electronic informed consent must be obtained (signed and dated) before study assessments and procedures can be performed, as described in Section 10.1.3.

The following sections describe the study procedures and data to be collected at planned time points per the SOA (see Table 1.a). Protocol waivers or exemptions are not allowed.

Repeat or unscheduled samples may be taken for safety reasons or due to technical issues with the samples. Whenever possible, the same person should perform each assessment.

The primary specimen collection table is provided in Table 8.a.

Table 8.a Primary Specimen Collection

Specimen name in Schedule of Events	Primary Specimen	Primary Specimen Derivative 1	Primary Specimen Derivative 2	Description of Intended Use	Sample Collection
Blood sample for DNA	Blood	DNA	NA		Optional
Plasma sample for TAK-861 PK	Plasma	NA	NA	PK measurements (Drug Concentrations)	Mandatory
Plasma sample for CYP3A4/5 activity	Plasma	NA	NA	PD measurements (Enzyme Activity)	Mandatory
CSF sample for OX assessment	Cerebrospinal Fluid	NA	NA	Biomarker Measurements	Optional

CSF: cerebrospinal fluid; NA: not applicable; OX: orexin

8.1 Demographics, Medical History, Medication History and Administrative Procedures

8.1.1. Demographics

Participant demographic information will be collected before the participant receives the first dose of study intervention.

Demographic information to be obtained will include: date of birth or age (as permitted by local regulations), sex, race (reported by the participant), caffeine consumption, alcohol consumption, substance use, smoking status. Information on the primary disease (narcolepsy) will also be collected including age of onset and year of diagnosis. The details about cataplexy symptoms of the participant may be also confirmed. If test results are available, CSF OX concentration data, and past PSG/MSLT data including the mean sleep latency and the number of sleep onset REM periods (SOREMPs) will be also collected.

8.1.2. Medical History

Medical and medication history, including concurrent medical conditions, will be collected and recorded in the participant's source documents and in the eCRF.

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases relevant to the disease under study that resolved before the participant signed the ICF. Ongoing conditions are considered concurrent medical conditions.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present when informed consent is provided. This includes clinically significant laboratory, ECG, physical examination, and/or vital signs abnormalities noted at screening/baseline examination, according to the judgment of the investigator.

8.1.3. Prior and Concomitant Treatments/Medications

Prior and concomitant treatments and medications will be collected and recorded in the participant's source document.

Such treatments/medications include but are not limited to

- Medications or vaccines.
- Over-the-counter or prescription medicines.
- Recreational drugs.
- Vitamins.
- Herbal supplements.
- Medications relevant to the eligibility criteria.
- Other specific categories of interest.

Prior medications/treatments are defined as those that were received within 60 days before the screening visit (Visit 1) (or PK equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol-defined follow-up period).

Concomitant medications/treatments are defined as those given in addition to the study intervention between the signing of the ICF and participant completion.

Concomitant medications may be prescribed by a physician or obtained by the participant over-the-counter. Concomitant medication is not provided by the sponsor.

At each study visit, participants will be asked whether they have taken any medication or received any treatment other than the study intervention.

Information to be recorded will include:

- Identification of the medication or treatment.
- Reason for use.
- Dates of treatment/medication administration: start and end dates.
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

8.1.4. Diagnostic Criteria/Disease Classification

8.1.4.1. Diagnostic Criteria for NT1

ICSD-3 criteria for NT1 are provided in [Appendix 3](#).

8.1.4.2. HLA Genotyping

HLA DQB1*06:02 typing will be obtained from participants during screening unless previous HLA results are reviewed and accepted by the PI and included in the source study documentation. Almost all patients with NT1 who experience cataplectic attacks have this HLA genotype (heterozygous or homozygous expression), which has been found to correlate with low OX concentrations in the CSF. Therefore, this genotype is viewed as a surrogate biomarker in the right clinical setting.

8.1.5. Administrative Procedures (Contingency Measures for 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 SOA (see [Table 1.a](#)), 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 participants active in the study, all attempts should be made to perform the assessments with the participant 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 the COVID-19 pandemic or similar unavoidable circumstances, must contact the sponsor or designee to discuss individual participant 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 participants in the study despite departures from the SOA (see [Table 1.a](#)). The PI is expected to evaluate the impact to the safety of the study participants and site personnel for participants to continue. In evaluating such requests, the sponsor or designee will give the highest priority to the safety and welfare of the participants. Participants must be willing and able to continue taking study drug and remain compliant with the protocol.
 - Alternative methods for conducting participant 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 participant to miss an in-person study visit, a study site physician will speak directly with the participant by telephone or other medium (eg, a

computer-based video communication) during each visit window to assess participant safety and overall clinical status.

- The study site physician or other qualified site personnel should conduct the following assessments within specified-visit window time frames: 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.
 - Vaccinations within 48 hours before check-in at any visit will not be allowed. Participants may choose to get a COVID-19 vaccine at any other 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 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 approximately 2 weeks between successive visits at which clinical laboratory tests are performed and vital signs are measured. Should the period of 4 weeks be met for a particular participant, the site should contact the sponsor or designee to discuss withdrawal of the participant. Local laboratories may be used if necessary.
- Study site personnel may dispense additional study drug to participants at a visit to allow for potentially longer intervals between visits than originally planned per protocol, or study drug may be supplied to participants via delivery by site personnel or by courier.
 - Early termination visits should be performed in person. When it is not possible for the participant 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 participant's residence and conduct the protocol-specified procedures in that location. Assessments collected at a participant'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.

8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SOA ([Table 1.a](#)).

8.2.1. Primary Efficacy Measurement

The MWT is a validated, objective measure that evaluates a person's ability to remain awake under soporific conditions for a defined period of time. Because there is no biological measure of wakefulness, wakefulness is measured indirectly by the inability or delayed tendency to fall asleep. This tendency to fall asleep is measured via electroencephalography-derived sleep latency in the MWT. One session, that includes four 40-minute MWTs, will be done on each day specified in the SOA. Sleep latency in each session will be recorded. Participants will be required to stay awake in between the 4 MWT tests in each session.

During each MWT, participants will be instructed to sit in a bed or reclining chair and remain awake for as long as possible in a dimly lit room. Sessions are ended after 40 minutes if no sleep occurs. 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.

8.2.2. Other

8.2.2.1. nPSG

The nPSG is a standardized procedure used to assess various sleep parameters, including sleep latency and sleep architecture. In this study, nPSG will be used to evaluate the effects of TAK-861 on sleep latency and nighttime sleep architecture. Participants with narcolepsy have disrupted nighttime sleep, with frequent awakenings and shorter REM latency that may cause sleep paralysis and hypnagogic/hypnopompic hallucinations. In this study, there will be exploratory evaluation for changes in nighttime sleep metrics after TAK-861 multiple dosing. The standard sleep parameters will be captured as described in the study procedure manual. The raw EEG data obtained in this study may be used for exploratory evaluation of PD effects.

Participants who use CPAP regularly at home should use CPAP during nPSG.

8.2.2.2. Cognitive Assessments

8.2.2.2.1. PVT

The PVT is a simple reaction performance task that aims to measure sustained attention with no learning effects over repeated administration. Differences between healthy controls and patients with narcolepsy have been found on PVT performance for reaction time, accuracy, and other measures. The PVT is sensitive to the effects of total sleep loss, partial sleep restriction, naps, and circadian variation in the healthy population. In this study, the PVT will be administered to assess sustained attention on selected days after TAK-861 administration.

Duration of test: 10 minutes

8.2.2.2.2. CPAL

The CPAL test is a measure of visual associate memory and uses a well-validated paired associate learning paradigm in which the participant must learn the locations of a number of

amoeba-like shapes on the computer screen. This test consists of a single amoeboid shape displayed in the center of the screen surrounded by a number of blue-filled circles. In the exposure phase of the test all of the to-be-remembered pattern-location associations are presented on the computer screen simultaneously. After a 5-second delay, a pattern is shown in the central location and this signals that the participant should touch the location in the periphery that contains the same pattern. This process continues until the participant has acknowledged all of the pattern-location associations. The learning phase begins with the same test display presented during the exposure phase except that now all of the peripheral locations are shown as blue spheres. One of the patterns presented in the exposure phase is presented in the center location. With the presentation of this pattern, the participant is required to select the peripheral location where an identical pattern is hidden beneath the blue sphere. This process continues until the correct location of each pattern is found. Finding the correct location for all patterns in the set is defined as a learning trial. The software records each move as an error or as a correct move.

Duration of test: 7 minutes

8.2.2.2.3. ONB

The ONB test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The participant is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The participant responds by pressing the Yes or No key. Because no card has been presented yet on the first trial, a correct first response is always No. The software measures the speed and accuracy of each response.

Duration of test: 4 minutes

8.2.2.2.4. iDSST-s

The iDSST-s is a processing speed test that is based on the pre-existing pencil and paper version of the Digit Symbol Substitution Test. In this test, participants are presented with a legend that defines 9 symbols, with each symbol corresponding to a digit from 1 to 9. The participant is then presented with a conveyer belt in the middle of the screen that displays a series of empty boxes labelled with a number. The participant must select the symbol that corresponds to the number of a given highlighted box from symbol options presented at the bottom of the screen. The participant must try to place as many correct symbols in the boxes as possible over the duration of the test. Performance is measured by calculating the total number of correct responses.

8.2.2.3. Clinical Outcome Assessments

8.2.2.3.1. 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) 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 reference range.

In this study, the ESS will be administered to assess sleep propensity on selected days after TAK-861 administration. Participants will be asked to evaluate their subjective sleepiness based on recalling their most recent daily life experiences.

8.2.2.3.2. Clinical Global Impression Scales

The Clinical Global Impression Scale provides an overall clinician-determined summary measure of a participant's treatment experience that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. The assessment consists of 2 subscales, the Clinical Global Impression-Severity (CGI-S) and the CGI-I, which assess severity and improvement of symptoms, respectively.

The CGI-S will assess severity of overall narcolepsy symptoms. It uses a 7-point Likert-type scale ranging from "normal, not at all ill" to "among the most extremely ill patients." The CGI-I asks clinicians to rate the extent to which their patients' current overall narcolepsy symptoms are improved (compared with the start of the study). This assessment uses a 7-point Likert-type scale ranging from "very much improved" to "very much worse". Clinicians will be trained on what aspects to take into consideration when rating the CGI-I to ensure consistency of responses.

It is strongly recommended that the same clinician administers the CGI-S at baseline and CGI-I at every visit after randomization, except for the follow-up visits, for the same participant.

8.2.2.3.3. Patient Global Impression Scales

The Patient Global Impression rating scales capture global effect of TAK-861 on daytime sleepiness, cataplexy, and overall narcolepsy symptoms as perceived by the participant and provide "anchors" to determine clinically relevant effects.

The Patient Global Impression - Severity (PGI-S) requires the participant to rate his/her disease severity at the time of assessment on a 4 point scale ranging from "normal" to "severe." The PGI-I measures improvement due to treatment relative to baseline on a 7-point scale ranging from "very much improved" to "very much worse".

In this study, the PGI-S will be administered at baseline to assess the severity of overall narcolepsy symptoms and the PGI-I will be administered thereafter to assess improvement in overall narcolepsy symptoms. Instructions will be provided to the participant to help ensure consistency in the tests. The PGI-I will be administered similarly to the CGI-S and CGI-I.

8.2.2.3.4. EQ-5D-5L

The EQ-5D-5L is a standardized 5-item measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal that has been used in a wide range of health conditions and treatments ([Herdman et al., 2011](#), [Janssen et al., 2013](#)). The EQ-5D-5L consists of a descriptive system and the EuroQol visual analog scale (VAS). The descriptive system comprises 5 dimensions: mobility, self-care, usual activities,

pain/discomfort, and anxiety/depression. The EuroQol VAS records the participant's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the participant's own judgment. The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared with other health profiles.

8.2.2.3.5. Functional Impacts of Narcolepsy

The Functional Impacts of Narcolepsy (FIN) is a narcolepsy-specific 11-item instrument that assesses functional impacts of narcolepsy across 3 domains: social activities, everyday activities, and everyday responsibilities.

In this study, the FIN will be administered to assess the effect of TAK-861 on NT1 functional impacts at specified time points during the study.

8.2.2.3.6. NSS-CT

The NSS-CT is a 15-item self-administered questionnaire (score: 0-57) that assesses the severity and consequences of the 5 major narcolepsy symptoms such as daytime sleepiness, cataplexy, hallucinations, sleep paralysis, and DNS. In a study conducted by Dauvilliers et al, the authors investigated the validity of the NSS and found that the mean symptom number, NSS total score, and number of narcolepsy symptoms were statistically significantly different between treated and untreated patients. Further, the symptom number was associated with diagnosis delay, age at onset, and ESS and Beck Depression Inventory scores (Dauvilliers et al., 2020).

In this study, the NSS-CT will be administered to assess the impact of TAK-861 on NT1 symptoms at specified time points during the study.

8.2.2.3.7. SF-36

The SF-36 is a 36-item, participant-reported survey of participant health. The SF-36 consists of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability, that is, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

8.2.2.3.8. TSQM

The TSQM vII is a generic patient-reported outcome assessment that measures satisfaction with treatment in 4 key dimensions: effectiveness, side effects, convenience and global satisfaction. TSQM vII is an 11-item questionnaire domains: effectiveness (items 1 - 2), side effects (items 3 - 6), convenience (items 7-9) and global satisfaction (items 10-11) (Atkinson et al., 2005). Responses to these 11 items are summed and transformed on a 0-100 score, with higher scores indicating better treatment satisfaction.

8.2.2.3.9. Daily e-diary

Participants will complete a daily e-diary to record self-reported narcolepsy symptoms. In cases where the e-diary becomes unavailable, a site may use alternative methods to collect these data with approval from sponsor or designee.

Participants will record partial or full episodes of cataplexy, including the time of occurrence in the e-diary.

Participants will record alcohol consumption in the e-diary.

Other narcolepsy symptoms, including sleep paralysis and hypnagogic/hypnopompic hallucinations, will be self-reported by participants in the e-diary. Information on nocturnal awakenings and naps during the day will also be recorded.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SOA (see [Table 1.a](#)).

8.3.1. Physical Examinations

At screening and at the first follow-up visit, a full physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

All subsequent physical examinations should assess clinically significant changes from the baseline physical examination.

Participants undergoing optional CSF sampling during screening will undergo ophthalmological assessment of the retina (fundoscopy), a nondilated ophthalmoscopy examination to evaluate for any evidence of increased intracranial pressure. If needed, a dilated examination 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 (or available pupil dilating drugs). After pupil dilatation, participants will be advised to wear sunglasses for the next 4 to 6 hours and avoid operating a car.

8.3.2. Vital Signs

When vital signs are scheduled at the same time as blood sample collection, the blood sample collection will take priority, and vital signs will be obtained within 1.0 hour before the scheduled blood draw.

Vital signs will include: body temperature (oral or tympanic measurement), respiratory rate, BP (systolic and diastolic, with the participant resting more than 5 minutes), and pulse (in beats per minute).

The participant should be resting for a minimum of 5 minutes sitting or lying in a bed with the head of the bed at 30 degrees.

For BP assessment, the same method (ie, the same size cuff, manual or automated, sitting or lying) must be used for all measurements for each individual participant and should be the same for all participants at the study site. For screening BP assessment, if the BP is slightly elevated, the measurement may be repeated 3 times, and the median of the 3 recordings used to assess eligibility. For all other visits, a single measurement may be taken.

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

The investigator will assess whether a change in vital signs from baseline may be deemed clinically significant on the Vital Signs eCRF and whether the change should be considered and recorded as an AE on the AE eCRF.

8.3.2.1. Weight, Height, and BMI

Weight, height, and BMI will be measured and recorded.

A participant should have weight and height measured while wearing indoor clothing and with shoes off. Weight is collected in kilograms (kg). Height is recorded in centimeters (cm).

8.3.3. ECG

Participants should be resting in a semirecumbent position for at least 5 minutes before each ECG measurement. The PI should arrange to have a study cardiologist available as needed to review ECG tracings with abnormalities.

A standard 12-lead ECG will be recorded and interpretation of the ECG will be made using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The time that the ECG was performed will be recorded.

The investigator will assess whether a change in ECG from baseline may be deemed clinically significant and whether the change should be considered and recorded as an AE on the AE eCRF.

The eligibility of the participant will be based on the assessment of the ECG by the investigator.

A baseline ECG will be obtained within approximately 1 hour before dosing of study drug. If a participant has an increase in QTcF interval ≥ 40 milliseconds compared with a predose baseline measurement, the ECG will be repeated within 5 minutes. The average value of the QTcF interval from the 2 ECGs will represent the value at that time point. If the average QTcF interval increase from baseline for any postdose time point is ≥ 40 milliseconds, the participant 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 ECG should be reviewed by a cardiologist. The participant should be monitored by telemetry (until the QTcF interval is < 500 milliseconds), or the participant should be considered for transfer to a location where closer monitoring is available.

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

8.3.4. Clinical Safety Laboratory Tests

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SOA. Details about these procedures and required safety monitoring will be given in the laboratory manual.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis.

The clinical laboratory will return these results, along with their reference ranges, to the investigator. The investigator is responsible for reviewing the laboratory report, documenting this review, and filing the laboratory report with the source documents.

Abnormal laboratory findings associated with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

Clinically significant abnormal laboratory values obtained during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or the baseline value or are no longer considered clinically significant by the investigator or medical monitor. The investigator should evaluate whether the laboratory result meets the AE criteria in Section 10.3.

For participants with treatment-emergent ALT or AST $> 3 \times$ ULN and (total bilirubin $> 2 \times$ ULN or INR > 1.5), see Section 10.3.5.1 for expedited reporting and Section 10.5 for additional monitoring, evaluation, and follow-up recommendations.

If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

Investigators must document their review of each laboratory safety report.

The investigator must record the following types of laboratory test results on the laboratory eCRF and if applicable on the AE eCRF:

- Any changes that are considered clinically significant by the investigator (eg, SAE or AE or dose modification).
- Any laboratory test results (central laboratory, local laboratory, non-protocol specific local laboratory) that are used to make a study intervention decision, that require a change in participant management, or that are used to make a response evaluation.

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8.3.5. Pregnancy Testing

A serum human chorionic gonadotropin (β -HCG) pregnancy test will be performed at screening for all participants of child-bearing potential. Urine pregnancy test will be performed on all participants of child-bearing potential at times described in the SOA and if pregnancy is suspected.

If a participant or a participant's partner becomes pregnant during the study, the pregnancy must be followed as described in Section [10.4.3](#).

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Two versions of C-SSRS will be used to assess suicidal ideation in this study: the Screening/Baseline C-SSRS Lifetime and the Since-Last-Visit C-SSRS. Any suicidal ideation or suicidal behavior during the study 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.

8.3.7. Other

8.3.7.1. Actigraphy (Accelerometry)

At screening and throughout the study until up to the first follow-up or rollover into the LTE, all participants will be instructed to wear a wrist device containing an accelerometer and photoplethysmography sensor as much as possible throughout the day and night.

8.3.7.2. ABPM

ABPM readings should be obtained over an approximately 24.5-hour period and participants should not be confined to the clinical site during most of the 24.5-hour recording period. The ABPM device should be applied on-site or by home healthcare personnel. Because it is a requirement that the ABPM devices begin recording in the morning before the first morning dose, site staff may opt to confine participants in the evening before fitting participants with the ABPM monitoring device. If the participant is travelling to the site for the ABPM fitting or waiting the arrival of home health personnel, they may delay their first morning dose of study medication (between 8:00 AM \pm 2 hours) if needed. Participants who are confined the evening prior should also take their study drug right after the ABPM recording starts. Participant will need to return to the clinic or be visited by home healthcare personnel 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 time frame (avoiding nights immediately before nPSG or MWT).

Participants will be trained on the use of the device.

8.3.8. AEs, SAEs, and Other Safety Reporting

The definitions of AEs and SAEs are provided in Section [10.3](#).

The investigator and any qualified designees are responsible for collecting, detecting, documenting, and recording events that meet the definition of an AE or SAE. They remain responsible for follow-up of these events (see Section 10.3.4).

8.3.8.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until final follow-up visit or rollover into the LTE at the time points specified in the SOA (see Table 1.a).

All SAEs will be recorded and reported to the sponsor or designee immediately. Under no circumstance should this exceed 24 hours. The investigator will also submit any updated SAE data within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor via the reporting method described in Section 10.3.4.6.

8.3.8.2. Method of Detecting AEs and SAEs

At each study visit specified in the SOA, participants will be questioned in a general way to ascertain if AEs have occurred since the previous visit. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences without introducing bias. Participants may report AEs occurring at any time during the study.

8.3.8.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All participants experiencing AEs, whether considered associated with the use of the study drug or not, will be documented in the AE page of the eCRF.

All AEs must be monitored until the end of the study or until the event resolves, stabilizes, is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

SAEs must be monitored until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

Information to be documented for each event is defined in Section 10.3.4.

Further information on follow-up procedures is provided in Section 10.3.

8.3.8.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific

regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with similar documents containing safety information and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.8.5. Pregnancy in a Participant or Participant's Partner During the Study

Details about all unplanned/accidental pregnancies in participants or their partners will be collected after the start of study intervention and until 5 half-lives PLUS 90 days after the last dose of study drug. Collection of pregnancy data from a participant's partner requires the partner's informed consent.

To the extent possible, the investigator will collect follow-up information on the outcome of the pregnancy and the neonate, and the information will be forwarded to the sponsor.

Once a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours.

Pregnancy itself is not considered to be an AE or SAE; however, AEs or SAEs associated with pregnancy must be reported as such, including:

- Any pregnancy complication or elective termination of a pregnancy for medical reasons (to be reported as an AE or SAE).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) (to be reported as SAEs).

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.3.4.6. Although the investigator is not obligated to actively seek post study pregnancy-related SAE information from former study participants or their partners, he or she may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.3.8.6. AEs of Special Interest

See Section 10.3.3.2.

8.4 PK

The PK parameters of TAK-861 for each treatment group will be determined from plasma concentrations on study days with serial PK sampling time points, as data permit (see Table 1.a) using noncompartmental analysis methods. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following PK parameters will be assessed: AUC_{last} , C_{max} , and t_{max} .

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

8.4.1. PK Sample Collection and Analysis

Blood samples (1 sample per scheduled time) for plasma TAK-861 concentration will be collected according to the SOA (Table 1.a). Additional blood samples will be collected pre 8AM dose on the days specified in the SOA (Table 1.a) for measurement of the 4 β -hydroxycholesterol/cholesterol ratio to assess cytochrome P450 (CYP) type 3A4/5 activity.

The actual date and time of sample collection and the date and time of study drug dosing for the most recent dose will be recorded on the source document and eCRF. Sampling time points may be adjusted on the basis of the preliminary emerging concentration data collected from prior participant(s), but the total number of samples collected per participant should not exceed the planned number.

Plasma concentrations of TAK-861 and plasma concentrations of 4 β -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.

Instructions for collecting, processing, and shipping of PK samples are provided in the laboratory manual.

8.5 Genetics

8.5.1. DNA Analysis Measurements

Sampling of whole blood genomics (DNA analysis) is optional in this study and will only be performed for participants who provide consent to participate in this assessment.

There is increasing evidence that an individual's genetic background may impact the PK (absorption, distribution, metabolism, and excretion), PD (pharmacologic effects), and/or clinical effects (efficacy and/or safety) of a drug. DNA research in this study may be conducted to understand how individual genetic variation in participants impacts their response to study drug treatment. This information may also be used, for example, to develop a better understanding of the safety, resistance to, and/or efficacy of TAK-861 and other study drugs; to increase understanding of the disease/condition being studied and other related conditions; to gain a better understanding of the drug pharmacology; and to generate information needed for research, development, and regulatory approval of tests to predict response to TAK-861.

A whole blood sample for DNA isolation will be collected from each participant who provides a separate informed consent. If necessary and feasible, another aliquot of blood may be taken at a later time point if isolation of DNA from the first sample was not successful or possible.

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

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

Detailed instructions for biological sample retention and destruction are provided in the ICF.

Detailed instructions for the handling and shipping of samples are provided in the Central Laboratory Reference Document.

8.5.2. HLA Genotyping

See Section [8.1.4.2](#)

8.6 CSF Orexin Measurements

CSF OX samples will be collected according to the SOA (see [Table 1.a](#)).

Participants with NT1 may 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, or exploratory biomarkers related to OX biology, will be measured in the CSF samples. Instructions for collecting, processing, and shipping of CSF samples are provided in the Central Laboratory Reference Document.

8.7 Immunogenicity Assessments

Not applicable.

9. Statistical Considerations

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

9.1 Statistical Hypotheses

9.1.1. Primary Endpoint

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the mean sleep latency (minutes) from the 4 sessions of a 40-minute MWT. The statistical null hypothesis is that the mean change from baseline to Week 8 in the mean sleep latency for each TAK-861 treatment group is the same as the mean change from baseline to Week 8 in the mean sleep latency for the placebo treatment group.

9.1.2. Secondary Endpoints

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the total ESS score. The statistical null hypothesis is that the mean change from baseline to Week 8 in the

total ESS score for each TAK-861 treatment group is the same as the mean change from baseline to Week 8 for the placebo treatment group.

TAK-861 is superior to placebo as measured by the WCR at Week 8. The statistical null hypothesis is that the incidence rate ratio (TAK-861 to placebo) of WCR at Week 8 is equal to 1.

9.2 Analysis Sets

9.2.1. Safety Set

The safety set will consist of all participants who received at least 1 dose of study drug. This analysis set will be used for demographic, baseline characteristic, and safety summaries.

9.2.2. PK Set

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

9.2.3. Full Analysis Set

The full analysis set will consist of all participants who were randomized and received at least 1 dose of study drug. The full analysis set will be used for summaries of efficacy endpoints.

9.3 Efficacy Analyses

9.3.1. Primary Efficacy Endpoint

The change from baseline in mean sleep latency will be analyzed using a linear mixed model for repeated measures (MMRM), with visit, treatment, and treatment-by-visit interaction as the fixed effects. Baseline age and mean sleep latency will be included as covariates. The estimated change from baseline in the mean sleep latency for each treatment and the associated SE and 95% CIs will be extracted from the model, along with all estimated treatment differences from placebo and associated SEs, 95% CIs, and p-values.

9.3.2. Secondary Efficacy Endpoints

The change from baseline in ESS total score will also be evaluated using a linear MMRM with the baseline value as a covariate.

The WCR will be analyzed by generalized estimating equations using a log-link featuring a Poisson distribution. The model will include fixed effects for visit, treatment, and treatment-by-visit interaction. The baseline WCR will be included as a covariate. The estimated incidence rate of weekly cataplexy for each treatment and the associated SE and 95% CIs will be extracted from the model, along with the incidence rate ratio of weekly cataplexy (TAK-861 to placebo) for all TAK-861 treatment groups, and the associated SEs, 95% CIs, and p-values.

9.3.3. Multiplicity Adjustment

There will be no multiplicity adjustment for this phase 2 dose ranging study.

9.4 Safety Analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of TEAEs will be presented by System Organ Class and Preferred Term. TEAEs will be further summarized by severity and relationship to the intervention(s). AEs related to the intervention(s), AEs leading to study drug discontinuation, SAEs, and deaths will be similarly summarized.

TEAEs will be summarized by treatment group. Observed values and change from baseline in safety clinical laboratory measurements, vital signs, and ECG parameters will be summarized by treatment group. The number and percent of participants meeting the MAV criteria for safety laboratory tests, vital signs, and ECGs will be summarized by treatment group.

9.5 Other Analyses

9.5.1. PK Analyses

Individual plasma concentrations of TAK-861 will be listed for each participant and summarized for each dose by using descriptive statistics (arithmetic mean, SD, coefficient of variation, median, minimum, maximum, and geometric mean), as deemed appropriate. Individual plasma noncompartmental analysis PK parameters will be tabulated and summarized descriptively by day for each dose. The 4 β -hydroxycholesterol/cholesterol ratio, measured pre 8AM dose throughout the treatment period, will also be summarized descriptively for each treatment to assess CYP3A4/5 activity over time.

TAK-861 plasma concentration-time data collected in this study may be combined with other clinical study data to develop a population PK model of TAK-861 in participants with NT1. 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.

9.5.2. PK/PD Analyses

Exploratory PK/PD evaluations may be carried out to assess the relationships between TAK-861 plasma concentrations and selected PD measures (eg, MWT sleep latency, ESS score, and WCR) and safety (eg, BP) will be explored, as deemed appropriate. The exposure metric (eg, instantaneous concentration or cumulative exposure, like area under the curve) will be appropriately selected by visual inspection of the relationship as well as the underlying pharmacology.

9.6 Interim/Intermediate Analysis

An interim analysis may occur when at least 40 participants have completed the Week 4 visit. In this case, an Internal Review Committee, composed of members who do not have study-related contact with sites, will review the study data. The decision criteria and review process will be described in the IRC charter and/or Statistical Analysis Plan. Based on review of efficacy and safety data, one or more dose arms or the study may be discontinued.

9.7 Determination of Sample Size

Assuming an SD of 11 minutes, a sample size of 16 participants per treatment group completing 8 weeks is enough to achieve >90% power to detect a difference of 14 minutes between a TAK-861 dose and placebo by a 2-sample t-test on the change from baseline to Week 8 in mean sleep latency from 4 MWT sessions at 0.05 2-sided significance level. Assuming a 20% dropout rate, 20 participants per treatment group may be enrolled for a total of up to 100 participants.

This sample size will also provide 88% power to detect a difference of 8 points between TAK-861 and placebo by a 2-sample t-test on the change from baseline to Week 8 in ESS total scores at 0.05 2-sided significance level, assuming an SD of 7 points.

In addition, this sample size will provide approximately 86% power to detect a 50% reduction in WCR relative to placebo with TAK-861 using a Poisson model at 0.025 1-sided significance level, assuming a baseline WCR of 4, with a placebo effect of 25% reduction from baseline.

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10. Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted with the highest respect for the individual participants according to the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP.

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, current ICH GCP Guidelines, as well as all applicable national and local laws and regulations.

10.1.2. Financial Disclosure

Takeda is funding this study and will make payments to the study site for the conduct of the study (and, if applicable, investigators and/or other study staff), as specified in the Clinical Study Site Agreement(s).

Regulatory authorities including the Food and Drug Administration require Takeda to submit disclosures of investigators' and subinvestigators' financial interests and arrangements. For this reason, Takeda will provide the investigators and sub-investigators with a form for the disclosure of their financial arrangements during the course of the study and for 1 year after the completion of the study.

The financial disclosure form must be signed by each investigator and sub-investigator before the study starts at their study site. Any potential conflicts of interest that are not covered by this form should be disclosed separately to Takeda before the start of the study at their site.

Specific financial arrangements requiring disclosure would include any arrangement whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. Examples include: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria; any proprietary interest in study intervention; and any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations 54.2(b) (1998).

The investigator and sub-investigator should declare all institutional affiliations on the curriculum vitae that they provided to sponsor before the start of the study.

10.1.3. Informed Consent Process

It is the responsibility of the investigator to obtain written and/or electronic informed consent from all participants before any study-related procedures including screening assessments. All eConsent documentation must be in accordance with applicable regulations and GCP:

The participants must receive an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the participant's rights

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and responsibilities. eConsent provides the same information as written consent forms, but in an electronic format that may include multimedia components. eConsent does not replace the important discussion between the study participant and site staff or investigator. Regardless of the consent format – written or eConsent – the investigational site is responsible for the consenting process.

After the participant has received and read (or been read) the participant information, they will be requested to sign and date the informed eConsent form or a certified translation if applicable. Persons consenting via eConsent, where available, will electronically sign consent forms. (Paper consent forms will be used instead, if required by local regulations.)

A copy of the informed eConsent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant, as applicable. This document may require translation into the local language. Signed eConsent forms must remain in each participant's study file at the site (either in their original, signed paper form or as a certified copy if applicable for electronic signature) and must be available for verification at any time.

The PI provides the sponsor with a copy of the eConsent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor before the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) before study start that another party is responsible for this action. Additionally, if the IRB/IEC requires modification of the sample participant information and eConsent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.1.4. Data Protection

The confidentiality of records that may be able to identify participants will be protected in accordance with applicable laws, regulations, and guidelines.

After participants have consented to take part in the study, the sponsor and/or its representatives reviews their source documents and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market TAK-861; national or local regulatory authorities; and the IRB(s)/IEC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of participants' identities. Participants are assigned a unique identifying number; however, their initials and date of birth may also be collected, if permitted under local laws governing privacy.

The results of studies containing participants' unique identifying number, relevant source documents, and possibly initials and dates of birth, where allowed per local law, may be transferred to, and used in, other countries that may not afford the same level of protection that

applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

- The sponsor will assign each participant a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The investigator must inform the participant that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.
- The investigator must inform the participant that their source documents may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

All United States-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996. A site that is not a covered entity as defined by Health Insurance Portability and Accountability Act must provide documentation of this fact to the sponsor or designee.

10.1.4.1. Notice Regarding the Use and Transfer of the Investigator's Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and telephone number, and other personally identifiable information such as education and professional details, payment-related details (if applicable), identity information (eg, medical registration number) and information relating to his or her interactions and activities with or involving Takeda. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world including the following:

- Takeda, its affiliates, and their licensing partners.
- Business partners assisting Takeda, its affiliates, and their licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.
- Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:
 - Assessment of the suitability of investigator for the study and/or other clinical studies.
 - Management, monitoring, inspection, and audit of the study.
 - Analysis, review, and verification of the study results.
 - Safety reporting and pharmacovigilance relating to the study.

- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

In addition, where required by law or industry codes of practice, Takeda and/or its affiliates may have to report or publicly disclose any payments or transfers of value made in connection with the study by or on behalf of Takeda and/or its affiliates or their service providers to the investigator or their institution.

The legal basis on which Takeda and its affiliates will process the investigator's personal information for the above purposes are to comply with a legal obligation; or to perform any contract in place with the investigator (if applicable); or to meet the legitimate research, scientific and business interests of Takeda and its affiliates, including ensuring the proper performance of this study to the applicable standards, appropriate reporting of study results and archiving of study-related records and information, and further development and registration of the study drug or other compounds. The investigator may not be able to opt-out of this processing, or the investigator's choice to opt-out may impact his or her ability to continue to participate in this study and/or future studies involving Takeda and/or its affiliates.

Takeda and its affiliates will maintain physical, administrative and technical safeguards to protect the investigator's personal information from loss, misuse, unauthorized access, disclosure, alteration or destruction. 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.

However, where investigator's personal information is transferred to Takeda affiliates, licensing partners, business partners or service providers in such countries, Takeda will ensure that all adequate safeguards are in place and that all applicable laws and regulations are complied with in connection with such transfers.

The investigator's personal information will only be stored as long as necessary for the purposes for which it was collected participant to local laws and regulations and legitimate scientific, research and business needs.

Individuals located in the European Economic Area and in certain other countries have certain data participant rights which may be participant to limitations and/or restrictions. These rights include the right to: (i) request access to and rectification or erasure of their personal data; (ii)

obtain restriction of processing or to object to processing of their personal data; (iii) the right to data portability; and (iv) obtain additional information regarding the safeguards Takeda has in place for cross-border transfers of their personal data. If the investigator wishes to exercise one of these rights, the investigator may use the contact information below.

Individuals located in the European Economic Area and in certain other countries may also have the right to lodge a complaint about the processing of their personal data with their local data protection authority.

The investigator can contact Takeda to exercise his or her rights, make inquiries or submit complaints concerning Takeda's processing of his or her personal information. Takeda will take appropriate steps to address requests, inquiries and complaints. Takeda will respond to such requests within thirty (30) business days.

Contact Details:

Mailing Address: Attn: Data Protection Officer, Legal Department, Takeda Pharmaceuticals International AG, Thurgauerstrasse 130, CH-8152 Glattpark-Opfikon (Zurich), Switzerland.

Email Address: dataprivacy@takeda.com

The investigator acknowledges and authorizes the use of his or her personal information by Takeda and other parties for the purposes described above.

10.1.5. Committees Structure

10.1.5.1. IRB and/or IEC Approval

IRBs/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 IRBs/IECs. If any member of the IRBs/IECs 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 Federalwide 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 IRBs/IECs for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRBs/IECs for approval.

The IRB's/IEC's written approval of the protocol and participant ICF 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 IRBs/IECs approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If

required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including screening may occur.

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

Participant incentives should not exert undue influence for participation. Payments to participants must be approved by the IRBs/IECs and sponsor.

10.1.5.2. Other Committees

An Internal Review Committee, composed of members who do not have contact with investigators or sites, may review the study data at IA and determine if dose arms or the study will be discontinued.

An external data monitoring committee (DMC) will be put in place for this study to review the safety and tolerability data on a quarterly basis, throughout the study. A DMC charter will provide full guidance on the function and practices to be followed by the DMC.

10.1.6. Dissemination of Clinical Study Data

10.1.6.1. Study Results Disclosure

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register all interventional clinical trials and disclose the results of those trials in a manner and time frame compliant with Takeda policy and all applicable laws and regulations. Clinical trial registration and results disclosures will occur on ClinicalTrials.gov, other clinical trial registries/databases as required by law, and on Takeda's corporate website(s).

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The sponsor will supply the eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF before transmitting it to the sponsor.

Guidance on completion of eCRFs will be provided in CRF completion guidelines.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan/contracts.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, participants' source documents, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations [CROs]).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.7.1. Protocol Deviations

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

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

10.1.7.2. 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 the study site head guarantee access to source documents by the sponsor or its designee (CRO and/or auditor) and by the IRB/IEC or any other health authority governing the study, per local/regional regulation.

Alternative approaches may be used to ensure data quality, data integrity, and participant safety (eg, remote source data review/source data verification via phone or video) as permitted by regional and local regulations. See the monitoring plan for additional details.

10.1.7.3. Audits

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. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately.

The investigator and head of the study site (Japan only) study site guarantee access for quality assurance auditors to all study documents as described in Section [10.1.8](#).

10.1.8. Source Documents

All key data must be recorded in the participant's source documents unless otherwise noted in the protocol. Source documents may be paper or electronic, including data obtained using electronic devices and associated technologies. Original source data to be reviewed during this study will include, but are not limited to: participant's medical file, appointment books, diaries, clinical outcome assessments, original clinical laboratory reports, histology reports, pathology reports, x-rays. The investigator is responsible for maintaining adequate and accurate source documents.

The investigator must provide direct access to inspect facilities, including original source records relevant to this study (regardless of media), to: the sponsor or its authorized representatives; the respective national, local, or foreign regulatory authorities; the IRB/IEC; and auditors. These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency or an auditor. The eConsent form includes a statement granting this access to source data.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.1.8.1. eCRFs

Completed eCRFs are required for each participant who has completed the consent process. The eCRFs are designed to record all observations and other data pertinent to the clinical investigation unless otherwise noted in the protocol. Laboratory data, electronic patient reported outcome, electronic clinical outcome assessment, MWT, nPSG, ECG, ABPM, and actigraphy data is collected electronically and will be transmitted directly via secure transfer.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor or designee will 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. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. eCRFs must be completed in English.

The investigator has full responsibility for the accuracy and authenticity of all data entered on the eCRFs. Details are provided in Section [10.1.11.2](#).

A study monitor from the sponsor or its designee will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Auditors, IRB/IEC members, or regulatory inspectors may also check the eCRF entries against the source documents.

Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel.

After the lock of the 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.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should also be included. The PI must review the data change for completeness and accuracy, and must sign, or sign and seal, and date. In Japan, the eCRF Data Clarification Form will be provided by the sponsor or designee.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values.

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.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

10.1.8.2. Documentation and Retention of Records

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. A definition of what constitutes source data and its origin can be found in Section [10.1.8.4](#).

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous source documents or transfer records, depending on the study. Also, current source documents must be available.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. A risk-based monitoring approach will be used.

10.1.8.3. Data Handling

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

Data are to be entered into a clinical database as specified in the data management plan or similar. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

10.1.8.4. Record Retention

The following procedure applies to countries other than Japan.

The investigator agrees to keep the records stipulated in Section 10.1.8.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, source documents, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed eConsent forms (including consent to use digital tools and applications, if applicable), participant authorization forms regarding the use of personal health information (if separate from the informed eConsent forms), query responses/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 participant's chart to ensure long-term legibility. Furthermore, ICH E6(R2) Section 5.5.11 requires the investigator to retain essential documents specified in ICH E6(R2) (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(R2) Section 5.5.11 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 study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

The following procedure applies to sites in Japan only:

The investigator and the head of the study site agree to keep the records stipulated in Section 10.1.8.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating participants, source documents, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed eConsent forms, participant authorization forms regarding the use of personal health information (if separate from the informed eConsent forms), telemedicine records, and query responses/ 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 participant's chart to ensure long-term legibility. The investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor:

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued).
2. The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

When proceeding to the local postmarketing study, the investigator and the head of the institution are required to retain essential relevant documents until the end of re-examination or re-evaluation, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The first act of recruitment is the first site open.

For clinical trial disclosure purposes, the study start date is the date when the first participant signed the ICF.

10.1.9.2. Study/Site Termination

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. The sponsor reserves the right to close the study site at its sole discretion. Study sites will be

closed on study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, CRO(s), and IRBs/IECs are notified as appropriate and as specified in applicable regulatory requirements. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. Further, the investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up. If the study is terminated, the sponsor will make an end of study declaration to the relevant competent authority as required by Article 10(e) of Directive 2001/20/EC and the European Union (EU) Clinical Trial Regulation.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- For study termination or suspension:
 - Discontinuation of further study intervention development.
 - New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known benefit-risk profile for TAK-861 such that the benefit-risk is no longer acceptable for participants participating in the study.
 - The DMC recommends that the study should be suspended or terminated.
 - A finding (eg, PK, PD) from another nonclinical or clinical study using the study drug leads to the study being stopped for reasons unrelated to safety.
 - Data from drug(s) of the same class or methodology (or methodologies) used in this study become available and result in the study being stopped for reasons unrelated to safety.
 - Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises participant safety.
 - The sponsor terminates or suspends the study at any time for any other clinical or administrative reasons, eg, slow enrollment.
- For site termination or suspension:
 - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
 - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
 - Total number of participants enrolled earlier than expected.

Finally, if any criterion below is met, the DMC will review the data and determine whether there is a need to terminate the study or any dose arms.

- LFT abnormalities: 2 or more participants meet the individual participant stopping criteria for LFT abnormalities.
- 4 or more participants meet individual participant stopping criteria for AEs or discontinue the study for other safety reasons.
- SAE: 3 or more experience a similar SAE that is drug-related in investigator's opinion.
- 1 or more deaths occur determined by the investigator to be related to study medication.

Duration of test: 3 minutes

10.1.9.3. Optional Study Participant Interviews

Participants who complete the TAK-861-2001 Phase 2 study may be asked whether they are interested in participating in a separate qualitative interview study to share their clinical trial experience. The qualitative interview study would have a separate protocol and ICF.

10.1.10. Publication Policy

Both during and after this study, all public disclosures containing data/information from this study must undergo **review and receive written approval** by the appropriate Takeda representative(s) **before** any public disclosure (including but not limited to submission, presentation, posting on online platforms for archiving, and distribution of unpublished preprints).

This policy applies to all publication types, including: abstracts and presentations (oral and poster, including invited presentations) for scientific congresses; articles (original research manuscripts, review articles, invited articles), letters to the editor, and editorials, in scientific peer-reviewed journals; print, electronic and enhanced multimedia publications associated with traditional congress and journal publishing (such as, but not limited to, audio, visual/graphical or video abstracts or manuscript summaries; video or animated posters; augmented reality); books and book chapters.

Authorship will be determined in line with the requirements of the International Committee of Medical Journal Editors Recommendation for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical journals, unless otherwise required by the journal or forum where the publication appears.

Publications derived from this study may never contain participants' direct identifiers (such as participant identification number, initials) but may contain indirect/quasi identifiers (for example sex/gender, age/birth date, geographic indicators). Publications derived from this study may not include products' direct identifiers (lot numbers or batch numbers) unless specifically required by the journal or conference guidelines and if approved by Takeda.

10.1.11. Responsibilities of the Sponsor and the Investigator

10.1.11.1. Sponsor Responsibilities

The sponsor is responsible for designing and performing the study in accordance with ICH GCP Guideline E6, EU Directive 2001/20/EC, other applicable regulatory requirements and guidelines, and rules considering the rights, safety, and well-being of human participants.

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform these activities either in full or in partnership with the sponsor.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required before release of study intervention for shipment to the site.

Takeda is funding the study and is responsible for collecting financial disclosure information from investigators and sub-investigators, for submission to regulatory authorities (Section 10.1.2).

The sponsor/ designee will supply the following:

- Documentation required for the study conduct including but not limited to the study protocol, IB, study operations manual, other study conduct/ management documents and sample informed consent.
- Access to the IEC/IRB-approved version via an eConsent platform (Section 10.1.3).
- eCRFs, data management, and site monitoring (Section 10.1.7), including reconciliation with source documents (Section 10.1.8).

The sponsor is responsible for protecting the confidentiality of participants' data (Section 10.1.4).

The sponsor will fulfill its role in forming and managing any special committees as described in Section 10.1.5.

The sponsor is responsible for the reporting of data to regulators and the public disclosure of data as described in (Section 10.1.6). The sponsor is also responsible for maintaining a publication policy (Section 10.1.10) that balances the protection of participants' data (Section 10.1.4), public disclosure requirements (Section 10.1.6), and industry publication standards.

The sponsor and/or designee selects sites and performs study site start and closure activities (Section 10.1.9).

The sponsor will supply insurance for each participant in the study in accordance with the regulations applicable to the site where the participant 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 participants. Refer to the study site agreement regarding the sponsor's

policy on participant compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

10.1.11.2. Investigator Responsibilities

The investigator must perform the study in accordance with ICH GCP Guideline E6, EU Directive 2001/20/EC, other applicable regulatory requirements and guidelines, and rules considering the rights, safety, and well-being of human participants.

The investigator and any sub-investigators must adhere to this protocol, with major responsibilities summarized below.

It is the investigator's responsibility to ensure that adequate time, resources, and appropriately trained personnel are available before committing to participate in this study.

Each of the investigators will maintain a list of appropriately qualified persons to whom they have delegated significant study-related tasks. Investigators will provide their own curricula vitae and those of their sub-investigators to the study sponsor (or designee) before starting the study, and will, on request of the sponsor, provide additional documentation of any licenses and certifications necessary to demonstrate these qualifications.

The investigator and sub-investigators are required to disclose any potential conflicts of interest during or within 1 year after the end of the study (Section 10.1.2).

The investigator will either conduct the activities in the protocol personally or provide guidance and supervision to the staff who assist. The investigator will provide necessary information about the protocol and the responsibilities of individual personnel. The investigator will ensure that study-related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential participants, before the receipt of written approval from relevant governing bodies/authorities.

The investigator will communicate with the local IRB/IEC to ensure that it has performed initial review, continuing review, and approval of the protocol. The investigator will promptly report all changes in research activity and all anticipated risks to participants to the IRB/IEC. The investigator will report on the progress of the study to the IRB/IEC at least once per year and will issue a final report within 3 months of study completion.

The investigator will obtain valid informed consent from each participant in the study (Section 10.1.3). The investigator is responsible for screening participants and for enrolling only those participants who have met protocol eligibility criteria. If a potential research participant has a primary care physician, the investigator should, with the participant's consent, inform them of the participant's participation in the study.

The investigator must protect the participant's privacy rights as described in Section 10.1.4 and explain to the participant how their data will be used. The publication policy also encompasses some elements designed to protect individual participants' data (Section 10.1.10).

The investigator will prepare and maintain adequate case histories of all participants entered into the study, including hospital records and laboratory results (Section 10.1.8). The investigator will

be responsible for reviewing data, reports, and interlaboratory/reader standardization methods (if applicable). The investigator or the investigator's designee (ie, authorized site personnel, as stated in the site delegation log) must enter data from the source documents (Section 10.1.8) into the eCRF with guidance from the study CRF Completion Guidelines or similar. The investigator will prepare correct and complete eCRFs for all participants and/or will check and confirm the contents of eCRFs entered by the subinvestigator or transcribed from the source data. The investigator will electronically sign the eCRFs as a means of attesting to the integrity of the data and will submit them to the sponsor. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs. The investigator will maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs (Section 10.1.7).

The investigator will 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 (Section 10.1.8).

The investigator will facilitate monitoring and auditing activities and will allow the regulatory authorities to inspect and copy GCP-specified essential documents.

The investigator has overall responsibility for dispensing study drug will return all unused sponsor-supplied study intervention, containers, and other study materials to the sponsor on completing or leaving the study. If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRBs/IECs and provide them with a detailed written explanation (Section 10.1.9).

Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by (inter)national regulations

10.1.11.2.1. PI/Coordinating Investigator

The PI/coordinating investigator will be required to review and sign the final clinical study report and by doing so agrees that it accurately describes the results of the study, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2 Clinical Laboratory Tests

Table 10.a lists the tests that will be performed for each laboratory specimen. These tests will be performed by the central laboratory.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10.a Protocol-Required Laboratory Tests

Laboratory Tests		Parameters		
Hematology	Platelet count	RBC count		WBC count with absolute differential
	Hemoglobin			Neutrophils
	Hematocrit			Lymphocytes
	PT/INR ^{a,b}			Monocytes
	PTT ^b			Eosinophils
				Basophils
Clinical Chemistry	BUN	Potassium	AST	Total bilirubin ^a
	Creatinine	Sodium	ALT	Total protein
	Creatine kinase	Chloride	Alkaline phosphatase	Albumin
	Triglycerides	Calcium	GGT	
	Lipid panel (HDL, LDL, total cholesterol)	Glucose		
		Bicarbonate		
Routine Urinalysis	Specific gravity, glucose, protein, blood, nitrites			
	Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	For participants of childbearing potential only: highly sensitive serum or urine hCG pregnancy test			
Other Screening Tests	If menopause is suspected: FSH and estradiol			
	Serology (HIV antibody, HBsAg, and HCV)			
	Alcohol screen			
	Drug screen			
	All study-required laboratory tests should be performed by a central laboratory. A local laboratory may be used for special circumstances after discussion with sponsor.			

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; FSH: follicle stimulating hormone; GGT: γ -glutamyl transferase; hBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HDL: high density lipoprotein; INR: international normalized ratio; LDL: low density lipoprotein; PT: prothrombin time; PTT: partial thromboplastin time; RBC: red blood cell; WBC: white blood cell.

^a If ALT or AST $>3 \times$ ULN, PT/INR will be performed and total bilirubin will be fractionated. Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1 and Section 10.5.

^b To confirm eligibility for optional CSF collection.

10.2.1. Clinical Laboratory Assessments and Other Safety Assessments

A change in the value of a clinical laboratory parameter, physical examination finding, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of study intervention, a shift of a parameter is observed from a value in the normative range to a value that is outside the reference range and considered clinically significant, or a further waning of an already clinically significant value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the study intervention, and the range of variation of the respective parameter within its reference range, should also be considered.

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If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), physical examination, vital sign, or ECG values that were not present at the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of the participant, whether a change in a clinical laboratory value, physical examination, vital sign, or ECG parameter is clinically significant and represents an AE. The assessment of clinical significance is recorded on the eCRF related to the assessment (for example, the clinical laboratory value eCRF), but an event that is also classified as an AE will be recorded on the AE page.

10.2.2. Biological Sample Retention and Destruction

Optional DNA samples will be stored at Takeda Development Center Americas, Inc., or its agents or its affiliated companies for up to 15 years from when the study results are reported or if less, the maximum period permitted under applicable law or until consent is withdrawn. After that time, the samples will be destroyed.

10.3 AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
<p>An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of the study intervention, whether or not the occurrence is considered related to the study intervention.</p> <p>An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the study intervention.</p> <p>An untoward finding generally may necessitate therapeutic intervention, require an invasive diagnostic procedure, or require discontinuation or a change in dose of study drug or a concomitant medication. (Repeated or additional noninvasive testing [eg, laboratory or ECG re-tests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.)</p>
Events Meeting the AE Definition
<ul style="list-style-type: none">• New condition detected or diagnosed after the use of the study intervention(s), even though it may have been present before the start of the study.• Exacerbation of a chronic or intermittent pre-existing condition including either an

increase in frequency or intensity of the condition.

- Event that is of greater intensity, frequency, or duration than expected for the individual participant, or an event with a reasonable possibility that it was related to the study intervention.
- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, physical examinations, vital signs measurements) that are clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease), including those that worsen from baseline.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction

- An intentional overdose taken with possible suicidal/self-harming intent, regardless of sequelae.

Events **NOT** Meeting the AE Definition

- Situations in which an untoward medical occurrence did not occur (eg preplanned or elective surgery^a).
- Presence or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen^b.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

^a Preplanned and elective surgeries are defined as those that were scheduled before signing of informed consent. See exceptions in Section 10.3.3.1. While these procedures are not considered AEs, they should be documented in the participant's source documents as described in Section 8.1.3.

^b Pre-existing conditions (present at the time of signing of informed eConsent) are considered concurrent medical conditions and should NOT be recorded as AEs. Likewise, baseline evaluations (eg, laboratory tests, ECG, x-rays) should NOT be recorded as AEs unless they are related to study procedures.

AE onset and resolution dates are defined as follows:

- Start date: the date when the first signs/symptoms were noted by the participant and/or investigator.

- End date: the date when the participant recovered, the event resolved but with sequelae, or the participant died.

10.3.2. Definition of SAE

SAEs are events that meet BOTH the AE criteria described in Section 10.3.1 AND the criteria for seriousness below.

SAE Definition
An SAE is defined as any untoward medical occurrence that meets one or more of the criteria listed:
<ul style="list-style-type: none">• Results in death
<ul style="list-style-type: none">• Is life threatening <p>Note: The term <i>life threatening</i> in the definition of <i>serious</i> refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.</p>
<ul style="list-style-type: none">• Requires inpatient hospitalization or prolongation of existing hospitalization <p>Note: In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.</p> <p>Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.</p>
<ul style="list-style-type: none">• Results in persistent or significant disability/incapacity <p>Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions.</p> <p>This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.</p>
<ul style="list-style-type: none">• Is a congenital anomaly/birth defect

- Other situations:
 - Is an important medical event.
 - May require intervention to prevent one of the outcomes listed above.
 - May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
 - ALT or AST $>3 \times$ ULN and (total bilirubin $>2 \times$ ULN or INR >1.5) for which an alternative etiology has not been identified (see Section 10.5).

10.3.3. Additional Considerations in Identifying and Defining AEs

10.3.3.1. Defining Discrete AEs

Each reported AE should represent a single diagnosis, if the diagnosis is known. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs UNLESS the diagnosis is unknown. Specific examples are as follows:

Laboratory values and ECG findings:

- 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 should be reported as the AE.

Worsening of a condition:

If the participant experiences a worsening or complication of a medical condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of...”). This includes:

- Pre-existing conditions present at the time of signing of informed eConsent.
- Pre-existing episodic concurrent medical conditions (eg, asthma, epilepsy): An episode should only be recorded as an AE if the condition becomes more frequent, serious, or severe in nature.
- A degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis): Worsening of the condition should only be recorded as an AE if it occurs to a greater extent than expected.

- Worsening or complication of an AE after any change in study drug: The worsening or complication should be recorded as a new AE.

Complications associated with preplanned procedures:

- Changes in plan and surgical complications associated with preplanned or elective surgeries, therapies, or procedures should be recorded as AEs.
- 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 recorded as an AE.
- Complications resulting from an elective surgery should be recorded as AEs.

Changes in intensity of AEs:

- If the participant experiences changes in intensity of an AE, the event should be recorded once with the maximum intensity recorded.

10.3.3.2. AEs of Special Interest

An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them.

On the basis of nonclinical data for TAK-861, clinical data for the compounds with the same mechanism of action and literature information on the association between OX2R agonism and cardiovascular effects, as well as effects on wakefulness in nonclinical models, the following are identified as potential risks and AEs of special interest for the study drug:

- BP and HR increases.
- Insomnia.
- Bladder events.

BP and HR are monitored throughout the study at every planned visit. The participant should be promptly discontinued from the study if they meet the BP/HR specific discontinuation criteria as specified in Section 7.1. ABPM data will also be collected at specific time points as mentioned in the SOA (see Table 1.a) to better understand the effects of TAK-861 on BP and HR.

There are no special monitoring requirements for insomnia and bladder events other than routine AE monitoring. However every attempt should be made to get more clarity on the type of bladder event and insomnia the participant experienced.

AEs of special interest must be recorded as AEs/SAEs in the eCRF. They will follow the same reporting procedures for AEs/SAEs as mentioned in Section 10.3.4. All AEs of special interest must be followed up until resolution.

10.3.4. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE information. Each event must be categorized in terms of the attributes below, over the entire course of the event, including the start and stop dates.

It is **not** acceptable for the investigator to send photocopies of the participant's source documents to the safety report contact listed in the study operations manual/the contact list in lieu of completion of the required Takeda Safety Reporting form.

There may be instances when copies of source documents for certain cases are requested by the CRO, the sponsor, or the responsible medical monitor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the source documents before submission to the CRO, the sponsor, or the responsible medical monitor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

10.3.4.1. Frequency

Assessment of Frequency

The investigator should assess and record the frequency of the event. Episodic AEs (eg, vomiting) or those that occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.3.4.2. Intensity

Assessment of Intensity

The investigator will assess the intensity for each AE and SAE (including any laboratory abnormality) reported during the study and assign it to one of the following categories:

Mild:	An AE that is usually transient, easily tolerated by the participant, 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 causes discomfort and interferes with usual activities of daily living, 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.
Please note: Intensity and seriousness are separate concepts. The terms “severe” and “serious” are not synonymous. Because serious events usually pose a threat to a participant’s life or ability to function, seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.	

10.3.4.3. Causality/Relatedness

Assessment of Causality	
The investigator must assess the relationship between the study drug and each occurrence of each AE/SAE based on the criteria below:	
Related:	<p>An AE that follows a reasonable temporal sequence from administration of the study intervention(s) (including the course after withdrawal of the intervention), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.</p> <p>A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.</p>
Not related:	An AE that does <i>not</i> follow a reasonable temporal sequence from administration of the study intervention(s) and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.
<p>The investigator will also consult the IB and/or product information, for marketed products, in their assessment.</p> <p>For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.</p> <p>There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data. The causality assessment is one of the criteria used when determining regulatory reporting requirements.</p> <p>The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.</p>	

10.3.4.4. Action Taken

Action Taken Concerning Intervention(s)
<p>The investigator must make note of the action taken concerning the study drug:</p> <ul style="list-style-type: none"> • Dose not changed. • Drug interrupted. • Drug withdrawn. • Dose delayed. • Unknown. • Not applicable: a study drug was stopped for a reason other than the particular AE (eg, the study has been terminated, the participant died, dosing with study drug was already stopped before the onset of the AE). <p>For any AE that was ongoing at the time of a participant's death, the study intervention action should reflect the most recent action that had been taken at the time of death (eg, drug interrupted, reduced, withdrawn). If the participant had never received the study intervention, the action taken should be recorded as "dose not changed" or "not applicable." The study intervention action of "withdrawn" should not be selected solely as a result of the participant's death.</p>

10.3.4.5. Outcome

Outcome
<p>Recovered/resolved: The participant returned to first assessment status with respect to the AE.</p> <p>Recovered/resolved with sequelae: The participant recovered from an acute AE but was left with permanent/significant impairment.</p> <p>Recovering/resolving: The intensity has decreased by 1 or more stages: the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value has improved, but has not returned to the reference range or to baseline; the participant died from a cause <i>other than</i> the this particular AE.</p> <p>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 is now worse than when it started; is an irreversible congenital anomaly; the participant died from another cause.</p> <p>Fatal: The AE is considered to be the cause of death or contributed to the participant's death.</p> <p>Unknown: The course of the AE cannot be followed up due to hospital change or residence</p>

change at the end of the participant's participation in the study.

10.3.4.6. Follow-Up

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally submitted documents.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4.6.1. Reference Safety Information

The reference safety information (RSI) for this study is the IB, which the sponsor has provided under separate cover to all investigators.

10.3.4.6.1.1. Unexpected AEs

An unexpected AE is an AE whose nature, severity, specificity, or outcome is not consistent with the term, representation, or description used in the RSI. "Unexpected" also refers to the AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the product, but are not specifically mentioned as occurring with the particular product under investigation.

The expectedness of AEs will be determined by the sponsor using the IB as the RSI. This determination will include considerations such as the number of AEs previously observed, but will not be based on what might be anticipated based on the pharmacological properties of a product.

10.3.4.6.2. TEAE

As described in Section 10.3.4, all AEs will be collected from the time when the ICF is signed. For reporting purposes in the study, a TEAE is defined as any event emerging or manifesting at or after the initiation of treatment with an study intervention or medicinal product or any existing event that worsens in either intensity or frequency following exposure to the study intervention or medicinal product.

10.3.5. Expedited Reporting of SAEs and Selected AEs

This section describes the expedited reporting required for certain types of events, in addition to eCRF completion:

- Sites must report SAEs immediately, and in no case in more than 24 hours.

SAE Reporting to the CRO/Sponsor via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE to the safety contact listed in the study operations manual/the contact list will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the contact provided on the contact list.

Contacts for SAE reporting can be found in study operations manual/the contact list.

10.3.5.1. Reporting of Abnormal Liver-Associated Test Results

For any participant with ALT $>3 \times \text{ULN}$ AND total bilirubin $>2 \times \text{ULN}$ OR INR >1.5 for which an alternative etiology has not been found, report the event as an SAE, contact the Medical Monitor and Takeda Trial Clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Section 10.5.

10.3.5.2. Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for identifying and reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs in accordance with national regulations in North America, Europe, and Asia Pacific. AEs that are already classified as expected (and therefore are not SUSARs) are listed in the RSI (see Section 10.3.4.6.1 for the location of the RSI).

- SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and lifethreatening events and 15 days for other serious events, relative to the first awareness of an event by/or further provision to the sponsor or sponsor's designee, unless otherwise required by national regulations.
- The sponsor will prepare an expedited reports for other safety issues that might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug, or that would

be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the study.

The study site will forward a copy of all expedited reports to its IRB or IEC in accordance with local regulations.

10.4 Contraceptive and Barrier Guidance

10.4.1. Definitions

For the purposes of this study, reproductive status is defined as follows:

- **Non-pregnant:** Negative urine and/or serum β -hCG pregnancy test result
- Person who is not of childbearing potential:
 - Premenarchal and 1 of the following:
 - Tanner stage 1.
 - Younger than 9 years of age.
 - Surgically sterile for at least 6 weeks at screening (defined as having undergone one of the following procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy).
 - Postmenopausal at screening (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.
- Person who **is of childbearing potential:** after menarche and until becoming post-menopausal unless permanently sterile by the definition above.
- Male who **is not fertile:** pre-puberty OR post-puberty but permanently sterile by bilateral orchidectomy. 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.
- Male who **is fertile:** post puberty, unless permanently sterile by the definition above.

10.4.2. Contraception Guidance

In this study, the use of highly effective contraception is generally required unless otherwise noted. In addition, contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

The failure rates of contraceptives that are used consistently and correctly may differ in typical use. Therefore, when study participation requires any of these methods of contraception to be used, participants must commit to using them:

- Consistently throughout the required period.
- Correctly, as described below and in any labeling associated with the method.

Contraception requirements depend in part on the reproductive status of the participant and the participant's partner.

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Table 10.b Acceptable Contraception Methods and Lactation Guidance for this Study

Highly Effective Contraceptives: Failure rate of <1% per year - when used consistently and correctly

User Dependent

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation^{a,b}
 - Oral
 - Intravaginal
 - Transdermal
- Progestogen only hormonal contraception associated with inhibition of ovulation^{a,b}
 - Oral
 - Injectable
- Sexual abstinence^c

Low User Dependency

- Implantable progestogen only hormonal contraception associated with inhibition of ovulation^{a,b}
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy; vasectomized partner^{d,e}

Measures Intended to Prevent Fetal and Neonatal Exposure via Sperm or Breastmilk

- Participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration throughout the duration of the study and for 5 half-lives plus 90 days after the last dose of study drug.

^a Hormonal contraceptives must be stabilized for at least 30 days before the start of the screening period.

^b Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Therefore, participants using hormonal contraception to fulfill the requirement for highly effective contraception must also use a barrier method of contraception (eg, condom use) during the treatment period and for 30 days plus 5 half-lives after the last dose of study treatment (i.e., a total of 35 days).

^c Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

^d A vasectomy is a highly effective contraceptive method *only if* the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

^e For participants of childbearing ability, having a vasectomized partner is a highly effective contraception method provided that the partner is the participant's sole partner and that the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Table 10.c Unacceptable Contraception Methods

Methods that are unacceptable in *any* study requiring contraception

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
 - Withdrawal (*coitus interruptus*)
 - Spermicides only
 - Lactational amenorrhea method
 - Use of both female condom and male condom together at the same time
-

Contraceptives that are effective but have a failure rate of >1% per year when used consistently and correctly are insufficient in a study requiring highly effective contraception (ie, <1% failure rate)

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
 - Male or female condom with or without spermicide
 - Cap, diaphragm or sponge with spermicide
-

In addition, male participants must be advised not to donate sperm from signing of the ICF to 5 half-lives PLUS 90 days after the last dose of study drug.

10.4.3. Pregnancy

If any participant is found to be pregnant during the study, the participant should be withdrawn and any sponsor-supplied intervention(s) should be immediately discontinued.

If a participant's partner becomes pregnant during the study or within 5 half-lives PLUS 90 days after the last dose, the participant's partner should be asked for consent to record and follow the pregnancy.

If the pregnancy occurs during or after administration of blinded intervention(s), the investigator must inform the participant of their right to receive treatment information. If the participant chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

If the pregnant participant or the participant's pregnant partner agrees, the investigator should notify their primary care physician that the participant/participant's partner was participating in a clinical study when they became pregnant and provide details about the intervention the participant received (blinded or unblinded, as applicable).

If the pregnancy occurs during administration of active study intervention (eg, from Day 1) until the last follow-up, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in the contact information list.

Pregnancies for which regulatory reporting is not required include:

- Pregnancies that occurred during the pretreatment phase.
- Pregnancies in participants (or their partners) who were unblinded and found to be randomized to placebo.

All pregnancies in participants on study intervention(s) including/excluding the comparator or their partners will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

10.5 Abnormal Liver-associated Test Result Monitoring and Follow-up Assessments

Investigators must be vigilant for abnormal liver-associated test results in participants during the clinical study. Transient fluctuations in serum aminotransferases occur commonly in clinical study participants, but it is crucial that the investigator identifies and evaluates participants with possible hepatic injury.

Even for mild elevations of liver tests (elevations that do not fall under discontinuation criteria), a thorough evaluation of medical history, lifestyle changes, etc, to assess causality is recommended. More frequent monitoring of LFTs may be required per investigator's discretion in such cases.

If a participant has elevated ALT or AST $>3 \times \text{ULN}$, collection of sample for repeat laboratory measurements will be performed no more than 72 hours after the initial elevation in AST or ALT $>3 \times \text{ULN}$ is noted.

If any of the LFT abnormality discontinuation criteria listed in Section 7.1 are met, the study drug should be discontinued with appropriate clinical follow-up, including repeat laboratory tests until the participant's laboratory profile has returned to its approximate baseline status. The investigator must contact the medical monitor for consideration of additional testing, close monitoring, and discussion of the participant's relevant details and possible alternative etiologies. If necessary, additional diagnostic tests should be performed. Components of hepatic investigations may include those listed in Table 10.d. The abnormality should be recorded as an AE or SAE:

- If a participant is noted to have ALT or AST elevated $>3 \times \text{ULN}$ on 2 consecutive occasions (at least 24 hours apart with no intervening measurements $\leq 3 \times \text{ULN}$), the abnormality should be recorded as an AE, and the participant should be withdrawn from the study (as described in Section 7.1).
- If a participant is noted to have ALT or AST $>3 \times \text{ULN}$ and (total bilirubin $>2 \times \text{ULN}$ or INR >1.5) for which an alternative etiology has not been identified, the participant should be withdrawn from the study (as described in Section 7.1) and the investigator must contact the medical monitor and Takeda study clinician within 24 hours of the abnormality being noted. Hepatic investigations, as suggested in Table 10.d, should be initiated. Consider consultation with a gastroenterologist or hepatologist. Any event of elevated ALT or AST $>3 \times \text{ULN}$ and (total bilirubin $>2 \times \text{ULN}$ or INR >1.5) for which an alternative etiology has not been identified must be reported as an SAE.

Reporting and follow-up of AEs is described in Section 10.3.4. Expedited reporting for LFT-related SAEs is described in Section 10.3.5.

All liver enzyme elevations irrespective of severity should be followed up until resolution. If no LFT abnormalities were observed at the time of final visit, the scheduled follow-up visits are enough.

If, at the participant's last clinic visit, (ALT or AST $> 1.5 \times$ ULN), follow-up laboratory tests should be performed until the participant's laboratory profile returns to its approximate baseline status. The participant will be asked to continue to refrain from using medications associated with liver enzyme elevations listed in [Appendix 2](#) during additional follow-up. The investigator must contact the medical monitor for consideration of additional testing, close monitoring, and discussion of the participant's relevant details and possible alternative etiologies.

Table 10.d Hepatic Investigation

Medical History	<ul style="list-style-type: none"> Concomitant medications (including over-the-counter medications, such as acetaminophen, and herbal supplements). Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis). Alcohol intake. Hepatobiliary disorder. Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia). Travel history.
Physical examination (symptoms, signs, and laboratory results)	<ul style="list-style-type: none"> General malaise, fatigue, nausea, or vomiting. Right upper quadrant pain or tenderness, fever, jaundice, rash. Eosinophilia $> 5\%$.
Hepatic/hepatobiliary imaging	Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging).
Viral hepatitis serology	<ul style="list-style-type: none"> Hepatitis A antibody (total and IgM). Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody (IgM), hepatitis C antibodies. Hepatitis E (IgG and IgM). Consider polymerase chain reaction test for hepatitis B, C, and E. Consider Epstein-Barr virus serology (viral capsid antigen, nuclear antigen, early antigen). Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	<ul style="list-style-type: none"> Anti-nuclear antibody. Anti-smooth muscle antibody. Anti-liver-kidney microsomal antibody.

10.6 Country-specific Requirements

Not applicable.

10.7 Abbreviations and Definitions

10.7.1. Abbreviations

ABPM	ambulatory blood pressure monitoring
AE	adverse event
AHI	apnea hypopnea index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC _{last}	area under the concentration-time curve from time 0 to time of the last concentration measured
BMI	body mass index
BP	blood pressure
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
C _{max}	maximum observed concentration
COVID-19	coronavirus disease 2019
CPAL	Continuous Paired Associate Learning
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DILI	drug-induced liver injury
DMC	data monitoring committee
DNS	disturbed nighttime sleep
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
eConsent	electronic consent
eCRF	electronic case report form
e-diary	electronic diary
EDS	excessive daytime sleepiness
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
ESS	Epworth Sleepiness Scale
EU	European Union
EudraCT	European Union clinical trials database
FIN	Functional Impacts of Narcolepsy
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
hCG	human chorionic gonadotropin
HR	heart rate

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IB	investigator's brochure
ICF	informed consent form (including electronic consent where applicable)
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSD-3	International Classification of Sleep Disorders, 3rd Edition
iDSST-s	international Digit Symbol Substitution Test-symbols
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRT	Interactive Response Technology
LFT	liver function test
LTE	long-term extension
MAV	markedly abnormal value
MDE	major depressive episode
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MSLT	multiple sleep latency test
MWT	Maintenance of Wakefulness Test
nPSG	nocturnal polysomnography
NSS-CT	Narcolepsy Severity Scale for Clinical Trials
NT1	narcolepsy type 1
NT2	narcolepsy type 2
ONB	one back test
OX	orexin
OX1R	orexin type-1 receptor
OX2R	orexin type-2 receptor
PD	pharmacodynamic(s)
PGI-I	Patient Global Impression–Improvement
PGI-S	Patient Global Impression–Severity
PI	principal investigator
PK	pharmacokinetic(s)
PSG	polysomnography
PVT	psychomotor vigilance test
QD	once daily
QTcF	QT interval with Fridericia correction method
REM	rapid eye movement
RSI	reference safety information
SAE	serious adverse event
SF-36	Short Form-36 Survey

SOA	schedule of activities
SOREMP	sleep onset REM period
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t _{max}	time of first occurrence of C _{max}
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
VAS	visual analog scale (score)
WCR	weekly cataplexy rate

10.8 Protocol Amendment History

Date	Document	Global/Country/Site Specific
17 Aug 2022	Original Protocol	Global

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Appendix 1: List of Inhibitors and Inducers of CYP3A and the Substrates of CYP3A4 and OATP1B1

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

Strong CYP3A inhibitors: clarithromycin, troleandomycin, cobicistat, conivaptan, boceprevir, danoprevir, ritonavir, elvitegravir, 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, crizotinib, cyclosporin, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, fluvoxamine, miconazole, imatinib, istradefylline, tofisopam, verapamil.

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

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

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.

Known sensitive OATP1B1 substrates including but not limited to pravastatin, rosuvastatin, pitavastatin, atorvastatin, elagolix, repaglinide, valsartan.

Appendix 2: Medications Associated with Liver Enzyme Elevations

acarbose	isoniazid
acetaminophen	isotretinoin
acetazolamide	itraconazole
allopurinol	ketoconazole
atomoxetine	labetalol
atorvastatin	lamotrigine
carbamazepine	levofloxacin
chlorzoxazone	mefenamic acid
ciprofloxacin	methyldopa
clarithromycin	miconazole
clomipramine	milnacipran
danazol	minocycline
dantrolene	nefazodone
diclofenac	niacin
diflunisal	nitrofurantoin
diltiazem	nortriptyline
disulfiram	orlistat
divalproex sodium	papaverine
duloxetine	phenytoin
erythromycin	sodium valproate
ethambutol	sulindac
etodolac	telithromycin
febuxostat	terbinafine
fenoprofen	testosterone
fluconazole	thiabendazole
gemfibrozil	ticlopidine
griseofulvin	tizanidine
indomethacin	voriconazole
interferon alfa-2a, recombinant	zafirlukast
interferon alfa-2b	zileuton
interferon alfacon-1	

Appendix 3: ICSD-3 Criteria for NT1

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

- a) The participant 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 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 less than one-third of the mean values obtained in normal participants with the same standardized assay.

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-861-2001

Study Title:

A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1)

Phase: 2

Version: Initial

Date: 30 Nov 2022

Prepared by: [REDACTED]

Based on:

Protocol Version: Initial

Protocol Date: 17 Aug 2022

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REVISION HISTORY

Version	Date	Primary Rationale for Revision
Initial	30 Nov 2022	Not Applicable

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ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
AE	adverse event
AHI	apnea hypopnea index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC _{last}	area under the concentration-time curve from time 0 to time of the last concentration measured
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
CI	Confidence interval
C _{max}	maximum observed concentration
CPAL	Continuous Paired Associate Learning
C-SSRS	Columbia Suicide Severity Rating Scale
CPAP	continuous positive airway pressure
DMC	data monitoring committee
DNS	disturbed nighttime sleep
ECG	electrocardiogram
e-diary	electronic diary
EDS	excessive daytime sleepiness
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
ESS	Epworth Sleepiness Scale
EU	European Union
FAS	Full Analysis Set
FIN	Functional Impacts of Narcolepsy
FWER	family-wise error rate
GEE	generalized estimating equations
HR	heart rate
iDSST-s	international Digit Symbol Substitution Test-symbols
INR	international normalized ratio
IRC	Internal review committee
LFT	liver function test
LS	Least square
LTE	long-term extension
MAMS	multi-arm multi-stage
MAV	markedly abnormal value
MCT	meaningful change threshold
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	mixed model for repeated measures
MWT	Maintenance of Wakefulness Test
nPSG	nocturnal polysomnography
NSS-CT	Narcolepsy Severity Scale for Clinical Trials
NT1	narcolepsy type 1
NT2	narcolepsy type 2
ONB	one back test
PD	pharmacodynamic(s)
PGI-I	Patient Global Impression–Improvement
PGI-S	Patient Global Impression–Severity
PK	pharmacokinetic(s)
PSG	polysomnography
PVT	psychomotor vigilance test
QD	once daily
QTcF	QT interval with Fridericia correction method
REM	rapid eye movement
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form-36 Survey
SL	Sleep latency
SOC	System Organ Class
TEAE	treatment-emergent adverse event
t_{\max}	time of first occurrence of C_{\max}
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
VAS	visual analog scale (score)
WCR	weekly cataplexy rate

Note: text in italics represents language copied directly from the protocol.

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

- *To assess the effect of TAK-861 on excessive daytime sleepiness (EDS) as measured by sleep latency from the Maintenance of Wakefulness Test (MWT).*

1.1.2 Secondary Objectives

- *To assess the effect of TAK-861 on EDS as measured by the Epworth Sleepiness Scale (ESS) total score.*
- *To assess the effect of TAK-861 on cataplexy as assessed by the weekly cataplexy rate (WCR).*
- *To evaluate the safety and tolerability of TAK-861.*

1.1.3 Exploratory/Additional Objectives

- *To evaluate the safety and tolerability of TAK-861.*
- *To assess the effect of discontinuation of TAK 861, as assessed by ESS, WCR, and patient-reported sleep parameters.*
- *To assess the effect of TAK-861 on sustained attention as measured by the psychomotor vigilance test (PVT).*
- *To assess the effect of TAK-861 on overall narcolepsy symptoms measured by the Clinical Global Impression Scale – Global Improvement Scale (CGI-I) and the Patient Global Impression of Improvement (PGI-I) scale.*
- *To assess the effect of TAK-861 on severity of narcolepsy symptoms measured by Narcolepsy Severity Scale for Clinical Trials (NSS-CT).*
- *To assess the effect of TAK-861 on mobility, self-care, usual activities, pain/discomfort and anxiety/depression as assessed by the EuroQol-5 Dimensions 5-Levels (EQ-5D-5L) scale.*
- *To assess the effect of TAK-861 on quality of life of participants, as assessed by the Short Form-36 Survey (SF-36).*
- *To assess the efficacy of TAK-861 on functional impacts of narcolepsy as assessed by the Functional Impacts of Narcolepsy (FIN) scale.*

- *To assess the effect of TAK-861 on quality of nocturnal sleep and presence or absence of rapid eye movement sleep-related abnormalities, including hypnagogic/hypnopompic hallucination, sleep paralysis, and nocturnal awakenings from the daily e-diary.*
- *To assess the effects of TAK-861 on memory, working memory, and processing speed as measured by the cognitive tests (Continuous Paired Associate Learning [CPAL] test, One Back test [ONB], and international Digit Symbol Substitution Test-symbols [iDSST-s]).*
- *To assess the treatment satisfaction with TAK-861 as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM).*
- *To assess the effect of TAK-861 on sleep architecture as measured by nocturnal polysomnography (nPSG).*
- *To assess the effect of TAK-861 on daily/nighttime activity as measured by actigraphy (accelerometry) and HR (photoplethysmography).*
- *To assess steady-state exposures of TAK 861.*
- *To assess the pharmacokinetic (PK)/ pharmacodynamic (PD) relationship(s) of TAK 861 for selected efficacy or safety measures.*

1.2 Endpoints

1.2.1 Primary Endpoint

- *Change from baseline to Week 8 in mean sleep latency from the MWT*

1.2.2 Secondary Endpoints

- *Change from baseline to Week 8 in ESS total score*
- *WCR at Week 8*
- *Occurrence of at least 1 treatment-emergent adverse event (TEAE).*

1.2.3 Exploratory/Additional Endpoints

- *Occurrence of at least 1 markedly abnormal value (MAV) for postdose laboratory values.*
- *Occurrence of at least 1 MAV for postdose vital signs.*
- *Occurrence of at least 1 MAV for postdose electrocardiogram (ECG) parameters.*
- *Time-matched change in blood pressure (BP) and heart rate (HR) from baseline to specified postdose time points.*
- *Change in ambulatory BP and HR parameters from baseline.*
- *Number (and percent) of participants with at least 1 endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS).*

- *Change from baseline in ESS total score, WCR, and sleep parameters reported in the patient-reported sleep electronic diary (e-diary) at the follow-up visit 1 week after drug discontinuation.*
- *Change from baseline in number of lapses on PVT.*
- *PGI-I and CGI-I scores.*
- *Change from baseline in NSS-CT.*
- *Change from baseline in EQ-5D-5L index score.*
- *Change from baseline in quality of life as measured by SF-36 domain scores.*
- *Change from baseline in the FIN domain scores.*
- *Change from baseline in frequency of refreshing nocturnal sleeps, sleep paralysis, hypnagogic/hypnopompic hallucinations, and nocturnal awakenings reported in the daily e diary.*
- *Change from baseline in CPAL, ONB, and iDSSTs measurements.*
- *Treatment satisfaction as measured by the 4 dimensions of the TSQM.*
- *Change from baseline in various nPSG measures, including nocturnal awakenings.*
- *Change from baseline in daily/nighttime activity metrics derived from continuous actigraphy (accelerometry) and HR (photoplethysmography) from a wrist-worn device.*
- *TAK-861 plasma concentrations and selected noncompartmental analysis PK parameters (maximum observed concentration [C_{max}], time of first occurrence of C_{max} [t_{max}], and area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration [AUC_{last}]).*

1.3 Estimand(s)

Not Applicable.

2.0 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, 8-week parallel group study to evaluate the efficacy, safety, and tolerability of 4 oral dose regimens of TAK-861.

Approximately 100 (male and female) participants with NT1, who satisfy the inclusion and exclusion criteria, will be randomized such that each participant has an equal chance of being assigned to any 1 of 5 treatment arms: 3 TAK-861 twice daily dose regimens, 1 TAK-861 QD dose regimen, or matching placebo. Randomization will be stratified by region. Starting on the morning of Day 1, the study drug will be administered at approximately the same time each day for 8 or 12 weeks. (If the participant wishes to enroll in the long-term extension [LTE] study but the LTE study has not started at the participant's site when the participant completes the Week 8

visit of the current study, the participant will be allowed to continue in the current study for an additional 4 weeks; see below.)

Participants who have provided informed consent will complete a screening period of up to 50 days to washout any NT1 medication (if applicable). Participants will be asked to complete an e-diary, starting from the initial screening visit, no later than Day -16. To be eligible for the study, participants must fill out self-reported cataplexy questions in the e-diary for at least 11 days of the 14-day period from Day -16 to Day -3 and have ≥ 4 partial and/or complete episodes of cataplexy/week (averaged over Days -16 to -3).

Participants will remain confined overnight at the study site during the following times:

- Days -2 to 1 (1 mandatory overnight at Day -2; 1 optional overnight at Day -1).
- Days 27 to 28 (1 overnight).
- Days 55 to 56 (1 overnight).

After the Week 8 visit, participants will have the option to participate in an LTE study under a separate protocol (assuming protocol is open for enrollment). Participants who enroll in the LTE study will not have follow-up visits in this study.

If a participant plans to enroll in the LTE study but the LTE study is not open for enrollment at the participant's site when the participant completes the Week 8 visit, the participant will be allowed to continue in the current study for an additional 4 weeks of treatment (continuing the same treatment regimen as the previous 8 weeks). This is to avoid a treatment gap for participants willing to roll over from this study to the LTE study.

For participants who do not participate in the LTE study (including any participant who completes the Week 12 visit and for any reason does not enroll in the LTE), every effort should be deployed to have them complete a first follow-up visit approximately 7 days after the final study drug intake and a second follow-up visit (home healthcare visit) approximately 28 days after the final study drug intake. For participants who early terminate the study, every effort should be deployed to have them complete an early termination visit as soon as possible and a follow-up visit (in-clinic visit or home healthcare, if available) approximately 28 days after the last dose of study drug. Participants not participating in the LTE study can restart their non-exclusionary medications after the first follow-up visit or early termination visit.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

3.1.1 Primary Endpoint

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the mean sleep latency (minutes) from the 4 sessions of a 40-minute MWT. The statistical null hypothesis is that the mean change from baseline to Week 8 in the mean sleep latency for each TAK-861

treatment group is the same as the mean change from baseline to Week 8 in the mean sleep latency for the placebo treatment group.

3.2 Secondary Endpoints

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the total ESS score. The statistical null hypothesis is that the mean change from baseline to Week 8 in the total ESS score for each TAK-861 treatment group is the same as the mean change from baseline to Week 8 for the placebo treatment group.

TAK-861 is superior to placebo as measured by the WCR at Week 8. The statistical null hypothesis is that the incidence rate ratio (TAK-861 to placebo) of WCR at Week 8 is equal to 1.

3.3 Statistical Decision Rules

Not applicable.

3.4 Multiplicity Adjustment

For the interim analysis the generalization of group sequential design to the multi-arm multi-stage (MAMS) setting 3 coupled with the hierarchical testing scheme for multiple endpoints in group-sequential trials 4 will be applied to control the family-wise error rate (FWER). Details of hypothesis testing at IA are described in Section 6.10. At the final analysis, hypothesis testing will proceed for each dose level according to the hierarchy: MWT → ESS → WCR. An endpoint will be tested for statistical significance only if the previous endpoint in the hierarchy has achieved statistical significance relative to its final-analysis MAMS efficacy boundary, which will be determined at the time of IA based on the observed information fraction.

If the interim analysis does not occur (e.g., enrollment is faster than expected), the multiplicity incurred by testing multiple treatment arms against placebo will be adjusted by a Bonferroni correction. Within each treatment arm, the endpoints will be tested sequentially according to the following hierarchy: MWT → ESS → WCR.

4.0 SAMPLE SIZE DETERMINATION

Assuming an SD of 11 minutes, a sample size of 16 participants per treatment group completing 8 weeks is enough to achieve >90% power to detect a difference of 14 minutes between a TAK-861 dose and placebo by a 2-sample t-test on the change from baseline to Week 8 in mean sleep latency from 4 MWT sessions at 0.05 2-sided significance level. Assuming a 20% dropout rate, 20 participants per treatment group may be enrolled for a total of up to 100 participants.

This sample size will also provide 88% power to detect a difference of 8 points between TAK-861 and placebo by a 2-sample t-test on the change from baseline to Week 8 in ESS total scores at 0.05 2-sided significance level, assuming an SD of 7 points.

In addition, this sample size will provide approximately 86% power to detect a 50% reduction in WCR relative to placebo with TAK-861 using a Poisson model at 0.05 2-sided significance level, assuming a baseline WCR of 4, with a placebo effect of 25% reduction from baseline.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety set will consist of all participants who received at least 1 dose of study drug. This analysis set will be used for demographic, baseline characteristic, and safety summaries.

5.2 Full Analysis Set

The full analysis set will consist of all participants who were randomized and received at least 1 dose of study drug and have at least one postdose efficacy measurement. Efficacy measurements include cataplexy, MWT, and ESS. The full analysis set will be used for summaries of efficacy and applicable exploratory endpoints.

5.3 Pharmacokinetic Analysis Set

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

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All p-values reported will be 2-sided and reported to 3 decimal places.

All continuous variables will be summarized with descriptive statistics (N, mean, median, standard deviation (SD), minimum, and maximum) unless stated otherwise. The denominator for any percentages will be based on the number of participants who provided non-missing responses to the categorical variable.

6.1.1 Handling of Treatment Misallocations

For efficacy, treatment misallocations will be analyzed as randomized. For safety, treatment allocations will be analyzed as treated.

6.1.2 Analysis Approach for Continuous Variables

Where appropriate continuous variables will be analyzed with a mixed model with repeated measures (MMRM). Unless specified otherwise, the MMRM model will contain fixed effects for the baseline value of the corresponding endpoint (as a continuous covariate), treatment, visit (categorical), and treatment-by-visit interaction, where visit is the repeated factor. An unstructured variance-covariance structure will be used initially. Other variance-covariance structures will be evaluated if there are convergence issues with the model. The Kenward and Roger adjustment for computing the denominator degrees of freedom for the tests of fixed effects will be used. The least square (LS) mean, standard error (SE) and 95% CI will be presented for each visit and treatment group. All pairwise differences from placebo and associated LS means, SEs, 95% CIs, and two-sided p-values will be reported.

In the case a continuous endpoint is not normally distributed based on the Shapiro-Wilk test, the Friedman test will be conducted to compare the population distributions across the treatment groups. The Friedman test is conducted approximately by a mixed effect model with repeated measures, taking the assumption that Q test statistics from Friedman test is approximately chi-square distributed, and the rank is approximately normally distributed. In the mixed effect model, the response variable is the change from baseline ranked within each visit, and the fixed effects are baseline rank, treatment, visit, and treatment-by-visit interaction. The Kenward and Roger adjustment for computing the denominator degrees of freedom for the tests of fixed effects will be used. The two-sided p-values will be reported.

6.1.3 Analysis Approach for Binary Variables

The analysis approach for binary variables will be described in the specific sections.

6.2 Disposition of Subjects

The number and percentage of participants in the following categories will be summarized by treatment group, TAK-861 overall, and total:

- Randomized
- Randomized and not treated (including reasons not treated)
- Randomized and treated
- Prematurely discontinued from study treatment
- Primary reason off study treatment
- Prematurely discontinued from the study
- Primary reason off study
- Continuing to Optional 4-Week Extension
- Continuing to the Long-Term Extension study

The number and percentage of participants randomized in each region (United States, Europe, and Asia Pacific), country, and site will be summarized by treatment group, TAK-861 overall, and total.

The number and percentage of participants in each analysis set will be summarized by treatment group, TAK-861 overall, and total.

The number and percentage of participants with significant protocol deviations will be summarized by treatment group, TAK-861 overall, and total.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

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

Demographics (age, gender, ethnicity, and race) will be summarized by treatment group, TAK-861 overall, and total based on the Safety Set. Descriptive statistics will be used to summarize data for continuous variables and for categorical variables the number and percentage of participants within each category will be summarized.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions that ended before signing of the informed consent. Concurrent medical conditions are those significant conditions that are ongoing at the signing of the informed consent. Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, Version 25 or higher) coding system.

Medical history and concurrent medical conditions will be summarized for each treatment group, TAK-861 overall, and total using the Safety Set. The number and percentage of participants with at least one event in each MedDRA system organ class (SOC) and preferred term (PT) will be summarized. A participant with multiple occurrences of medical history or concurrent medical conditions within a SOC or PT will be counted only once in that SOC or PT.

6.3.3 Baseline Characteristics

Baseline characteristics (alcohol, caffeine, and tobacco use at time of informed consent, human leukocyte antigen (HLA) status, years since diagnosis (relative to informed consent), age at diagnosis, years since symptom onset (relative to informed consent), age at symptom onset, prior use of narcolepsy medications (requiring washout), mean sleep latency from the MWT, ESS total score, weekly cataplexy rate, cerebrospinal fluid orexin level, continuous positive airway pressure (CPAP) ventilation use, compliant with CPAP use, use of oral appliance therapy for sleep apnea) will be summarized by treatment group, TAK-861 overall, and total based on the Safety Set. Descriptive statistics will be used to summarize continuous variables and the number and percentage of participants within each category will be summarized for categorical variables.

6.4 Medication History and Concomitant Medications

All medications will be coded using World Health Organization Drug Dictionary (WHO Drug) (WHO Drug Global B3 March 2022 or higher).

6.4.1 Prior Medications

Prior medications are defined as any medications that stopped prior to the first dose of study drug. Prior medications will be summarized by standardized medication name within each therapeutic class for each treatment group, TAK-861 overall and total based on the Safety Set. If

a subject reports taking 2 medications belonging to the same class, he/she will only be counted once within that class. Prior medications for narcolepsy (requiring washout) will also be summarized by standardized medication name.

6.4.2 Concomitant Medications

Concomitant medications are defined as any medications that started prior to the first dose of study drug and are ongoing at the time of the first dose or started after the first dose of study drug. Concomitant medications will be summarized by standardized medication name within each therapeutic class for each treatment group, TAK-861 overall and total based on the Safety Set. If a subject reports taking 2 medications belonging to the same class, he/she will only be counted once within that class.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint(s) Analysis

6.5.1.1 Derivation of Endpoint(s)

Four MWT sessions are recorded on Day -1, Week 4 (day 28) and Week 8 (day 56). The mean of the Sleep Latency (SL) from the 4 MWT sessions on a given day will be calculated for each subject. If there are 2 or more missing values, the mean will be assigned as missing for that day. The change from baseline for the mean of the 4 MWT sessions will be derived for each subject at each postdose visit.

6.5.1.2 Main Analytical Approach

All descriptive statistics as specified in section 6.1.2 will be prepared for SL for each MWT session and the mean of the 4 MWT sessions at baseline and each postdose visit by treatment group and TAK-861 overall. Descriptive statistics will also be prepared for the change from baseline.

The primary efficacy endpoint, change from baseline in mean SL to Week 8, will be analyzed using the linear mixed-effect models for repeated measures (MMRM) specified in section 6.1.2. Change from baseline in mean SL will be the response. The model will include the fixed effect of visit (Week 4, Week 8). Baseline age, baseline mean SL, and prior use of narcolepsy medications will be used as covariates in the model.

The LS mean change from baseline (and associated 95% CI) in SL over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols. The LS mean differences from placebo will also be plotted.

In addition, mean SL will be categorized into five categories: <10 minutes, 10 - <20 minutes, 20 - <30 minutes, 30 - <40 minutes, and 40 minutes. For each treatment group and TAK-861 overall, the number and percentage of participants in each category will be summarized by visit.

6.5.1.3 *Sensitivity Analyses*

In addition, to evaluate change from time-matched baseline in sleep latency at each session, a linear mixed effect model for repeated measures will be performed. The model will include fixed effects of baseline, treatment, visit (Week 4, Week 8), session (2, 4, 6 and 8 hours postdose), treatment-by-visit interaction, treatment-by-session interaction, visit-by-session interaction, and the 3-way interaction of treatment, visit, and session. Both visit and session are repeated factors. Baseline age, baseline mean SL, and prior use of narcolepsy medications will be used as covariates in the model. Kronecker product UN@UN will be used for the covariance structure. Other Kronecker product structures such as UN@AR(1), and UN@CS will also be used if there are convergence issues. If the model does not converge, separate MMRM models for each visit will be generated. The estimated sleep latency in the MWT for each treatment on each visit and session, and the associated SE and 95% CI will be estimated along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values. An additional contrast to estimate the change from baseline in mean sleep latency will also be calculated as the average over the four sessions for each treatment from the same model. The associated SE and 95% CI will be calculated, along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values.

6.5.1.4 *Supplementary Analyses*

In order to explore the sensitivity of the primary analysis to the ceiling effect in MWT, a tobit (censored regression) mixed effect model will be implemented if any participant's sleep latency value from an MWT session is equal to the 40-minute maximum session duration. The response variable will be the time-matched change in sleep latency from MWT at each session (2, 4, 6, and 8-hour postdose) at the Week 8 visit. The model will include treatment and session as fixed effects, time-matched baseline sleep latency, age, and prior use of narcolepsy medications as covariates, as well as a random intercept to account for within-subject correlation. The maximum likelihood estimate of the change from baseline in mean sleep latency will be calculated by averaging over the four sessions for each treatment. The associated SE and 95% CI will be calculated, along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values.

6.5.2 **Secondary Endpoints Analysis**

6.5.2.1 *Derivation of Endpoint(s)*

The ESS is a self-administered questionnaire with 8 questions with response on a 4-point scale (0-3) for each question. The ESS will be measured at screening, baseline day -1, Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56) and Week 12 (Day 84, optional 4-week extension), and at the 7-day follow-up visit. If one or more item-scores are missing, the questionnaire is invalid, and the ESS total score will be missing. The total score will be derived (the sum of 8 item-scores) for each subject at each visit. The change from baseline in the ESS total scores to each postdose visit will be derived for each subject.

Participants will complete a daily ePRO diary to record cataplexy episodes. Participants will record partial or complete episodes of cataplexy, including the time of occurrence in the diary. Weekly cataplexy rate (WCR) at baseline will be derived as the average number of cataplexy episodes over the last 2 weeks prior to the first dose of the study drug (Day -16 to Day -3) over non-missing diary days, where a minimum of 11 out of 14 compliant days in completion of the self-reported electronic diary for cataplexy episodes is required. Otherwise, the baseline WCR will be considered missing.

WCR will be calculated every 2 weeks (Week 2, Week 4, Week 6, and Week 8, Week 10 (part of optional 4-week extension), and Week 12 (part of optional 4-week extension)) as:

$$\left(\frac{\text{Total number of cataplexy episodes over the non – missing diary days for a given 2 weeks}}{\text{number of non – missing diary days in these 2 weeks}} \right) * 7$$

WCR for the 7-day post last dose follow-up visit will be calculated as:

$$\left(\frac{\text{Total number of cataplexy episodes over the follow – up period}}{\text{number of non – missing diary days in the follow – up period}} \right) * 7$$

If a diary for a given day reports ≥ 0 cataplexy, the day will be counted as a non-missing diary day. If a diary for a given day or for the 24 hour recall does not have any entries, the day will be counted as a missing diary day.

6.5.2.2 Main Analytical Approach

6.5.2.2.1 ESS

Descriptive statistics as specified in section 6.1.2 will be provided by treatment group and TAK-861 overall for ESS total score at screening, baseline (day -1) and postdose visits, as well as for the change from baseline. In addition, the number and percentage of participants with total ESS score in the following categories will be summarized at each visit by treatment group and TAK-861 overall:

- ≤ 10 (Normal daytime sleepiness)
- 0-5 (Lower normal daytime sleepiness)
- 6-10 (Higher normal daytime sleepiness)
- 11-12 (Mild excessive daytime sleepiness)
- 13-15 (Moderate excessive daytime sleepiness)
- 16-24 (Severe excessive daytime sleepiness)

A linear mixed effect model for repeated measures (MMRM) as specified in section 6.1.2 will be used to evaluate the effect of TAK-861 on the change from baseline in the total ESS score. Baseline total ESS score, age, and prior use of narcolepsy medications will be included as

covariates in the model. The optional 4-week extension (Week 12) and 7-day follow-up visit will not be included in the model.

The LS mean change from baseline (and associated 95% CI) in total ESS score over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols. The LS mean differences from placebo will also be plotted.

6.5.2.2.2 WCR

WCR will be summarized by treatment group and TAK-861 overall at baseline and postdose visits (Week 2, Week 4, Week 6, Week 8, Week 10 (optional), Week 12 (optional) and 7-day follow-up visit), including change from baseline. The geometric mean for the observed WCR will also be presented.

The WCR will be analyzed by generalized estimating equations (GEE) using a log-link function featuring a Poisson distribution. The model will include fixed effects for visit, treatment, and treatment-by-visit interaction, and will be adjusted for baseline WCR, age, and prior use of narcolepsy medications. In case of overdispersion (the estimated scale parameter >2), a negative binomial regression will be used. An unstructured variance-covariance structure will be used initially in these models. Other variance-covariance structures will be evaluated if there are convergence issues with the model. If lack-of-convergence still exists, the analysis will be done for Week 4 and Week 8 separately. The estimated incidence rate of weekly cataplexy for each treatment group and the associated SE and 95% CIs will be extracted from the model, along with the incidence rate ratio of weekly cataplexy (TAK-861 to placebo) for all TAK-861 treatment groups, and the associated SEs, 95% CIs, and two-sided p-values. The optional 4-week extension visits (week 10 and 12) and the 7-day follow-up visit will not be included in the GEE model.

The estimated weekly cataplexy incidence rate ratio and the associated 95% CI of all TAK-861 treatment groups relative to placebo will be presented in forest plots, with one plot per visit (Week 2, Week 4, Week 6, and Week 8).

6.5.2.3 Sensitivity Analysis

Not applicable.

6.5.2.4 Supplementary Analyses

The number of cataplexy-free days per week is calculated as:

$$\left(\frac{\text{number of days without cataplexy over the non – missing diary days for a given 2 weeks}}{\text{number of non – missing diary days in 2 weeks}} \right) * 7$$

Descriptive statistics as specified in section 6.1.2 will be provided by treatment group and TAK-861 overall for cataplexy-free days at each visit (Week 2, Week 4, Week 6, Week 8). The number of cataplexy-free days will be analyzed using a Kruskal-Wallis test.

The WCR will be calculated based on full cataplexy episodes separately for baseline, Week 2, Week 4, Week 6, and Week 8 as noted below:

$$WCR_{full} = \left(\frac{\text{Total number of full cataplexy episodes over the non – missing diary days for a given 2 weeks}}{\text{number of non – missing diary in these 2 weeks}} \right) * 7$$

WCR based on partial cataplexy episodes will be calculated as described above. Descriptive statistics and the GEE model specified in section 6.5.2.2 for WCR will be used to analyze WCR based on full and partial cataplexy.

6.5.3 Subgroup Analyses

Not applicable.

6.6 Safety Analysis

The criteria for markedly abnormal laboratory, vital signs, and ECG parameters will be provided in a programming specifications document.

6.6.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA (v25.0 or higher). A treatment-emergent adverse event (TEAE) is defined as an AE whose date/time of onset occurs on or after the first dose of study drug.

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

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

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

For the subset of participants with at least one urinary symptom, the frequency of participants with ≥ 1 instance of increased urinary frequency, and a summary of the number of times participants normally urinate during night-time hours prior to start of treatment and at the time of the urinary events will be generated.

6.6.2 Adverse Events of Special Interest

The adverse events of special interest (AESI) are noted below:

- BP and HR increases
- Insomnia
- Bladder events

A separate summary of AESIs will be generated.

6.6.3 Other Safety Analysis

6.6.3.1 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis. A list of all the clinical laboratory evaluations can be found in Protocol Section 10.2.

Descriptive statistics of clinical laboratory variables will be summarized for baseline and postdose values, as well as change from baseline to postdose values by study visit and treatment group and TAK-861 overall. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

The number and percentage of participants meeting each markedly abnormal laboratory criteria, and any MAV criteria will be summarized overall postdose visits, at Day 1, Week 2, Week 4, Week 6, and Week 8 by treatment group, TAK-861 overall, and total. The evaluation of the MAV criteria will include scheduled and unscheduled visits.

6.6.3.2 Vital Signs

Vital sign measurements include blood pressure (SBP and DBP), heart rate, respiratory rate, body temperature, and weight. Only the scheduled measurements will be included in summary tables or statistical analysis of VS measurements.

SBP, DBP and heart rate collected on Day 1, Week 4, and Week 8 will be summarized with descriptive statistics including the pre-dose value, postdose visit, and change from time-matched baseline (Day -1) by treatment group and TAK-861 overall. The Day 1 VS measurement at 3 hours postdose will be time-matched to the Day -1 3.5 hour measurement. The Day 1 discharge measurement will not be time-matched.

Trough SBP, DBP, and HR measurements (pre-dose) on Week 2 (Day 14), Week 6 (Day 42), Week 10 (Day 70, optional 4-week extension), and Week 12 (Day 84, optional 4-week extension) will be summarized with descriptive statistics including the time-matched baseline, trough (pre 8AM dose timepoint), and change from time-matched baseline at each post baseline visit by treatment group and TAK-861 overall. Baseline is the last time-matched non-missing measurement prior to the first dose.

SBP, DBP, and HR measurements collected 1 hour before nPSG lights off (Day -2, Day 27, and Day 55) will be summarized with descriptive statistics including the time-matched baseline (Day -2), 1 hour before nPSG results, and change from time-matched baseline at each post baseline visit by treatment group and TAK-861 overall.

Respiratory rate, weight and temperature will be summarized with descriptive statistics including the change from baseline at each visit by treatment group and TAK-861 overall. Baseline is the last non-missing measurement prior to the first dose.

In addition, the drug effect on clinic BP and heart rate will be analyzed using an MMRM model with change from time-matched baseline as the response variable. Separate models will be generated for Day 1, Week 4, and Week 8. In the MMRM model, treatment, time point, and treatment-by-time point interaction will be the fixed effects and baseline will be the covariate. The LS mean change from time-matched baseline (and associated 95% CI) in HR, SBP and DBP over time will be plotted for Day 1, Week 4, and Week 8. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols. The LS mean differences from placebo will also be plotted.

The number and percentage of participants meeting each markedly abnormal criteria, and any MAV criteria will be summarized overall postdose visits, at Day 1, Week 4, and Week 8 by treatment group, TAK-861 overall, and total. The evaluation of the MAV criteria will include scheduled and unscheduled visits.

6.6.3.3 ABPM

The ABPM is recorded during screening (starting any day up to Day -4 and ending no later than Day -3) and during the treatment period starting between days 38 and 45 (approximately Week 6). During the day (6AM to 10PM) inflations will occur every 15 min (4 per hour) and during the night (10PM to 6AM) inflations will occur every 30 minutes (2 per hour) for a total of 80 inflations.

The derivations of the ABPM parameters are summarized in [Table 6.a](#) below:

Table 6.a Derivation of ABPM Parameters

ABPM Parameters (SBP, DBP, HR)	Derivation
Baseline Hourly mean Week 6 Hourly mean	Average (arithmetic mean) of ABPM measurements in each hour after the time of the first AM dose on the day of the ABPM recording (for plots only).
Baseline 24 hour mean Week 6 24 hour mean	Average (arithmetic mean) of ABPM measurements after the time of the first AM dose on the day of the ABPM recording and including all observations recorded over the subsequent 24 hours.
Baseline daytime mean Week 6 daytime mean	Average (arithmetic mean) of ABPM measurements recorded between the hours of 6 AM (inclusive) and 10 PM (exclusive).
Baseline nighttime mean Week 6 nighttime mean	Average (arithmetic mean) of ABPM measurements recorded between the hours of 12 AM (inclusive) and 6 AM (exclusive).
Note: The baseline parameters are time-matched to the time of the first dose (approx. 8AM) of the Week 6 ABPM (between days 38 to 42).	

The baseline and Week 6 ABPM parameters and the change from baseline will be summarized with descriptive statistics by treatment group and TAK-861 overall. The change from baseline to Week 6 for the ABPM 24 hour, daytime and nighttime mean will be analyzed with an analysis of covariance (ANCOVA) model with baseline ABPM as a covariate and treatment as the fixed effect. The LS mean change from baseline in ABPM parameters for each treatment and the associated SE and 95% CI will be extracted from the ANCOVA model, along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values.

Only observed data will be used for the summary and analyses of ABPM parameters. No imputation will be performed for missing data.

The following figures will be generated:

- Average ABPM for SBP, DBP, HR by hour for the 24 hour interval:
Baseline, Week 6, Change from baseline
- Average ABPM for SBP, DBP, HR by clock hour for daytime [6 AM to 10 PM]:
Baseline, Week 6, Change from baseline
- Average ABPM for SBP, DBP, HR by clock hour for nighttime [12 AM to 6 AM]:
Baseline, Week 6, Change from baseline

The following blood pressure dipping categories 1 will be defined using the ratio of mean day-time and night-time ABPM for SBP and DBP (day-time defined as (0900 to 2100h) and night-time defined as (0100 to 0600h):

- Non-dipping or riser: Night-time/Day-time ≥ 1.0
- Mild dipper: $0.9 < \text{Night-time/Day-time} < 1.0$
- Dipper: $0.8 < \text{Night-time/Day-time} \leq 0.9$

- Extreme Dipping: Night-time/Day-time ≤ 0.8

The number and percentage of participants in each dipping category at baseline and Week 6 will be summarized by treatment group and TAK-861 overall. Shift tables (baseline vs. Week 6) will be presented.

6.6.3.4 ECG

The continuous ECG parameters (heart rate, PR interval, QRS interval, QT interval, QT interval with Bazett correction method (QTcB) and QT interval with Fridericia correction method (QTcF) at each visit, and the change from baseline will be summarized with descriptive statistics by treatment group and TAK-861 overall. Only the ECGs collected at the scheduled visits will be included in the summary.

The ECG interpretation (Within Normal Limits; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant, Not Evaluable) will be summarized at each visit by treatment group and TAK-861 overall.

The number and percentage of participants meeting each markedly abnormal criteria and any MAV criteria will be summarized over all postdose visits, at Week 2, Week 3, Week 8, Week 12 (optional 4-week extension) and at the 7-day follow-up visit by treatment group, TAK-861 overall, and total. The evaluation of the MAV criteria will include scheduled and unscheduled visits.

6.6.3.5 C-SSRS

The number and percentage of participants with at least 1 endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) at any postdose visit will be summarized by treatment group, and TAK-861 overall.

6.6.4 Extent of Exposure and Compliance

The summary of study drug exposure and compliance will be based on the Safety Set. The treatment duration is defined as (date of last dose – date of first dose +1). Treatment duration (days) will be summarized using descriptive statistics for each treatment group and TAK-861 overall.

Table 6.b below describes the bottle types dispensed assuming 32 tablets per bottle:

Table 6.b Bottle Types Dispensed for Each Treatment Group

Treatment Group	8AM		11 AM Bottle
	Bottle 1	Bottle 2	
Placebo	Placebo	Placebo	Placebo
0.5 mg twice daily	0.5 mg	Placebo	0.5 mg
2 mg twice daily	2 mg	Placebo	2 mg
2 mg followed by 5 mg	2 mg	Placebo	5 mg
7 mg QD	2 mg	5 mg	Placebo

TAK-861 bottle compliance will be calculated for each bottle type:

$$\frac{(\text{number of tablets dispensed from the bottle type} - \text{number of tablets returned from the bottle type})}{(\text{date of last dose} - \text{date of first dose} + 1)} * 100\%$$

For active treatment groups, only the active bottle types are counted.

Placebo bottle compliance will be calculated as:

$$\frac{(\text{total number of tablets dispensed} - \text{total number of tablets returned})}{3 * (\text{date of last dose} - \text{date of first dose} + 1)} * 100\%$$

The overall compliance for active treatment groups is the average of the compliance for the active bottle types.

The percent compliance for each bottle type and overall will be summarized with descriptive statistics by treatment group, and TAK-861 overall. In addition, the number and percentage of participants in the following compliance categories will be summarized: <70%, 70 to 100%, and >100% by treatment group.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

All PK summaries and analyses will be based on the PK set by dose levels within each part or each group.

Plasma concentrations of TAK-861 will be summarized with descriptive statistics (N, arithmetic mean, SD, coefficient of variation, median, minimum, maximum) by each scheduled time point and TAK-861 dose level. Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summary of plasma concentration values.

The following PK parameters will be calculated from plasma concentrations of TAK-861 on Day 1, Week 4 (Day 28), and Week 8 (Day 56), as data permit using non-compartmental analysis.

Table 6.c Plasma PK Parameters Definition

Symbol/Term	Definition
AUC_{last}	AUC from time 0 to time of the last quantifiable concentration on Day 1
$C_{max,1}$	Maximum observed concentration during first dosing interval
$C_{max,2}$	Maximum observed concentration during second dosing interval
C_{last}	Last observed concentration
$t_{max,1}$	Time to reach $C_{max,1}$
$t_{max,2}$	Time to reach $C_{max,2}$

Note:

¹ C_{max} and t_{max} at Week 4 and Week 8 is expected to be at steady-state exposures of TAK-861.

² $C_{max,2}$ and $t_{max,2}$ is applicable for twice daily dosing regimen only.

Additional PK parameters may be calculated as appropriate. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The treatment of BLQs for the calculation of PK parameters, and exclusions/flagging of PK concentration and parameter data will follow the processes detailed in the Clinical Pharmacology Analysis Plan.

PK parameters will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, maximum) by day and TAK-861 dose level.

Additionally, all individual TAK-861 plasma concentration-time data collected in this study will be combined with other clinical study data to develop a population PK model of TAK-861 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.

The intrinsic CYP3A4/5 activity will be evaluated by the ratio of 4 β -hydroxycholesterol vs cholesterol concentrations. The ratios of 4 β -hydroxycholesterol over cholesterol, and the ratios of the post-dose values to that of baseline will be summarized by day and TAK-861 dose level.

A scatterplot of TAK-861 plasma concentration (x-axis) versus the sleep latency on the MWT (y-axis) will be produced overall, and at each scheduled MWT timepoint (panel). TAK-861 plasma concentrations for placebo data will be included in the plot with a concentration of 0. The TAK-861 treatment groups will be displayed together in the plot with different symbols. The pairing of timepoints (based on nominal time post the first dose) for the scatter plot are outlined below:

MWT Timepoint	PK Timepoint
2	1.5
4	3.5
6	5.5
8	7.5

A scatterplot of TAK-861 plasma concentration (x-axis) versus time-matched change from baseline in HR, SBP and DBP will be produced for Day 1, Week 4, and Week 8. TAK-861 plasma concentrations for placebo data will be included in the plot with a concentration of 0. Only measurements from time points common to both vital signs and PK assessments will be used.

In addition, mean plots of TAK-861 plasma concentration and placebo corrected time-matched change from baseline in HR, SBP, and DBP will be produced for the active TAK-861 treatment groups for Day 1, Week 4, and Week 8. The scheduled time point will be the x-axis, mean (\pm SD) TAK-861 plasma concentration will be on the left y-axis, and time-matched change from baseline in the mean (\pm SD) of TAK-861 in HR, SBP, or DBP will be on the right y-axis. All TAK-861 treatment groups will be presented on the same plot.

6.7.2 Pharmacodynamic Analysis

Refer to the efficacy section for analysis of pharmacodynamic endpoints.

6.7.3 Biomarker Analysis

Not applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

Clinical outcome assessment (COA) compliance and COA completion over time will be calculated at the questionnaire level for all COAs at each visit from baseline to provide context for the interpretation of COA results. The COAs include PGI-I, CGI-I, NSS-CT, EQ-5D-5L, FIN, SF-36, and TSQM. A similar analysis will be generated for the cognition endpoints (PVT, CPAL, ONB, and iDSST-s).

COA compliance at each visit will be calculated as follows:

$$\frac{\text{number of participants with the COA score available}}{\text{number of participants for whom a COA score is expected}}$$

COA completion at each visit will be calculated as follows:

$$\frac{\text{number of participants with the COA score available}}{\text{number of participants in the full analysis set}}$$

6.8.1.1 Patient and Clinical Global Impression

The CGI-S will ask clinicians to assess severity of overall narcolepsy symptoms at baseline, using a 7-point Likert-type scale ranging from “1=normal, not at all ill” to “7=among the most extremely ill”. The CGI-I will ask clinicians to rate the extent to which their patients’ current overall narcolepsy symptoms are improved (compared with the start of the study) at Week 4 (day

28) and Week 8 (day 56), using a 7-point Likert-type scale ranging from “1=very much improved” to “7=very much worse”.

The PGI-S requires the participant to rate his/her disease severity at baseline on a 4-point scale ranging from “normal” to “severe.” The PGI-I will assess improvement in overall narcolepsy symptoms due to treatment relative to baseline at Week 4 (day 28) and Week 8 (day 56), on a 7-point scale ranging from “1=very much improved” to “7=very much worse”.

Summary statistics for CGI-S and PGI-S will be provided by treatment group and for TAK-861 overall. The number and percentage of participants in each response category will be summarized by treatment group, and for TAK-861 overall. Summary statistics for CGI-I and PGI-I will be provided at postdose visits by treatment group and TAK-861 overall.

Participants will be categorized as a responder based on two definitions of improvement:

- CGI-I/PGI-I score is “1=very much improved” or “2=much improved”
- CGI-I/PGI-I score is “1=very much improved” or “2=much improved” or “3=minimally improved”

The number and percentage of participants in each CGI-I/PGI-I response category and reported as improved based on the above responder definitions will be summarized at each postdose visit by treatment group and TAK-861 overall.

A generalized linear mixed model for binomial data with a logit link function will be used to analyze the CGI-I/PGI-I responder definitions. The observed values for the responder definition will be used as the response in the model. The model will include treatment group, postdose visit, and the treatment-by-visit interaction as fixed effects and subjects will be random effects. The CGI-S/PGI-S score will be included in the model as covariate. If the model does not converge, a logistic regression model at each visit will be used. The odds ratio of being a responder for each TAK-861 treatment group relative to placebo for each visit and the associated 95% CIs, and two-sided p-values will be estimated. The probabilities of being a responder for each treatment group and associated 95% CIs will be estimated.

6.8.1.2 NSS-CT

The NSS-CT is a 15-item self-administered questionnaire (score: 0-57) that assesses the severity and consequences of narcolepsy in 3 domains (sleep paralysis and hallucinations, excessive daytime sleepiness and nighttime sleep, and cataplexy). The NSS Severity is classified as follows 2:

Severity	NSS-CT Total Score
Mild	0-14
Moderate	15-28
Severe	29-42
Very severe	43-57

The NSS-CT Total Score and the change from baseline will be summarized using descriptive statistics at each visit by treatment group and TAK-861 overall. The number and percentage of participants in each NSS-CT severity category will be summarized by visit, treatment group and for TAK-861 overall. The change from baseline will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) in NSS-CT Total Score over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.1.3 EQ-5D-5L

The EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) comprises questions on five domains: mobility, self-care, pain/discomfort, usual activities, and anxiety/depression with five possible answers for each domain (1=no problem, 2=slight problem, 3=moderate problem; 4=severe problem, 5=unable to). EQ-5D-5L index scores are calculated from the five individual domain scores via country-specific algorithms. The index scores generally range from less than 0 (where 0 is the value of a health state equivalent to death) to 1, with higher scores indicating higher health utility. The EQ visual analogue scale (EQ VAS) (0-100) will be used to indicate the best health state of the day, where higher scores indicate more severe or frequent problems.

The number and percentage of participants in each level will be summarized for each of the five domains at baseline and postdose visits by treatment group and TAK-861 overall. The EQ-5D-5L Index Score and Visual Analogue Scale will be summarized with descriptive statistics including the baseline, postdose, and change from baseline (Day -1) at each visit by treatment group and TAK-861 overall. The change from baseline will be analyzed with an MMRM model.

Boxplots of the EQ-5D-5L Index Score and Visual Analogue Scale at baseline, Week 4, and Week 8 and including change from baseline (with quartiles and extreme scores) will be produced. The change from baseline will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) in over time will be plotted for the EQ-5D-5L Index Score and Visual Analogue Scale. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.1.4 FIN

The Functional Impacts of Narcolepsy (FIN) is a narcolepsy-specific 11-item instrument that assesses functional impacts of narcolepsy across 3 domains: social activities (items 1 to 4), everyday activities (items 5 to 8), and everyday responsibilities (items 9 to 11). The response to each question is on a 5-point scale:

1. Never
2. Rarely
3. Sometimes
4. Usually

5. Always

The FIN is assessed on Day -1, Week 4, and Week 8.

The scoring instructions are noted below:

1. Rescore each item from a 1 – 5 response scale to a 0 – 4 response scale where 0 indicates the best health and 4 the worst.
2. For each participant, calculate the average score for each domain, if at least half the items in the domain have been answered:
(sum of responses in the domain / number of completed items in the domain)
3. Standardize the average score to a 0 – 100 scale:
 - a) Standardized score = average score/4 x 100.
 - b) 0 indicates the best health and 100 the worst health. A decrease from baseline would indicate improved health.

For example, if the 4 items in one domain had the responses 1, 2, 3, 2 (re-scored to 0 to 4 response scale), the average score would be 2 and the standardized score would be 50 points.

The 3 standardized domain scores at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. The change from baseline will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

Cumulative distribution plots of the change from baseline for each of the 3 domains will be generated for Week 4 and Week 8.

Participants will be categorized as a responder based on the meaningful change threshold (MCT) for each domain:

- Change from baseline in social activities score ≤ -40 .
- Change from baseline in everyday activities score ≤ -40 .
- Change from baseline in everyday responsibilities score ≤ -30 .

The number and percentage of participants who are responders in each domain will be summarized at each postdose visit by treatment group and TAK-861 overall. A sensitivity analysis will be performed excluding all participants with a baseline score less than the MCT.

A generalized linear mixed model for binomial data with a logit link function will be used to analyze the response rate for each domain (see section 6.8.1.1). If the model does not converge, a logistic regression model at each visit will be used.

6.8.1.5 SF-36

The SF-36 is a 36-item, participant-reported survey of participant health. The SF-36 consists of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability, that is, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

The physical and mental component summary scores will also be derived per the SF-36 coding manual.

The domain and summary scores at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. The change from baseline for each domain and summary score will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.1.6 TSQM

The TSQM vII is an 11-item questionnaire that measures satisfaction with treatment in 4 domains: effectiveness (items 1 - 2), side effects (items 3 - 6), convenience (items 7-9) and global satisfaction (items 10-11). The domain scores are derived from the item scores and have values from 0 to 100 where higher scores indicate better treatment satisfaction:

Domain	All domain items are completed	Exactly 1 domain item is missing
Effectiveness	$[(\text{Item 1} + \text{Item 2}) - 2] \text{ divide by } 12) * 100$	$[(\text{Use the completed item}) - 1] / 6) * 100$
Side Effects (All 'NA' responses are coded as '5' indicating 'Not at all Dissatisfied')	If Question 3 is answered 'No' then score = 100 Otherwise $[(\text{Item 4 to Item 6}) - 3] \text{ divide by } 12) * 100$	$[(\text{Sum (the two completed items)}) - 2] \text{ divide by } 8) * 100$
Convenience	$[(\text{Item 7 to Item 9}) - 3] \text{ divided by } 18) * 100$	$[(\text{Sum (the two completed items)}) - 2] \text{ divided by } 12) * 100$
Global Satisfaction	$[(\text{Item 10} + \text{Item 11}) - 2] / 12) * 100$	$[(\text{Use the completed item}) - 1] / 6) * 100$
Note: a score can be computed for a domain only if no more than one item is missing from the domain.		

The 4 TSQM domains at each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. The TSQM domains will be analyzed with an MMRM model. The LS mean (and associated 95% CI) over time will be plotted. The scheduled time points will be on

the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.2 Health Care Utilization Analysis

Not applicable.

6.9 Other Analyses

6.9.1 Cognitive Endpoints

Completion and compliance will be calculated for each of the cognition endpoints (PVT, CPAL, ONB, and iDSST-s) similar to the COA endpoints (see section 6.8.1 for definitions).

6.9.1.1 PVT

The PVT is a simple reaction performance task that aims to measure sustained attention with no learning effects over repeated administration. The PVT will be administered on Day -1 (at same time as 1 and 7 hour post 8AM dose assessments), and 1 (morning) and 7 (afternoon) hours post the 8AM dose at Week 4 and Week 8. The PVT endpoints are the number of lapses, mean reaction time (RT), and mean 1/RT.

The PVT endpoints will be summarized with descriptive statistics including the Day -1 (baseline) sessions, postdose sessions at each visit, and the change from time-matched baseline at each visit by treatment group and TAK-861 overall.

For each PVT endpoint, box plots will be prepared for observed values at baseline, Week 4, and Week 8 for each treatment group (separate displays for 1 hour postdose and 7 hour postdose evaluations).

For the change from time-matched baseline in the PVT endpoints, the normality assumption will be tested using the Shapiro-Wilk test. If there is no statistically significant departure from the normal distribution assumption, then the change from time-matched baseline will be analyzed with an MMRM model. The MMRM model will include fixed effects for the time-matched baseline value, treatment, visit (Week 4, Week 8), timepoint (morning and afternoon), treatment-by-visit interaction, treatment-by-timepoint interaction, visit-by-timepoint interaction and the 3-way interaction of treatment, visit, and timepoint. Both visit and timepoint are repeated factors. Kronecker product UN@UN will be used for the covariance structure. Other Kronecker product structures such as UN@AR(1), and UN@CS will also be used if there are convergence issues. If the model does not converge then the change from time-matched baseline will be analyzed with an MMRM model at each visit (Week 4, Week 8).

Otherwise, the normality assumption will be tested on the square root transformation of the change from time-matched baseline. If there is no statistically significant departure from the normal distribution assumption, the square root transformed values will be analyzed with an MMRM model as described above. The LS means and 95% confidence intervals will be transformed back to the original scale.

In the case where the normality assumption does not hold after the square root transformation, the endpoint will be analyzed with a zero-inflated negative binomial model. Separate models for the change from time-matched baseline will be generated for each visit and postdose timepoint (morning and afternoon).

Other transformation of the endpoints may be evaluated if appropriate. If the normality assumptions do not hold after all interpretable transformations, Friedman's test will be performed to compare the population distributions of the treatments.

6.9.1.2 CPAL/ONB/iDSST-s

The CPAL test is a measure of visual associate memory and uses a well-validated paired associate learning paradigm in which the participant must learn the locations of a number of amoeba-like shapes on the computer screen. The CPAL endpoint is number of errors, where lower scores indicate better performance.

The ONB test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. The ONB endpoints are speed of performance (mean of the log 10 transformed reaction times for correct responses) where a lower score indicates better performance and accuracy of performance (arcsine square root of the proportion of correct responses) where a higher score indicates better performance.

The iDSST-s is a processing speed test that is based on the pre-existing pencil and paper version of the Digit Symbol Substitution Test. The iDSST-s endpoints are the number of correct responses where a higher score indicates better performance) and speed of performance (mean of the log 10 transformed times for correct responses) where a lower score indicates better performance.

The CPAL, ONB, and iDSST-s tests are administered on Day -1 (baseline), Week 4 and Week 8. The results at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall.

The normality assumption for each endpoint will be tested using the Shapiro-Wilk test for the change from baseline. If there is no statistically significant departure from the normal distribution assumption, then the change from baseline will be analyzed with an MMRM model.

For number of errors from CPAL and number of correct responses from iDSST-s, the normality assumption will be tested on the square root transformation of the change from time-matched baseline. If there is no statistically significant departure from the normal distribution assumption, the square root transformed values will be analyzed with an MMRM model. The LS means and 95% confidence intervals will be transformed back to the original scale.

In the case where the normality assumption does not hold after the square root transformation, the endpoint will be analyzed with a zero-inflated negative binomial model or other appropriate model. Separate models for the change from baseline will be generated for each visit.

Other transformation of the endpoints may be evaluated if appropriate for number of errors from CPAL and number of correct responses from iDSST-s.

If the normality assumptions do not hold after all interpretable transformations, Friedman's test will be performed to compare the population distributions across the treatment groups.

6.9.2 nPSG Parameters

The nPSG parameters (minutes between lights off and lights on, sleep onset latency, latency to stage R, total sleep time, latency to persistent sleep, wake after persistent sleep, total number of nocturnal awakenings, sleep efficiency, Stage N1 percentage, Stage N2 percentage, Stage N3 percentage, and Stage R percentage) at each visit (baseline, Week 4, and Week 8) will be summarized with descriptive statistics by treatment group and TAK-861 overall. Descriptive statistics will be provided for both observed values and change from baseline.

Additional exploratory analyses to be performed by Takeda Quantitative Sciences will be described in a separate Biomarker Analysis Plan. The results will not be included in the CSR.

6.9.3 Actigraphy Derived Sleep and Activity Parameters

The actigraphy (accelerometry) device (Empatica) will be worn continuously (as much as possible throughout the day and night) from informed consent to the first follow-up visit or rollover into the LTE study. The definitions of the sleep and activity parameters are shown below:

Table 6.d Sleep and Activity Parameters from the Actigraphy Device

Parameter Type	Parameter	Definition
Sleep (nightly)	Total sleep time (TST)	the assumed time spent actually sleeping after the sleep onset (min)
	Sleep Efficiency (SE)	expressed as a percentage: TST / TIB (the total length of the time in bed period, from time in bed start to time in bed stop)
	Wake after sleep onset (WASO)	The amount of time spent awake after the sleep onset latency (min)
Activity	Activity count	Activity count per minute collected continuously
	Total daily time spent in motion	Classified as light, moderate, vigorous intensity activities, or no motion (minutes) in each day.
Note: sleep and activity parameters are estimated by Empatica proprietary algorithms		

For each nightly sleep parameter presented in Table 6.d, the weekly mean is the average (arithmetic mean) of the nightly values over a 2-week period converted to a weekly rate (multiply by 7) for baseline, Week 2, Week 4, Week 6, and Week 8. Baseline will be generated by taking the average (arithmetic mean) of the nightly values over the last 14 days prior to the date of the first dose. The mean is based on the number of nights with non-missing values in the 2-week period.

The daily activity count will be calculated based on activity from 8AM to 8PM. The weekly mean is the average (arithmetic mean) of the daily values over a 2-week period converted to a

weekly rate (multiply by 7) for baseline, Week 2, Week 4, Week 6, and Week 8. Baseline will be generated by taking the average (arithmetic mean) of the daily values over the last 14 days prior to the date of the first dose. The mean is based on the number of days with non-missing values in the 2-week period.

The weekly mean time in light/moderate, vigorous, and no motion will be calculated similar to the nightly sleep parameters.

The weekly parameters at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. Mean plots of the observed weekly parameters at each visit (baseline, Week 2, Week 4, Week 6, and Week 8) will be generated. The change from baseline will be analyzed with an MMRM model.

Additional exploratory analyses to be performed by Takeda Quantitative Sciences will be described in a separate Biomarker Analysis Plan. The results will not be included in the CSR.

6.9.4 Narcolepsy Symptoms (eDiary)

Weekly episodes for the following narcolepsy symptoms will be derived from the eDiary collection at baseline, Week 2, Week 4, Week 6, Week 8, and the 7-day post last dose follow-up visit:

- Sleep paralysis
- Refreshing Sleep (response of refreshed or somewhat refreshed)
- Hypnagogic/hypnopompic hallucinations
- Nocturnal awakenings
- Disturbing and frightening dreams/nightmares
- Dreaming a lot or all night
- Problems falling asleep
- Good sleep quality (response of very good or fairly good)
- Number of naps

Weekly episodes (WE) at baseline will be based on the number of episodes as averaged over 2 weeks minimum, with 11 out of 14 compliant days in completion of the self-reported electronic diary. WE for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:

$$WE = \left(\frac{\text{number of episodes over a 2 week period}}{\text{number of non - missing diary days in the 2 week period}} \right) * 7$$

Weekly episodes for the 7-day post last dose follow-up visit is calculated as follows:

$$WE = \left(\frac{\text{number of episodes over the follow - up period}}{\text{number of non - missing diary days in the follow - up period}} \right) * 7$$

If a diary for a given day reports ≥ 0 episodes, the day will be counted as non-missing diary day. Otherwise, the day will be counted as a missing diary day for the symptom.

The number of naps and weekly episodes of each narcolepsy symptom at each visit, change from baseline, and percent change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall.

Box plots of the number of naps and weekly episodes of each narcolepsy symptom by visit and treatment group will be generated.

The number of naps will be analyzed with a GEE model using a log-link function featuring a Poisson distribution similar to WCR. The weekly episodes for narcolepsy symptoms will be analyzed using a Kruskal-Wallis test.

6.10 Interim Analyses

An interim analysis will occur when at least 40 participants have completed the Week 4 visit. In this case, an Internal Review Committee (IRC), composed of members who do not have study-related contact with sites, will review the study data.

The efficacy endpoints to be included in the IA are MWT, ESS, and WCR. Statistical analyses will include all observed data up to the IA data cut, including incomplete follow-up. The same statistical models described in Sections 6.5.1.2 and 6.5.2.1 will be applied.

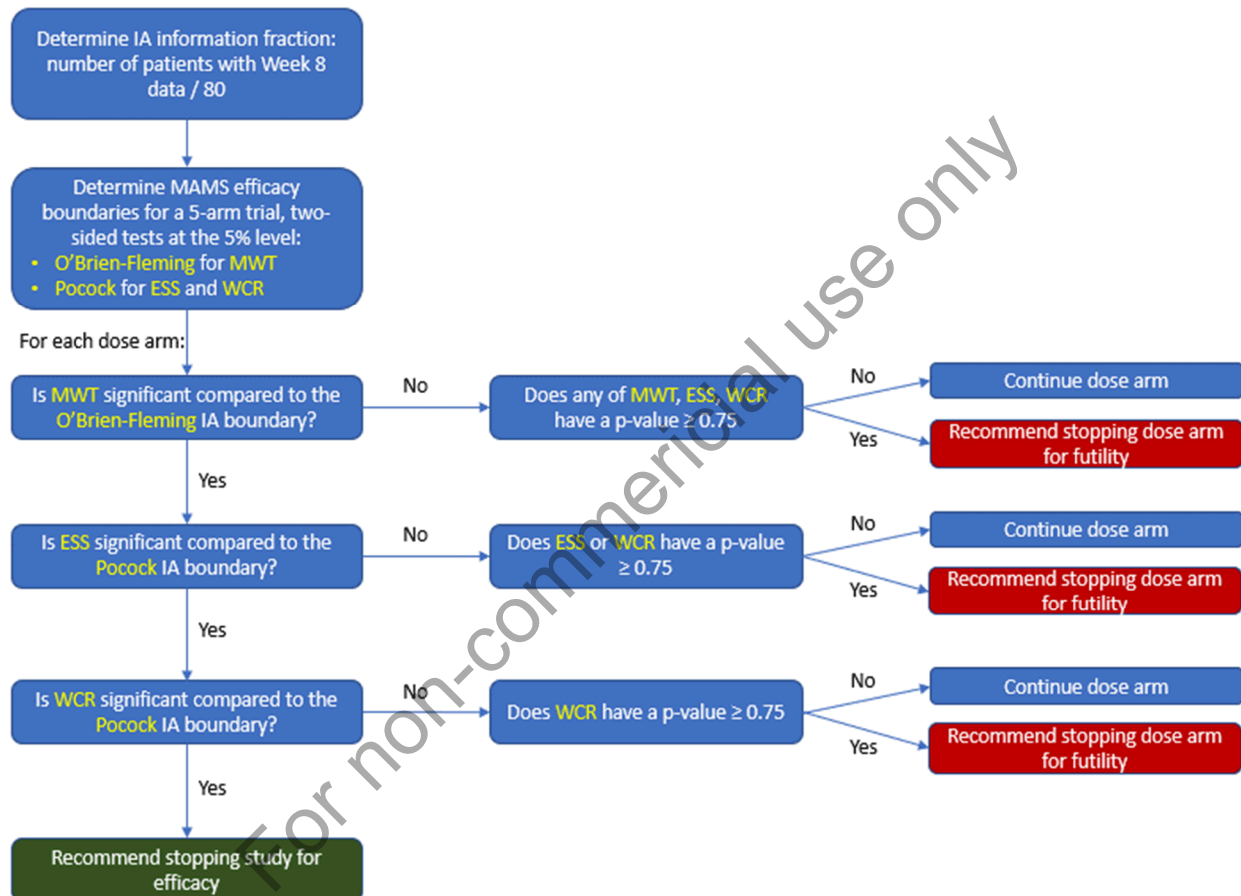
The generalization of group sequential design to the multi-arm multi-stage (MAMS) setting 3 coupled with the hierarchical testing scheme for multiple endpoints in group-sequential trials 4 will be applied to control the family-wise error rate (FWER). More specifically, at IA and final analysis, the O'Brien-Fleming efficacy boundaries under the MAMS framework will be applied to MWT, and the Pocock efficacy boundaries under the MAMS framework will be applied to ESS and WCR. Since the number of patients who have completed the Week 8 visit at IA is unknown at the planning stage of the trial, the information fraction will be determined at the time of IA data cut based on blinded data by dividing the total number of patients with Week 8 data at IA by 80 (the planned number of patients with complete follow-up for the entire study), and the corresponding O'Brien-Fleming and Pocock efficacy boundaries for two-sided tests at the 5% level for both the IA and final analysis will be determined accordingly using the MAMS Group-Sequential module of the EAST software. The boundaries for a range of IA completers will be provided in the IRC charter.

At both the IA and final analysis, for each dose level, hypothesis testing will proceed according to the hierarchy: MWT \rightarrow ESS \rightarrow WCR. At either the IA or final analysis, an endpoint will be tested for statistical significance only if the previous endpoint in the hierarchy has achieved statistical significance relative to its MAMS efficacy boundary at that look. Early stopping of the trial for efficacy may be considered if a dose level achieves statistical significance for all three endpoints at IA. On the other hand, if any endpoint in a dose level yields a p-value ≥ 0.75 at IA, the recommendation is to stop that dose level for futility. The futility assessment will be non-binding.

The list of tables, listings, and figures to be generated for the IA efficacy and safety summary will be specified in the IRC charter. The final decision of stopping the trial for efficacy or a dose level for futility will be made at the IRC's discretion based on the totality of evidence.

Figure 6.a illustrates the hypothesis testing process at the IA.

Figure 6.a Hypothesis Testing Flowchart at the IA



6.11 Data Monitoring Committee/Internal Review Committee

An IRC, composed of members who do not have contact with investigators or sites, will review the study data at the IA and determine if dose arms or the study will be discontinued based on efficacy (see section 6.10). An IRC charter will provide details on the conduct and procedures for the IRC.

An external data monitoring committee (DMC) will review the safety and tolerability data on a quarterly basis, throughout the study. A DMC charter will provide full guidance on the function and practices to be followed by the DMC.

7.0 REFERENCES

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3. Ghosh, P., Liu, L., Senchaudhuri, P., Gao, P., & Mehta, C. (2017). Design and monitoring of multi-arm multi-stage clinical trials. Biometrics, 73(4), 1289-1299.
4. Glimm, E., Maurer, W., & Bretz, F. (2010). Hierarchical testing of multiple endpoints in group-sequential trials. Statistics in Medicine, 29(2), 219-228.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

- Updated the definition of full analysis set to include participants with at least one postdose efficacy measurement.
- Added multiplicity testing.
- Added baseline age to MMRM model for analysis of ESS and WCR and added prior use of narcolepsy medications as a baseline covariate to the MMRM model for the analysis of MWT, ESS, and WCR.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Not applicable.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Refer to programming specifications.

9.2.2 Definition of Baseline

The definition of baseline is addressed in the specific section of the SAP.

9.2.3 Definition of Visit Windows

Refer to programming specifications.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Mogg, Robin	Biostatistics Approval	02-Dec-2022 16:01 UTC

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STATISTICAL ANALYSIS PLAN

Study Number: TAK-861-2001

Study Title:

A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-861 for the Treatment of Narcolepsy With Cataplexy (Narcolepsy Type 1)

Phase: 2

Version: Amendment 3

Date: 11 December 2023

Prepared by: [REDACTED]

Based on:

Protocol Version: Initial

Protocol Date: 17 Aug 2022

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REVISION HISTORY

Version	Date	Primary Rationale for Revision
Initial	29 Nov 2022	Not Applicable
Amendment 1	24 Jul 2023	Add estimand framework to align with FDA E9 (R1) guidance in clinical trials, add multiplicity adjustment based on graphical approach, and remove possibility of stopping for efficacy at IA.
Amendment 2	August 28 2023	Remove estimand framework. Given there is an interim analysis, the study will not be used as confirmatory evidence and therefore utilizing the estimand framework is unnecessary.
Amendment 3	December 11 2023	Adjusted analytical approach to WCR, cognitive endpoints, and number of naps based on the underlying distribution assumptions

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ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
AE	adverse event
AHI	apnea hypopnea index
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC _{last}	area under the concentration-time curve from time 0 to time of the last concentration measured
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
CGI-I	Clinical Global Impression–Improvement
CGI-S	Clinical Global Impression–Severity
CI	Confidence interval
C _{max}	maximum observed concentration
CPAL	Continuous Paired Associate Learning
C-SSRS	Columbia Suicide Severity Rating Scale
CPAP	continuous positive airway pressure
DMC	data monitoring committee
DNS	disturbed nighttime sleep
ECG	electrocardiogram
e-diary	electronic diary
EDS	excessive daytime sleepiness
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
ESS	Epworth Sleepiness Scale
EU	European Union
FAS	Full Analysis Set
FIN	Functional Impacts of Narcolepsy
FWER	family-wise error rate
GEE	generalized estimating equations
HR	heart rate
iDSST-s	international Digit Symbol Substitution Test-symbols
INR	international normalized ratio
IRC	Internal review committee
LFT	liver function test
LS	Least square
LTE	long-term extension
MAMS	multi-arm multi-stage
MAV	markedly abnormal value
MCT	meaningful change threshold
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures

MWT	Maintenance of Wakefulness Test
nPSG	nocturnal polysomnography
NSS-CT	Narcolepsy Severity Scale for Clinical Trials
NT1	narcolepsy type 1
NT2	narcolepsy type 2
ONB	one back test
PD	pharmacodynamic(s)
PGI-I	Patient Global Impression–Improvement
PGI-S	Patient Global Impression–Severity
PK	pharmacokinetic(s)
PSG	polysomnography
PVT	psychomotor vigilance test
QD	once daily
QTcF	QT interval with Fridericia correction method
REM	rapid eye movement
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form-36 Survey
SL	Sleep latency
SOC	System Organ Class
TEAE	treatment-emergent adverse event
t_{\max}	time of first occurrence of C_{\max}
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
VAS	visual analog scale (score)
WCR	weekly cataplexy rate

Note: text in italics represents language copied directly from the protocol.

1.0 OBJECTIVES AND ENDPOINTS

1.1 Objectives

1.1.1 Primary Objective

- *To assess the effect of TAK-861 on excessive daytime sleepiness (EDS) as measured by sleep latency from the Maintenance of Wakefulness Test (MWT).*

1.1.2 Secondary Objectives

- *To assess the effect of TAK-861 on EDS as measured by the Epworth Sleepiness Scale (ESS) total score.*
- *To assess the effect of TAK-861 on cataplexy as assessed by the weekly cataplexy rate (WCR).*
- *To evaluate the safety and tolerability of TAK-861.*

1.1.3 Exploratory/Additional Objectives

- *To evaluate the safety and tolerability of TAK-861.*
- *To assess the effect of discontinuation of TAK 861, as assessed by ESS, WCR, and patient-reported sleep parameters.*
- *To assess the effect of TAK-861 on sustained attention as measured by the psychomotor vigilance test (PVT).*
- *To assess the effect of TAK-861 on overall narcolepsy symptoms measured by the Clinical Global Impression Scale – Global Improvement Scale (CGI-I) and the Patient Global Impression of Improvement (PGI-I) scale.*
- *To assess the effect of TAK-861 on severity of narcolepsy symptoms measured by Narcolepsy Severity Scale for Clinical Trials (NSS-CT).*
- *To assess the effect of TAK-861 on mobility, self-care, usual activities, pain/discomfort and anxiety/depression as assessed by the EuroQol-5 Dimensions 5-Levels (EQ-5D-5L) scale.*
- *To assess the effect of TAK-861 on quality of life of participants, as assessed by the Short Form-36 Survey (SF-36).*
- *To assess the efficacy of TAK-861 on functional impacts of narcolepsy as assessed by the Functional Impacts of Narcolepsy (FIN) scale.*

- *To assess the effect of TAK-861 on quality of nocturnal sleep and presence or absence of rapid eye movement sleep-related abnormalities, including hypnagogic/hypnopompic hallucination, sleep paralysis, and nocturnal awakenings from the daily e-diary.*
- *To assess the effects of TAK-861 on memory, working memory, and processing speed as measured by the cognitive tests (Continuous Paired Associate Learning [CPAL] test, One Back test [ONB], and international Digit Symbol Substitution Test-symbols [iDSST-s]).*
- *To assess the treatment satisfaction with TAK-861 as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM).*
- *To assess the effect of TAK-861 on sleep architecture as measured by nocturnal polysomnography (nPSG).*
- *To assess the effect of TAK-861 on daily/nighttime activity as measured by actigraphy (accelerometry) and HR (photoplethysmography).*
- *To assess steady-state exposures of TAK 861.*
- *To assess the pharmacokinetic (PK)/ pharmacodynamic (PD) relationship(s) of TAK 861 for selected efficacy or safety measures.*

1.2 Endpoints

1.2.1 Primary Endpoint

- *Change from baseline to Week 8 in mean sleep latency from the MWT*

1.2.2 Secondary Endpoints

- *Change from baseline to Week 8 in ESS total score*
- *WCR at Week 8*
- *Occurrence of at least 1 treatment-emergent adverse event (TEAE).*

1.2.3 Exploratory/Additional Endpoints

- *Occurrence of at least 1 markedly abnormal value (MAV) for postdose laboratory values.*
- *Occurrence of at least 1 MAV for postdose vital signs.*
- *Occurrence of at least 1 MAV for postdose electrocardiogram (ECG) parameters.*
- *Time-matched change in blood pressure (BP) and heart rate (HR) from baseline to specified postdose time points.*
- *Change in ambulatory BP and HR parameters from baseline.*
- *Number (and percent) of participants with at least 1 endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS).*

- *Change from baseline in ESS total score, WCR, and sleep parameters reported in the patient-reported sleep electronic diary (e-diary) at the follow-up visit 1 week after drug discontinuation.*
- *Change from baseline in number of lapses on PVT.*
- *PGI-I and CGI-I scores.*
- *Change from baseline in NSS-CT.*
- *Change from baseline in EQ-5D-5L index score.*
- *Change from baseline in quality of life as measured by SF-36 domain scores.*
- *Change from baseline in the FIN domain scores.*
- *Change from baseline in frequency of refreshing nocturnal sleeps, sleep paralysis, hypnagogic/hypnopompic hallucinations, and nocturnal awakenings reported in the daily e diary.*
- *Change from baseline in CPAL, ONB, and iDSSTs measurements.*
- *Treatment satisfaction as measured by the 4 dimensions of the TSQM.*
- *Change from baseline in various nPSG measures, including nocturnal awakenings.*
- *Change from baseline in daily/nighttime activity metrics derived from continuous actigraphy (accelerometry) and HR (photoplethysmography) from a wrist-worn device.*
- *TAK-861 plasma concentrations and selected noncompartmental analysis PK parameters (maximum observed concentration [C_{max}], time of first occurrence of C_{max} [t_{max}], and area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration [AUC_{last}]).*

2.0 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, multicenter, 8-week parallel group study to evaluate the efficacy, safety, and tolerability of 4 oral dose regimens of TAK-861.

Approximately 100 (male and female) participants with NT1, who satisfy the inclusion and exclusion criteria, will be randomized such that each participant has an equal chance of being assigned to any 1 of 5 treatment arms: 3 TAK-861 twice daily dose regimens, 1 TAK-861 QD dose regimen, or matching placebo. Randomization will be stratified by region. Starting on the morning of Day 1, the study drug will be administered at approximately the same time each day for 8 or 12 weeks. (If the participant wishes to enroll in the long-term extension [LTE] study but the LTE study has not started at the participant's site when the participant completes the Week 8 visit of the current study, the participant will be allowed to continue in the current study for an additional 4 weeks; see below.)

Participants who have provided informed consent will complete a screening period of up to 50 days to washout any NT1 medication (if applicable). Participants will be asked to complete

an e-diary, starting from the initial screening visit, no later than Day -16. To be eligible for the study, participants must fill out self-reported cataplexy questions in the e-diary for at least 11 days of the 14-day period from Day -16 to Day -3 and have ≥ 4 partial and/or complete episodes of cataplexy/week (averaged over Days -16 to -3).

Participants will remain confined overnight at the study site during the following times:

- *Days -2 to 1 (1 mandatory overnight at Day -2; 1 optional overnight at Day -1).*
- *Days 27 to 28 (1 overnight).*
- *Days 55 to 56 (1 overnight).*

After the Week 8 visit, participants will have the option to participate in an LTE study under a separate protocol (assuming protocol is open for enrollment). Participants who enroll in the LTE study will not have follow-up visits in this study.

If a participant plans to enroll in the LTE study but the LTE study is not open for enrollment at the participant's site when the participant completes the Week 8 visit, the participant will be allowed to continue in the current study for an additional 4 weeks of treatment (continuing the same treatment regimen as the previous 8 weeks). This is to avoid a treatment gap for participants willing to roll over from this study to the LTE study.

For participants who do not participate in the LTE study (including any participant who completes the Week 12 visit and for any reason does not enroll in the LTE), every effort should be deployed to have them complete a first follow-up visit approximately 7 days after the final study drug intake and a second follow-up visit (home healthcare visit) approximately 28 days after the final study drug intake. For participants who early terminate the study, every effort should be deployed to have them complete an early termination visit as soon as possible and a follow-up visit (in-clinic visit or home healthcare, if available) approximately 28 days after the last dose of study drug. Participants not participating in the LTE study can restart their non-exclusionary medications after the first follow-up visit or early termination visit.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

3.1.1 Primary Endpoint

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the mean sleep latency (minutes) from the 4 sessions of a 40-minute MWT. The statistical null hypothesis is that the mean change from baseline to Week 8 in the mean sleep latency for each TAK-861 treatment group is the same as the mean change from baseline to Week 8 in the mean sleep latency for the placebo treatment group.

3.2 Secondary Endpoints

TAK-861 is superior to placebo as measured by the change from baseline to Week 8 in the total ESS score. The statistical null hypothesis is that the mean change from baseline to Week 8 in the

total ESS score for each TAK-861 treatment group is the same as the mean change from baseline to Week 8 for the placebo treatment group.

TAK-861 is superior to placebo as measured by the WCR at Week 8. The statistical null hypothesis is that the incidence rate ratio (TAK-861 to placebo) of WCR at Week 8 is equal to 1.

3.3 Statistical Decision Rules

Not applicable.

3.4 Multiplicity Adjustment

To adjust for multiplicity and provide strong control of the family-wise error rate (FWER), the graphical approach of Bretz et al. (2009) [1] will be used in testing the primary endpoint (MWT) and the secondary efficacy endpoints (ESS and WCR) for the four dose groups. No multiplicity adjustment will be made for exploratory endpoints. Compared to a fixed-sequence hypothesis testing procedure encompassing all dose levels, the proposed graphical approach increases the likelihood that one dose achieves statistical significance on all three endpoints. Under the protocol assumptions, the power of demonstrating statistical significance on all three endpoints for at least one dose is 78%. Figure 1 displays the directed graph representing the hypothesis testing scheme where, the 12 elementary hypotheses (three endpoints \times four dose groups) are represented by vertices, the initial α -allocation (total $\alpha = 0.05$, two-sided) for each elementary hypothesis is presented within the corresponding vertex, and the weight associated with a directed edge indicates the fraction of the local significance level at the initial vertex (tail) that is added to the significance level at the terminal vertex (head) if the hypothesis at the tail is rejected. The numeric subscripts within the vertices index the dose groups. Below is a detailed description of the 12 elementary hypotheses.

- $H_{1,MWT}$: 0.5 mg twice daily is superior to placebo in the primary endpoint MWT
- $H_{1,ESS}$: 0.5 mg twice daily is superior to placebo in the secondary endpoint ESS
- $H_{1,WCR}$: 0.5 mg twice daily is superior to placebo in the secondary endpoint WCR
- $H_{2,MWT}$: 2 mg twice daily is superior to placebo in the primary endpoint MWT
- $H_{2,ESS}$: 2 mg twice daily is superior to placebo in the secondary endpoint ESS
- $H_{2,WCR}$: 2 mg twice daily is superior to placebo in the secondary endpoint WCR
- $H_{3,MWT}$: 2 mg followed by 5 mg is superior to placebo in the primary endpoint MWT
- $H_{3,ESS}$: 2 mg followed by 5 mg is superior to placebo in the secondary endpoint ESS
- $H_{3,WCR}$: 2 mg followed by 5 mg is superior to placebo in the secondary endpoint WCR
- $H_{4,MWT}$: 7 mg once daily is superior to placebo in the primary endpoint MWT
- $H_{4,ESS}$: 7 mg once daily is superior to placebo in the secondary endpoint ESS
- $H_{4,WCR}$: 7 mg once daily is superior to placebo in the secondary endpoint WCR

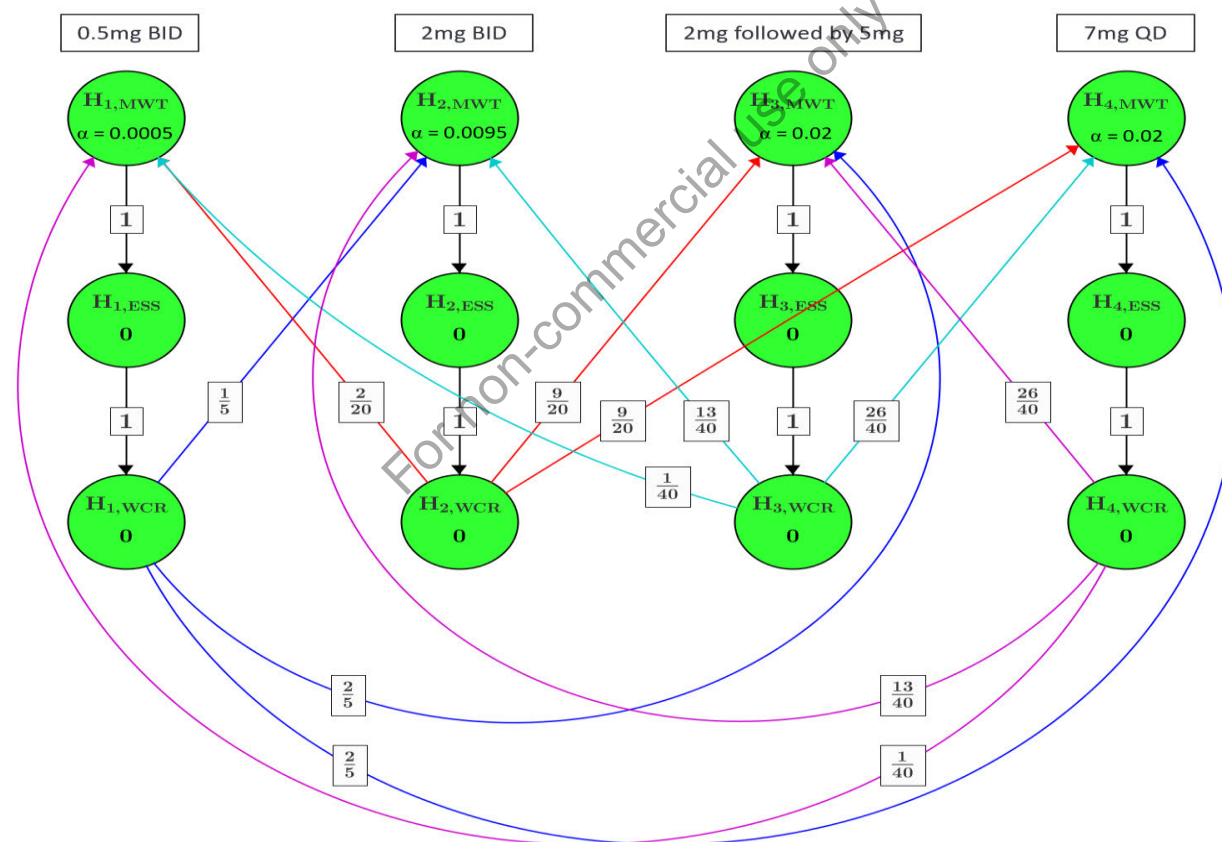


Figure 1 Graphical Approach for Testing Primary and Secondary Efficacy Endpoints

4.0 SAMPLE SIZE DETERMINATION

Assuming an SD of 11 minutes, a sample size of 16 participants per treatment group completing 8 weeks is enough to achieve >90% power to detect a difference of 14 minutes between a TAK-861 dose and placebo by a 2-sample t-test on the change from baseline to Week 8 in mean sleep latency from 4 MWT sessions at 0.05 2-sided significance level. Assuming a 20% dropout rate, 20 participants per treatment group may be enrolled for a total of up to 100 participants.

This sample size will also provide 88% power to detect a difference of 8 points between TAK-861 and placebo by a 2-sample t-test on the change from baseline to Week 8 in ESS total scores at 0.05 2-sided significance level, assuming an SD of 7 points.

In addition, this sample size will provide approximately 86% power to detect a 50% reduction in WCR relative to placebo with TAK-861 using a Poisson model at 0.05 2-sided significance level, assuming a baseline WCR of 4, with a placebo effect of 25% reduction from baseline.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety set will consist of all participants who received at least 1 dose of study drug. This analysis set will be used for demographic, baseline characteristic, and safety summaries.

5.2 Full Analysis Set

The full analysis set will consist of all participants who were randomized and received at least 1 dose of study drug and have at least one postdose efficacy measurement. Efficacy measurements include cataplexy, MWT, and ESS. The full analysis set will be used for summaries of efficacy and applicable exploratory endpoints.

5.3 Pharmacokinetic Analysis Set

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

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

All p-values reported will be 2-sided and reported to 3 decimal places.

All continuous variables will be summarized with descriptive statistics (N, mean, median, standard deviation (SD), minimum, and maximum) unless stated otherwise. The denominator for any percentages will be based on the number of participants who provided non-missing responses to the categorical variable.

6.1.1 Handling of Treatment Misallocations

For efficacy, treatment misallocations will be analyzed as randomized. For safety, treatment allocations will be analyzed as treated.

6.1.2 Analysis Approach for Continuous Variables

Where appropriate continuous variables will be analyzed with a mixed model with repeated measures (MMRM). Unless specified otherwise, the MMRM model will contain fixed effects for the baseline value of the corresponding endpoint (as a continuous covariate), treatment, visit (categorical), and treatment-by-visit interaction, where visit is the repeated factor. An unstructured variance-covariance structure will be used initially. Other variance-covariance structures will be evaluated if there are convergence issues with the model. The Kenward and Roger adjustment for computing the denominator degrees of freedom for the tests of fixed effects will be used. The least square (LS) mean, standard error (SE) and 95% CI will be presented for each visit and treatment group. All pairwise differences from placebo and associated LS means, SEs, 95% CIs, and two-sided p-values will be reported.

In the case a continuous endpoint is not normally distributed based on the Shapiro-Wilk test, the Friedman test will be conducted to compare the population distributions across the treatment groups. The Friedman test is conducted approximately by a mixed effect model with repeated measures, taking the assumption that Q test statistics from Friedman test is approximately chi-square distributed, and the rank is approximately normally distributed. In the mixed effect model, the response variable is the change from baseline ranked within each visit, and the fixed effects are baseline rank, treatment, visit, and treatment-by-visit interaction. The Kenward and Roger adjustment for computing the denominator degrees of freedom for the tests of fixed effects will be used. The two-sided p-values will be reported.

6.1.3 Analysis Approach for Binary Variables

The analysis approach for binary variables will be described in the specific sections.

6.2 Disposition of Subjects

The number and percentage of participants in the following categories will be summarized by treatment group, TAK-861 overall, and total:

- Randomized
- Randomized and not treated (including reasons not treated)
- Randomized and treated
- Prematurely discontinued from study treatment
- Primary reason off study treatment
- Prematurely discontinued from the study
- Primary reason off study
- Continuing to Optional 4-Week Extension
- Continuing to the Long-Term Extension study

The number and percentage of participants randomized in each region (United States, Europe, and Asia Pacific), country, and site will be summarized by treatment group, TAK-861 overall, and total.

The number and percentage of participants in each analysis set will be summarized by treatment group, TAK-861 overall, and total.

The number and percentage of participants with significant protocol deviations will be summarized by treatment group, TAK-861 overall, and total.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

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

Demographics (age, gender, ethnicity, and race) will be summarized by treatment group, TAK-861 overall, and total based on the Safety Set. Descriptive statistics will be used to summarize data for continuous variables and for categorical variables the number and percentage of participants within each category will be summarized.

6.3.2 Medical History and Concurrent Medical Conditions

Medical history includes any significant conditions that ended before signing of the informed consent. Concurrent medical conditions are those significant conditions that are ongoing at the signing of the informed consent. Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, Version 25 or higher) coding system.

Medical history and concurrent medical conditions will be summarized for each treatment group, TAK-861 overall, and total using the Safety Set. The number and percentage of participants with at least one event in each MedDRA system organ class (SOC) and preferred term (PT) will be summarized. A participant with multiple occurrences of medical history or concurrent medical conditions within a SOC or PT will be counted only once in that SOC or PT.

6.3.3 Baseline Characteristics

Baseline characteristics (alcohol, caffeine, and tobacco use at time of informed consent, human leukocyte antigen (HLA) status, years since diagnosis (relative to informed consent), age at diagnosis, years since symptom onset (relative to informed consent), age at symptom onset, prior use of narcolepsy medications (requiring washout), mean sleep latency from the MWT, ESS total score, PVT number of lapses and mean 1/RT, weekly cataplexy rate, cerebrospinal fluid orexin level, continuous positive airway pressure (CPAP) ventilation use, compliant with CPAP use, use of oral appliance therapy for sleep apnea) will be summarized by treatment group, TAK-861 overall, and total based on the Safety Set. Descriptive statistics will be used to summarize continuous variables and the number and percentage of participants within each category will be summarized for categorical variables.

6.4 Medication History and Concomitant Medications

All medications will be coded using World Health Organization Drug Dictionary (WHO Drug) (WHO Drug Global B3 March 2022 or higher).

6.4.1 Prior Medications

Prior medications are defined as any medications that stopped prior to the first dose of study drug. Prior medications will be summarized by standardized medication name within each therapeutic class for each treatment group, TAK-861 overall and total based on the Safety Set. If a subject reports taking 2 medications belonging to the same class, he/she will only be counted once within that class. Prior medications for narcolepsy (requiring washout) will also be summarized by standardized medication name.

6.4.2 Concomitant Medications

Concomitant medications are defined as any medications that started prior to the first dose of study drug and are ongoing at the time of the first dose or started after the first dose of study drug but before the date of last TAK-861 dose. Concomitant medications will be summarized by standardized medication name within each therapeutic class for each treatment group, TAK-861 overall and total based on the Safety Set. If a subject reports taking 2 medications belonging to the same class, he/she will only be counted once within that class.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint Analysis

6.5.1.1 Derivation of Endpoint

Four MWT sessions are recorded on Day -1, Week 4 (day 28) and Week 8 (day 56). The mean of the Sleep Latency (SL) from the 4 MWT sessions on a given day will be calculated for each subject. If there are 2 or more missing values, the mean will be assigned as missing for that day. The change from baseline for the mean of the 4 MWT sessions will be derived for each subject at each postdose visit.

6.5.1.2 Main Analytical Approach

All descriptive statistics as specified in section 6.1.2 will be prepared for SL for each MWT session and the mean of the 4 MWT sessions at baseline and each postdose visit by treatment group and TAK-861 overall. Descriptive statistics will also be prepared for the change from baseline.

The primary efficacy endpoint, change from baseline in mean SL to Week 8, will be analyzed using the linear mixed-effect models for repeated measures (MMRM) specified in section 6.1.2. Change from baseline in mean SL will be the response. The model will include the fixed effect of visit (Week 4, Week 8). Baseline age, baseline mean SL, and prior use of narcolepsy medications will be used as covariates in the model.

The LS mean change from baseline (and associated 95% CI) in SL over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols. The LS mean differences from placebo will also be plotted.

In addition, mean SL will be categorized into five categories: <10 minutes, 10 - <20 minutes, 20 - <30 minutes, 30 - <40 minutes, and 40 minutes. For each treatment group and TAK-861 overall, the number and percentage of participants in each category will be summarized by visit.

6.5.1.3 *Additional Analyses of the Primary Endpoint*

In addition, to evaluate change from time-matched baseline in sleep latency at each session, a linear mixed effect model for repeated measures will be performed. The model will include fixed effects of baseline, treatment, visit (Week 4, Week 8), session (2, 4, 6 and 8 hours postdose), treatment-by-visit interaction, treatment-by-session interaction, visit-by-session interaction, and the 3-way interaction of treatment, visit, and session. Both visit and session are repeated factors. Baseline age, baseline mean SL, and prior use of narcolepsy medications will be used as covariates in the model. Kronecker product UN@UN will be used for the covariance structure. Other Kronecker product structures such as UN@AR(1), and UN@CS will also be used if there are convergence issues. If the model does not converge, separate MMRM models for each visit will be generated. The estimated sleep latency in the MWT for each treatment on each visit and session, and the associated SE and 95% CI will be estimated along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values. An additional contrast to estimate the change from baseline in mean sleep latency will also be calculated as the average over the four sessions for each treatment from the same model. The associated SE and 95% CI will be calculated, along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values.

In order to explore the sensitivity of the primary analysis to the ceiling effect in MWT, a tobit (censored regression) mixed effect model will be implemented if any participant's sleep latency value from an MWT session is equal to the 40-minute maximum session duration. The response variable will be the time-matched change in sleep latency from MWT at each session (2, 4, 6, and 8-hour postdose). The model will include treatment and session as fixed effects, time-matched baseline sleep latency, age, and prior use of narcolepsy medications as covariates, as well as a random intercept to account for within-subject correlation. The analysis will be done for Week 4 and Week 8 separately. The maximum likelihood estimate of the change from baseline in mean sleep latency will be calculated by averaging over the four sessions for each treatment. The associated SE and 95% CI will be calculated, along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values.

No imputation for missing data will be performed for these additional analyses.

6.5.2 Secondary Endpoints Analysis

6.5.2.1 Derivation of Endpoints

The ESS is a self-administered questionnaire with 8 questions with response on a 4-point scale (0-3) for each question. The ESS will be measured at screening, baseline day -1), Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56) and Week 12 (Day 84, optional 4-week extension), and at the 7-day follow-up visit. If one or more item-scores are missing, the questionnaire is invalid, and the ESS total score will be missing. The total score will be derived (the sum of 8 item-scores) for each subject at each visit. The change from baseline in the ESS total scores to each postdose visit will be derived for each subject.

Participants will complete a daily ePRO diary to record cataplexy episodes. Participants will record partial or complete episodes of cataplexy, including the time of occurrence in the diary. Weekly cataplexy rate (WCR) at baseline will be derived as the average number of cataplexy episodes over a consecutive 2 week period prior to the Day -2 visit g adjusting for non-missing diary days, where a minimum of 11 out of 14 compliant days in completion of the self-reported electronic diary for cataplexy episodes is required.

For the calculation of post baseline WCR, there is no requirement for compliant days. WCR will be calculated every 2 weeks (Week 2, Week 4, Week 6, and Week 8, Week 10 (part of optional 4-week extension), and Week 12 (part of optional 4-week extension) as:

$$\left(\frac{\text{Total number of cataplexy episodes over the non - missing diary days for a given 2 weeks}}{\text{number of non - missing diary days in these 2 weeks}} \right) * 7$$

WCR for the 7-day post last dose follow-up visit will be calculated as:

$$\left(\frac{\text{Total number of cataplexy episodes over the follow - up period}}{\text{number of non - missing diary days in the follow - up period}} \right) * 7$$

If a diary for a given day reports ≥ 0 cataplexy, the day will be counted as a non-missing diary day. If a diary for a given day or for the 24 hour recall does not have any entries, the day will be counted as a missing diary day.

The cataplexy diary compliance will be summarized for each 2-week period. The number and percentage of participants with 0 days, 1 to 6 days, and ≥ 7 days with cataplexy diary collection will be summarized at baseline, week 2, week 4, week 6, and week 8.

6.5.2.2 Main Analytical Approach

6.5.2.2.1 Main Analytical Approach for ESS

Descriptive statistics as specified in section 6.1.2 will be provided by treatment group and TAK-861 overall for ESS total score at baseline (day -1) and postdose visits (Week 2, Week 4, and

Week 8), as well as for the change from baseline. In addition, the number and percentage of participants with total ESS score in the following categories will be summarized at each visit (Baseline, Week 2, Week 4, and Week 8), by treatment group and TAK-861 overall:

- ≤ 10 (Normal daytime sleepiness)
- 0-5 (Lower normal daytime sleepiness)
- 6-10 (Higher normal daytime sleepiness)
- 11-12 (Mild excessive daytime sleepiness)
- 13-15 (Moderate excessive daytime sleepiness)
- 16-24 (Severe excessive daytime sleepiness)

A linear mixed effect model for repeated measures (MMRM) as specified in section 6.1.2 will be used to evaluate the effect of TAK-861 on the change from baseline in the total ESS score. Baseline total ESS score, age, and prior use of narcolepsy medications will be included as covariates in the model. The optional 4-week extension (Week 12) and 7-day follow-up visit will not be included in the model.

The LS mean change from baseline (and associated 95% CI) in total ESS score over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols. The LS mean differences from placebo will also be plotted.

6.5.2.2.2 Main Analytical Approach for WCR

WCR will be summarized by treatment group and TAK-861 overall at baseline and postdose visits (Week 2, Week 4, Week 6, and Week 8), including change/percent change from baseline.

The WCR will be analyzed by generalized estimating equations (GEE) featuring a negative binomial distribution. The model will include fixed effects for visit, treatment, and treatment-by-visit interaction, and will be adjusted for baseline WCR, age, and prior use of narcolepsy medications. An unstructured variance-covariance structure will be used initially in these models. If there are convergence issues with the model, an exchangeable variance-covariance structure will be used, followed by an independent structure. If lack-of-convergence still exists, the analysis will be done for Week 4 and Week 8 separately. The estimated incidence rate of weekly cataplexy for each treatment group and the associated SE and 95% CIs will be extracted from the model, along with the incidence rate ratio of weekly cataplexy (TAK-861 to placebo) for all TAK-861 treatment groups, and the associated SEs, 95% CIs, and two-sided p-values. The optional 4-week extension visits (week 10 and 12) and the 7-day follow-up visit will not be included in the GEE model.

The estimated weekly cataplexy incidence rate ratio and the associated 95% CI of all TAK-861 treatment groups relative to placebo will be presented in forest plots, with one plot per visit (Week 2, Week 4, Week 6, and Week 8).

6.5.2.3 Additional Analyses

The number of cataplexy-free days per week is calculated as:

$$\left(\frac{\text{number of days without cataplexy over the non – missing diary days for a given 2 weeks}}{\text{number of non – missing diary days in 2 weeks}} \right) * 7$$

Descriptive statistics (change/percent change from baseline) as specified in section 6.1.2 will be provided by treatment group and TAK-861 overall for cataplexy-free days at each visit (Week 2, Week 4, Week 6, Week 8).

The WCR will be calculated based on full cataplexy episodes separately for baseline, Week 2, Week 4, Week 6, and Week 8 as noted below:

$$WCR_{full} = \left(\frac{\text{Total number of full cataplexy episodes over the non – missing diary days for a given 2 weeks}}{\text{number of non – missing diary in these 2 weeks}} \right) * 7$$

WCR based on partial cataplexy episodes will be calculated as described above. Descriptive statistics and the GEE model specified in Section 6.5.2.2.2 will be used to analyze WCR based on full and partial cataplexy.

6.5.3 Subgroup Analyses

Not applicable.

6.6 Safety Analysis

The criteria for markedly abnormal laboratory, vital signs, and ECG parameters will be provided in a programming specifications document.

6.6.1 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using MedDRA (v25.0 or higher). A treatment-emergent adverse event (TEAE) is defined as an AE whose date/time of onset occurs on or after the first dose of study drug.

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

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

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

For the subset of participants with at least one urinary symptom, the frequency of participants with ≥ 1 instance of increased urinary frequency, and a summary of the number of times participants normally urinate during night-time hours prior to start of treatment and at the time of the urinary events will be generated.

6.6.2 Adverse Events of Special Interest

The adverse events of special interest (AESI) are noted below:

- BP and HR increases
- Insomnia
- Bladder events

A separate summary of AESIs will be generated.

6.6.3 Other Safety Analysis

6.6.3.1 Clinical Laboratory Evaluations

Clinical safety laboratory tests include clinical chemistry, hematology, and urinalysis. A list of all the clinical laboratory evaluations can be found in Protocol Section 10.2.

Descriptive statistics of clinical laboratory variables (chemistry and hematology) will be summarized for baseline and postdose values, as well as change from baseline to postdose values by study visit and treatment group and TAK-861 overall. Only the scheduled measurements will be included in the summary. No statistical tests will be performed.

The number and percentage of participants meeting each markedly abnormal laboratory criteria, and any MAV criteria will be summarized overall postdose visits, at Day 1, Week 2, Week 4, Week 6, and Week 8 by treatment group, TAK-861 overall, and total. The evaluation of the MAV criteria will include scheduled and unscheduled visits.

6.6.3.2 Vital Signs

Vital sign measurements include blood pressure (SBP and DBP), heart rate, respiratory rate, body temperature, and weight. Only the scheduled measurements will be included in summary tables or statistical analysis of VS measurements.

SBP, DBP and heart rate collected on Day 1, Week 4, and Week 8 will be summarized with descriptive statistics including the pre-dose value, postdose visit, and change from time-matched baseline (Day -1) by treatment group and TAK-861 overall. The Day 1 VS measurement at 3

hours postdose will be time-matched to the Day -1 3.5 hour measurement. The Day 1 discharge measurement will not be time-matched.

Trough SBP, DBP, and HR measurements (pre-dose) on Week 2 (Day 14), Week 6 (Day 42), Week 10 (Day 70, optional 4-week extension), and Week 12 (Day 84, optional 4-week extension) will be summarized with descriptive statistics including the time-matched baseline, trough (pre 8AM dose timepoint), and change from time-matched baseline at each post baseline visit by treatment group and TAK-861 overall. Baseline is the last time-matched non-missing measurement prior to the first dose.

SBP, DBP, and HR measurements collected 1 hour before nPSG lights off (Day -2, Day 27, and Day 55) will be summarized with descriptive statistics including the time-matched baseline (Day -2), 1 hour before nPSG results, and change from time-matched baseline at each post baseline visit by treatment group and TAK-861 overall.

Respiratory rate and temperature will be summarized with descriptive statistics at baseline, Week 2 (Day 14), Week 4 (Day 28), Week 6 (Day 42), and Week 8 (Day 56), including the change from baseline at each visit, by treatment group and TAK-861 overall. Baseline is the last non-missing measurement prior to the first dose.

Weight will be summarized with descriptive statistics at baseline, Week 4 and Week 8, including the change from baseline at each visit, by treatment group and TAK-861 overall. Baseline is the last non-missing measurement prior to the first dose.

In addition, the drug effect on clinic BP and heart rate will be analyzed using an MMRM model with change from time-matched baseline as the response variable. Separate models will be generated for Day 1, Week 4, and Week 8. In the MMRM model, treatment, time point, and treatment-by-time point interaction will be the fixed effects and baseline will be the covariate. An additional contrast to estimate the change from baseline will also be calculated as the average over the time points for each treatment from the same model. The LS mean change from time-matched baseline (and associated 95% CI) in HR, SBP and DBP over time will be plotted for Day 1, Week 4, and Week 8. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols. The LS mean differences from placebo will also be plotted.

The number and percentage of participants meeting each markedly abnormal criteria, and any MAV criteria will be summarized overall postdose visits, at Day 1, Week 4, and Week 8 by treatment group, TAK-861 overall, and total. The evaluation of the MAV criteria will include scheduled and unscheduled visits.

6.6.3.3 ABPM

The ABPM is recorded during screening (starting any day up to Day -4 and ending no later than Day -3) and during the treatment period starting between days 38 and 45 (approximately Week 6). During the day (6AM to 10PM) inflations will occur every 15 min (4 per hour) and during

the night (10PM to 6AM) inflations will occur every 30 minutes (2 per hour) for a total of 80 inflations.

The derivations of the ABPM parameters are summarized in [Table 6.i](#) below:

Table 6.i. Derivation of ABPM Parameters

ABPM Parameters (SBP, DBP, HR)	Derivation
Baseline Hourly mean Week 6 Hourly mean	Average (arithmetic mean) of ABPM measurements in each hour after the time of the first AM dose on the day of the ABPM recording (for plots only).
Baseline 24 hour mean Week 6 24 hour mean	Average (arithmetic mean) of ABPM measurements after the time of the first AM dose on the day of the ABPM recording and including all observations recorded over the subsequent 24 hours.
Baseline daytime mean Week 6 daytime mean	Average (arithmetic mean) of ABPM measurements recorded between the hours of 6 AM (inclusive) and 10 PM (exclusive).
Baseline nighttime mean Week 6 nighttime mean	Average (arithmetic mean) of ABPM measurements recorded between the hours of 12 AM (inclusive) and 6 AM (exclusive).
Note: The baseline parameters are time-matched to the time of the first dose (approx. 8AM) of the Week 6 ABPM (between days 38 to 42).	

The baseline and Week 6 ABPM parameters and the change from baseline will be summarized with descriptive statistics by treatment group and TAK-861 overall. The change from baseline to Week 6 for the ABPM 24 hour, daytime and nighttime mean will be analyzed with an analysis of covariance (ANCOVA) model with baseline ABPM as a covariate and treatment as the fixed effect. The LS mean change from baseline in ABPM parameters for each treatment and the associated SE and 95% CI will be extracted from the ANCOVA model, along with all pairwise differences from placebo and associated SEs, 95% CIs, and two-sided p-values.

Only observed data will be used for the summary and analyses of ABPM parameters. No imputation will be performed for missing data.

The following figures will be generated:

- Average ABPM for SBP, DBP, HR by hour for the 24 hour interval:
Baseline, Week 6, Change from baseline
- Average ABPM for SBP, DBP, HR by clock hour for daytime [6 AM to 10 PM]:
Baseline, Week 6, Change from baseline
- Average ABPM for SBP, DBP, HR by clock hour for nighttime [12 AM to 6 AM]:

Baseline, Week 6, Change from baseline

The following blood pressure dipping categories [2] will be defined using the ratio of mean day-time and night-time ABPM for SBP and DBP (day-time defined as (0900 to 2100h) and night-time defined as (0100 to 0600h):

- Non-dipping or riser: Night-time/Day-time ≥ 1.0
- Mild dipper: $0.9 < \text{Night-time/Day-time} < 1.0$
- Dipper: $0.8 < \text{Night-time/Day-time} \leq 0.9$
- Extreme Dipping: Night-time/Day-time ≤ 0.8

The number and percentage of participants in each dipping category at baseline and Week 6 will be summarized by treatment group and TAK-861 overall. Shift tables (baseline vs. Week 6) will be presented.

6.6.3.4 ECG

The continuous ECG parameters (heart rate, PR interval, QRS interval, QT interval, QT interval with Bazett correction method (QTcB) and QT interval with Fridericia correction method (QTcF) at each visit, and the change from baseline will be summarized with descriptive statistics by treatment group and TAK-861 overall. Only the ECGs collected at the scheduled visits will be included in the summary.

The ECG interpretation by the investigator (Within Normal Limits; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant; Not Evaluable) will be summarized at each visit by treatment group and TAK-861 overall.

The number and percentage of participants meeting each markedly abnormal criteria and any MAV criteria will be summarized over postdose visits, at Week 2, Week 4, and Week 8, by treatment group, TAK-861 overall, and total. The evaluation of the MAV criteria will include scheduled and unscheduled visits.

6.6.3.5 C-SSRS

The number and percentage of participants with at least 1 endorsement of Item 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS) at any postdose visit will be summarized by treatment group, and TAK-861 overall.

6.6.4 Extent of Exposure and Compliance

The summary of study drug exposure and compliance will be based on the Safety Set. The treatment duration is defined as (date of last dose – date of first dose +1). Treatment duration (days) will be summarized using descriptive statistics for each treatment group and TAK-861 overall.

Table 6.ii below describes the bottle types dispensed assuming 32 tablets per bottle:

Table 6.ii. Bottle Types Dispensed for Each Treatment Group

Treatment Group	8AM		11 AM Bottle
	Bottle 1	Bottle 2	
Placebo	Placebo	Placebo	Placebo
0.5 mg twice daily	0.5 mg	Placebo	0.5 mg
2 mg twice daily	2 mg	Placebo	2 mg
2 mg followed by 5 mg	2 mg	Placebo	5 mg
7 mg QD	2 mg	5 mg	Placebo

TAK-861 bottle compliance will be calculated for each bottle type:

$$\frac{(\text{number of tablets dispensed from the bottle type} - \text{number of tablets returned from the bottle type})}{\text{Scheduled number of tablets associated with that bottle type} * (\text{date of last dose} - \text{date of first dose} + 1)} * 100\%$$

For example, in the 2 mg twice daily group, the scheduled number of tablets associated with the 2 mg bottle type is 2.

For active treatment groups, only the active bottle types are counted.

Placebo bottle compliance will be calculated as:

$$\frac{(\text{total number of tablets dispensed} - \text{total number of tablets returned})}{3 * (\text{date of last dose} - \text{date of first dose} + 1)} * 100\%$$

The overall compliance for active treatment groups is the average of the compliance for the active bottle types.

The percent compliance for each bottle type and overall will be summarized with descriptive statistics by treatment group, and TAK-861 overall. In addition, the number and percentage of participants in the following compliance categories will be summarized: <70%, 70 to 100%, and >100% by treatment group.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

All PK summaries and analyses will be based on the PK set by dose levels within each part or each group.

Plasma concentrations of TAK-861 will be summarized with descriptive statistics (N, arithmetic mean, SD, coefficient of variation, median, minimum, maximum) by each scheduled time point and TAK-861 dose level. Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero in the summary of plasma concentration values.

The following PK parameters will be calculated from plasma concentrations of TAK-861 on Day 1, Week 4 (Day 28), and Week 8 (Day 56), as data permit using non-compartmental analysis.

Table 6.iii. Plasma PK Parameters Definition

Symbol/Term	Definition
AUC_{last}	AUC from time 0 to time of the last quantifiable concentration on Day 1
$C_{max,1}$	Maximum observed concentration during first dosing interval
$C_{max,2}$	Maximum observed concentration during second dosing interval
C_{last}	Last observed concentration
$t_{max,1}$	Time to reach $C_{max,1}$
$t_{max,2}$	Time to reach $C_{max,2}$

Note:

- 1) C_{max} and t_{max} at Week 4 and Week 8 is expected to be at steady-state exposures of TAK-861
- 2) $C_{max,2}$ and $t_{max,2}$ is applicable for twice daily dosing regimen only

Additional PK parameters may be calculated as appropriate. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The treatment of BLQs for the calculation of PK parameters, and exclusions/flagging of PK concentration and parameter data will follow the processes detailed in the Clinical Pharmacology Analysis Plan.

PK parameters will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, coefficient of variation, median, minimum, maximum) by day and TAK-861 dose level.

Additionally, all individual TAK-861 plasma concentration-time data collected in this study will be combined with other clinical study data to develop a population PK model of TAK-861 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.

The intrinsic CYP3A4/5 activity will be evaluated by the ratio of 4 β -hydroxycholesterol vs cholesterol concentrations. The ratios of 4 β -hydroxycholesterol over cholesterol, and the ratios of the post-dose values to that of baseline will be summarized by day and TAK-861 dose level.

A scatterplot of TAK-861 plasma concentration (x-axis) versus the sleep latency on the MWT (y-axis) will be produced overall, and at each scheduled MWT timepoint (panel). TAK-861 plasma concentrations for placebo data will be included in the plot with a concentration of 0. The TAK-861 treatment groups will be displayed together in the plot with different symbols. The pairing of timepoints (based on nominal time post the first dose) for the scatter plot are outlined below:

MWT Timepoint	PK Timepoint
2	1.5
4	3.5
6	5.5
8	7.5

A scatterplot of TAK-861 plasma concentration (x-axis) versus time-matched change from baseline in HR, SBP and DBP will be produced for Day 1, Week 4, and Week 8. TAK-861 plasma concentrations for placebo data will be included in the plot with a concentration of 0. Only measurements from time points common to both vital signs and PK assessments will be used.

In addition, mean plots of TAK-861 plasma concentration and placebo corrected time-matched change from baseline in HR, SBP, and DBP will be produced for the active TAK-861 treatment groups for Day 1, Week 4, and Week 8. The scheduled time point will be the x-axis, mean (\pm SD) TAK-861 plasma concentration will be on the left y-axis, and time-matched change from baseline in the mean (\pm SD) of TAK-861 in HR, SBP, or DBP will be on the right y-axis. All TAK-861 treatment groups will be presented on the same plot.

6.7.2 Pharmacodynamic Analysis

Refer to the efficacy section for analysis of pharmacodynamic endpoints.

6.7.3 Biomarker Analysis

Not applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

Clinical outcome assessment (COA) compliance will be calculated at the questionnaire level for all COAs at baseline, week 4, and week 8 to provide context for the interpretation of COA results. The COAs include PGI-S (baseline only), PGI-I, CGI-S (baseline only), CGI-I, NSS-CT, EQ-5D-5L, FIN, SF-36, and TSQM (week 4 and week 8 only). A similar analysis will be generated for the cognition endpoints (PVT, CPAL, ONB, and iDSST-s).

COA compliance at each visit will be calculated as follows:

$$\frac{\text{number of participants with the COA score available}}{\text{number of participants for whom a COA score is expected}}$$

6.8.1.1 Patient and Clinical Global Impression

The CGI-S will ask clinicians to assess severity of overall narcolepsy symptoms at baseline, using a 7-point Likert-type scale ranging from “1=normal, not at all ill” to “7=among the most

extremely ill”. The CGI-I will ask clinicians to rate the extent to which their patients’ current overall narcolepsy symptoms are improved (compared with the start of the study) at Week 4 (day 28) and Week 8 (day 56), using a 7-point Likert-type scale ranging from “1=very much improved” to “7=very much worse”.

The PGI-S requires the participant to rate his/her disease severity at baseline on a 4-point scale ranging from “normal” to “severe.” The PGI-I will assess improvement in overall narcolepsy symptoms due to treatment relative to baseline at Week 4 (day 28) and Week 8 (day 56), on a 7-point scale ranging from “1=very much improved” to “7=very much worse”.

The number and percentage of participants in each response category will be summarized by treatment group, and for TAK-861 overall.

Participants will be categorized as a responder based on two definitions of improvement:

- CGI-I/PGI-I score is “1=very much improved” or “2=much improved”
- CGI-I/PGI-I score is “1=very much improved” or “2=much improved” or “3=minimally improved”

The number and percentage of participants in each CGI-I/PGI-I response category and reported as improved based on the above responder definitions will be summarized at each postdose visit by treatment group and TAK-861 overall.

A generalized linear mixed model for binomial data with a logit link function will be used to analyze the CGI-I/PGI-I responder definitions. The observed values for the responder definition will be used as the response in the model. The model will include treatment group, postdose visit, and the treatment-by-visit interaction as fixed effects and subjects will be random effects. The CGI-S/PGI-S score will be included in the model as covariate. If the model does not converge, a logistic regression model at each visit will be used. The odds ratio of being a responder for each TAK-861 treatment group relative to placebo for each visit and the associated 95% CIs, and two-sided p-values will be estimated. The probabilities of being a responder for each treatment group and associated 95% CIs will be estimated.

6.8.1.2 NSS-CT

The NSS-CT is a 15-item self-administered questionnaire (score: 0-57) that assesses the severity and consequences of narcolepsy in 3 domains (sleep paralysis and hallucinations, excessive daytime sleepiness and nighttime sleep, and cataplexy). The NSS Severity is classified as follows [3]:

Severity	NSS-CT Total Score
Mild	0-14
Moderate	15-28
Severe	29-42
Very severe	43-57

The NSS-CT Total Score and the change from baseline will be summarized using descriptive statistics at each visit by treatment group and TAK-861 overall. The number and percentage of participants in each NSS-CT severity category will be summarized by visit, treatment group and for TAK-861 overall. The change from baseline will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) in NSS-CT Total Score over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.1.3 EQ-5D-5L

The EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) comprises questions on five domains: mobility, self-care, pain/discomfort, usual activities, and anxiety/depression with five possible answers for each domain (1=no problem, 2=slight problem, 3=moderate problem, 4=severe problem, 5=unable to). EQ-5D-5L index scores are calculated from the five individual domain scores using USA values sets across all countries. The index scores generally range from 0 (where 0 is the value of a health state equivalent to death) to 1, with higher scores indicating higher health utility. The EQ visual analogue scale (EQ VAS) (0-100) will be used to indicate the health state of the day, where 100 means the best health.

The number and percentage of participants in each level, and “any problems” (level 2 to 5) will be summarized for each of the five domains at baseline and postdose visits by treatment group and TAK-861 overall. The EQ-5D-5L Index Score and Visual Analogue Scale will be summarized with descriptive statistics including the baseline, postdose, and change from baseline (Day -1) at each visit by treatment group and TAK-861 overall. The change from baseline will be analyzed with an MMRM model.

Boxplots of the EQ-5D-5L Index Score and Visual Analogue Scale at baseline, Week 4, and Week 8 and including change from baseline (with quartiles and extreme scores) will be produced. The change from baseline will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) over time will be plotted for the EQ-5D-5L Index Score and Visual Analogue Scale. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.1.4 FIN

The Functional Impacts of Narcolepsy (FIN) is a narcolepsy-specific 11-item instrument that assesses functional impacts of narcolepsy across 3 domains: social activities (items 1 to 4), everyday activities (items 5 to 8), and everyday responsibilities (items 9 to 11). The response to each question is on a 5-point scale:

1. Never
2. Rarely
3. Sometimes
4. Usually
5. Always

The FIN is assessed on Day -1, Week 4, and Week 8.

The scoring instructions are noted below:

1. Rescore each item from a 1 – 5 response scale to a 0 – 4 response scale where 0 indicates the best health and 4 the worst.
2. For each participant, calculate the average score for each domain, if at least half the items in the domain have been answered:
(sum of responses in the domain / number of completed items in the domain)
3. Standardize the average score to a 0 – 100 scale:
 - a) Standardized score = average score/4 x 100
 - b) 0 indicates the best health and 100 the worst health. A decrease from baseline would indicate improved health.

For example, if the 4 items in one domain had the responses 1, 2, 3, 2 (re-scored to 0 to 4 response scale), the average score would be 2 and the standardized score would be 50 points.

The 3 standardized domain scores at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. The change from baseline will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

Cumulative distribution plots of the change from baseline for each of the 3 domains will be generated for Week 4 and Week 8.

Participants will be categorized as a responder based on the meaningful change threshold (MCT) for each domain [4]:

- Change from baseline in social activities score ≤ -40
- Change from baseline in everyday activities score ≤ -40
- Change from baseline in everyday responsibilities score ≤ -30

The number and percentage of participants who are responders in each domain will be summarized at each postdose visit by treatment group and TAK-861 overall. A sensitivity analysis will be performed excluding all participants with a baseline score less than the MCT.

A generalized linear mixed model for binomial data with a logit link function will be used to analyze the response rate for each domain (see section 6.8.1.1) including baseline domain score as a covariate. If the model does not converge, a logistic regression model at each visit will be used.

Additional analyses will be performed by calculating the percentage of participants reaching the mean healthy control thresholds derived from a healthy control study [5]:

	Reaching healthy control mean score	Reaching healthy control mean score plus one standard deviation
Social activities	≤ 16	≤ 33
Everyday activities	≤ 13	≤ 24
Everyday responsibilities	≤ 12	≤ 27

The number and percentage of participants meeting the above criteria in each domain will be summarized at each postdose visit by treatment group and TAK-861 overall.

6.8.1.5 SF-36

The SF-36 is a 36-item, participant-reported survey of participant health. The SF-36 consists of 8 scaled scores (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0 to 100 scale on the assumption that each question carries equal weight. The lower the score the more disability. The higher the score the less disability, that is, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability.

The physical and mental component summary scores will also be derived per the SF-36 coding manual.

The domain and summary scores at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. The change from baseline for each domain and summary score will be analyzed with an MMRM model. The LS mean change from baseline (and associated 95% CI) over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.1.6 TSQM

The TSQM vII is an 11-item questionnaire that measures satisfaction with treatment in 4 domains: effectiveness (items 1 - 2), side effects (items 3 - 6), convenience (items 7-9) and

global satisfaction (items 10-11). The domain scores are derived from the item scores and have values from 0 to 100 where higher scores indicate better treatment satisfaction:

Domain	All domain items are completed	Exactly 1 domain item is missing
Effectiveness	$\frac{[(\text{Item 1} + \text{Item 2}) - 2]}{12} * 100$	$\frac{[(\text{Use the completed item}) - 1]}{6} * 100$
Side Effects (All 'NA' responses are coded as '5' indicating 'Not at all Dissatisfied')	If Question 3 is answered 'No' then score = 100 Otherwise $\frac{[(\text{Item 4 to Item 6}) - 3]}{12} * 100$	$\frac{[(\text{Sum (the two completed items)}) - 2]}{8} * 100$
Convenience	$\frac{[(\text{Item 7 to Item 9}) - 3]}{18} * 100$	$\frac{[(\text{Sum (the two completed items)}) - 2]}{12} * 100$
Global Satisfaction	$\frac{[(\text{Item 10} + \text{Item 11}) - 2]}{12} * 100$	$\frac{[(\text{Use the completed item}) - 1]}{6} * 100$
Note: a score can be computed for a domain only if no more than one item is missing from the domain.		

The 4 TSQM domains at each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. The TSQM domains will be analyzed with an MMRM model. The LS mean (and associated 95% CI) over time will be plotted. The scheduled time points will be on the x-axis; the LS mean (estimated from model above) will be on the y-axis. All treatments will be displayed on the same plot and differentiated by different symbols.

6.8.2 Health Care Utilization Analysis

Not applicable.

6.9 Other Analyses

6.9.1 Cognitive Endpoints

Compliance will be calculated for each of the cognition tests (PVT, CPAL, ONB, and iDSST-s) similar to the COAs (see section 6.8.1 for definitions).

6.9.1.1 PVT

The PVT is a simple reaction performance task that aims to measure sustained attention with no learning effects over repeated administration. The PVT will be administered on Day -1 (at same time as 1 and 7 hour post 8AM dose assessments), and 1 (morning) and 7 (afternoon) hours post

the 8AM dose at Week 4 and Week 8. The PVT endpoints are the number of lapses, mean reaction time (RT), and mean 1/RT.

The PVT endpoints will be summarized with descriptive statistics including the Day -1 (baseline) sessions, postdose sessions at each visit, and the change from time-matched baseline at each visit by treatment group and TAK-861 overall.

For each PVT endpoint, box plots will be prepared for observed values at baseline, Week 4, and Week 8 for each treatment group (separate displays for 1 hour postdose and 7 hour postdose evaluations).

The number of lapses will be analyzed by generalized estimating equations (GEE) featuring a negative binomial distribution. The model will include fixed effects for visit, treatment, timepoint, treatment-by-timepoint, visit-by-timepoint, treatment-by-visit, and treatment-by-visit-by-timepoint interactions, and will be adjusted for time-matched baseline number of lapses. Subject will be the repeated factor and an unstructured variance-covariance structure will be used in the model. If lack-of-convergence exists, an exchangeable variance-covariance structure will be used, then an independent variance-covariance structure, and if lack of convergence still exists the analysis will be done for Week 4 and Week 8 separately. The estimated number of lapses for each treatment group and the associated SE and 95% CI will be extracted from the model, along with the ratio of number of lapses between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values.

The mean reaction time will be analyzed by generalized estimating equations (GEE) using a log-link function featuring a gamma distribution. The model will include fixed effects for visit, treatment, timepoint, treatment-by-timepoint, visit-by-timepoint, treatment-by-visit, and treatment-by-visit-by-timepoint interactions, and will be adjusted for time-matched baseline mean reaction time. Subject will be the repeated factor and an unstructured variance-covariance structure will be used in the model. If lack-of-convergence exists, an exchangeable variance-covariance structure will be used, then an independent variance-covariance structure, and if lack of convergence still exists the analysis will be done for Week 4 and Week 8 separately. The estimated mean reaction time for each treatment group and the associated SE and 95% CI will be extracted from the model, along with the ratio of mean reaction times between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values.

The mean inverse reaction time (1/RT) will be analyzed with an MMRM model. The MMRM model will include fixed effects for the time-matched baseline value, treatment, visit (Week 4, Week 8), timepoint (morning and afternoon), treatment-by-visit interaction, treatment-by-timepoint interaction, visit-by-timepoint interaction and the 3-way interaction of treatment, visit, and timepoint. Both visit and timepoint are repeated factors. Kronecker product UN@UN will be used for the covariance structure. Other Kronecker product structures such as UN@AR(1), and UN@CS will also be used if there are convergence issues. If the model does not converge then the mean 1/RT will be analyzed with an MMRM model at each visit (Week 4, Week 8). The estimated mean 1/RT for each treatment group and the associated SE and 95% CIs will be extracted from the model, along with the difference in mean 1/RTs between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values.

For mean inverse reaction time, Friedman's test will be performed to compare the population distributions of the treatments.

6.9.1.2 CPAL/ONB/iDSST-s

The CPAL test is a measure of visual associate memory and uses a well-validated paired associate learning paradigm in which the participant must learn the locations of a number of amoeba-like shapes on the computer screen. The CPAL endpoint is number of errors, where lower scores indicate better performance.

The ONB test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. The ONB endpoints are speed of performance (mean of the log 10 transformed reaction times for correct responses) where a lower score indicates better performance and accuracy of performance (arcsine square root of the proportion of correct responses) where a higher score indicates better performance.

The iDSST-s is a processing speed test that is based on the pre-existing pencil and paper version of the Digit Symbol Substitution Test. The iDSST-s endpoints are the number of correct responses where a higher score indicates better performance) and speed of performance (mean of the log 10 transformed times for correct responses) where a lower score indicates better performance.

The CPAL, ONB, and iDSST-s tests are administered on Day -1 (baseline), Week 4 and Week 8. The results at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall.

CPAL number of errors will be analyzed using a GEE model featuring a negative binomial distribution. The model will include fixed effects for visit, treatment and treatment-by-visit interaction, and will be adjusted for baseline number of errors. Subject will be the repeated factor and an unstructured variance-covariance structure will be used in the model. If lack-of-convergence exists, an exchangeable variance-covariance structure will be used, then an independent variance-covariance structure, and if lack of convergence still exists the analysis will be done for Week 4 and Week 8 separately. The estimated number of errors for each treatment group and the associated SE and 95% CI will be extracted from the model, along with the ratio of number of errors between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values.

The iDSST-s number of correct responses will be analyzed using the same model as CPAL number of errors.

ONB speed of performance, ONB accuracy of performance, and iDSST-s speed of performance will all be analyzed using an MMRM model specified in Section 6.1.2. For ONB speed of performance, the model will provide estimated speed of performance and the associated SE and 95% CI for correct responses for each treatment group, as well as difference in speed of performance between TAK-861 and placebo, along with the associated SEs, 95% CIs, and two-sided p-values. For ONB accuracy of performance, the model will provide estimated accuracy of performance and the associated SE and 95% CI for each treatment group, as well as difference in

accuracy of performance between TAK-861 and placebo, along with the associated SEs, 95% CIs, and two-sided p-values. For iDSST-s speed of performance, the model will provide estimated speed of performance for each treatment group and the associated SE and 95% CI, as well as difference in speed of performance for correct responses between TAK-861 and placebo, along with the associated SEs, 95% CIs, and two-sided p-values.

For ONB speed of performance, ONB accuracy of performance, and iDSST-s speed of performance, Friedman's test will be performed to compare the population distributions across the treatment groups.

6.9.2 nPSG Parameters

The nPSG parameters (minutes between lights off and lights on, sleep onset latency, latency to stage R, total sleep time, latency to persistent sleep, wake after persistent sleep, total number of nocturnal awakenings, sleep efficiency, Stage N1 percentage, Stage N2 percentage, Stage N3 percentage, and Stage R percentage) at each visit (baseline, Week 4, and Week 8) will be summarized with descriptive statistics by treatment group and TAK-861 overall. Descriptive statistics will be provided for both observed values and change from baseline.

Additional exploratory analyses to be performed by Takeda Quantitative Sciences will be described in a separate Biomarker Analysis Plan. The results will not be included in the CSR.

6.9.3 Actigraphy Derived Sleep and Activity Parameters

The actigraphy (accelerometry) device (Empatica) will be worn continuously (as much as possible throughout the day and night) from informed consent to the first follow-up visit or rollover into the LTE study. The definitions of the sleep and activity parameters are shown below:

Table 6.iv Sleep and Activity Parameters from the Actigraphy Device

Parameter Type	Parameter	Definition
Sleep (nightly)	Total sleep time (TST)	the assumed time spent actually sleeping after the sleep onset (min)
	Sleep Efficiency (SE)	expressed as a percentage: TST / TIB (the total length of the time in bed period, from time in bed start to time in bed stop)
	Wake after sleep onset (WASO)	The amount of time spent awake after sleep onset (min)
Activity	Activity count	Activity count per minute collected continuously
Note: sleep parameters are estimated by Takeda algorithms and activity parameters are based on the Empatica proprietary algorithms.		

For each nightly sleep parameter presented in Table 6.iv, the weekly mean is the average (arithmetic mean) of the nightly values over a 2-week period converted to a weekly rate (multiply by 7) for baseline, Week 2, Week 4, Week 6, and Week 8. Baseline will be generated by taking the average (arithmetic mean) of the nightly values over the last 14 days prior to the date of the first dose. The mean is based on the number of nights with non-missing values in the 2-week period.

The daily activity count will be calculated based on activity from 8AM to 8PM. The weekly mean is the average (arithmetic mean) of the daily values over a 2-week period converted to a weekly rate (multiply by 7) for baseline, Week 2, Week 4, Week 6, and Week 8. Baseline will be generated by taking the average (arithmetic mean) of the daily values over the last 14 days prior to the date of the first dose. The mean is based on the number of days with non-missing values in the 2-week period.

The weekly parameters at each visit, and the change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall. Mean plots of the observed weekly parameters at each visit (baseline, Week 2, Week 4, Week 6, and Week 8) will be generated. The change from baseline will be analyzed with an MMRM model.

Additional exploratory analyses to be performed by Takeda Quantitative Sciences will be described in a separate Biomarker Analysis Plan. The results will not be included in the CSR.

6.9.4 Narcolepsy Symptoms (eDiary)

Weekly episodes for the following narcolepsy symptoms will be derived from the eDiary collection at baseline, Week 2, Week 4, Week 6, Week 8, and the 7-day post last dose follow-up visit:

- Sleep paralysis
- Refreshing Sleep (response of refreshed or somewhat refreshed)
- Hypnagogic/hypnopompic hallucinations
- Nocturnal awakenings
- Disturbing and frightening dreams/nightmares
- Dreaming a lot or all night
- Problems falling asleep
- Good sleep quality (response of very good or fairly good)
- Number of naps

For number of naps, weekly episodes (WE) at baseline will be based on the number of episodes averaged over 2 weeks minimum, and for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:

$$WE = \left(\frac{\text{number of episodes over a 2 week period}}{\text{number of non - missing diary days in the 2 week period}} \right) * 7$$

Weekly episodes for number of naps in the 7-day post last dose follow-up visit is calculated as follows:

$$WE = \left(\frac{\text{number of episodes over the follow-up period}}{\text{number of non-missing diary days in the follow-up period}} \right) * 7$$

For all other endpoints, weekly episodes (WE) at baseline will be based on the number of episodes averaged over 2 weeks minimum, and for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:

$$WE = \left(\frac{\text{number of nights with an episode over a 2 week period}}{\text{number of non-missing diary days in the 2 week period}} \right) * 7$$

Weekly episodes for all other endpoints for the 7-day post last dose follow-up visit is calculated as follows:

$$WE = \left(\frac{\text{number of nights with an episode over the follow-up period}}{\text{number of non-missing diary days in the follow-up period}} \right) * 7$$

If a diary for a given day reports ≥ 0 episodes, the day will be counted as non-missing diary day. Otherwise, the day will be counted as a missing diary day for the symptom.

The diary compliance for narcolepsy symptoms will be summarized for each 2-week period. The number and percentage of participants with 0 days, 1 to 6 days, and ≥ 7 days with diary collection for narcolepsy symptoms will be summarized at baseline, week 2, week 4, week 6, and week 8.

The number of naps and weekly episodes of each narcolepsy symptom at each visit, change from baseline, and percent change from baseline for each visit will be summarized with descriptive statistics by treatment group and TAK-861 overall.

Box plots of the number of naps and weekly episodes of each narcolepsy symptom by visit and treatment group will be generated.

The number of naps will be analyzed with a GEE model featuring a negative binomial distribution similar to WCR.

6.10 Interim Analyses

An interim analysis will occur when at least 40 participants have completed the Week 4 visit. In this case, an Internal Review Committee (IRC), composed of members who do not have study-related contact with sites, will review the study data.

The efficacy endpoints to be included in the IA are MWT, ESS, and WCR. Statistical analyses will include all observed data up to the IA data cut, including incomplete follow-up. The same statistical models described in Sections 6.5.1.2 and 6.5.2.2 will be applied, without imputation for missing data.

If any endpoint in a dose level yields a 2-sided p-value ≥ 0.75 at IA, the recommendation is to stop that dose level for futility. The futility assessment will be non-binding.

The list of tables, listings, and figures to be generated for the IA efficacy and safety summary will be specified in the IRC charter. The final decision of stopping a dose level for futility will be made at the IRC's discretion based on the totality of evidence.

6.11 Data Monitoring Committee/Internal Review Committee

An IRC, composed of members who do not have contact with investigators or sites, will review the study data at the IA and determine if dose arms will be discontinued based on efficacy (see section 6.10). An IRC charter will provide details on the conduct and procedures for the IRC.

An external data monitoring committee (DMC) will review the safety and tolerability data on a quarterly basis, throughout the study. A DMC charter will provide full guidance on the function and practices to be followed by the DMC.

7.0 REFERENCES

- [1] Bretz, F., Maurer, W., Brannath, W., Posch, M. (2009). A graphical approach to sequentially rejective multiple test procedures. *Statistics in Medicine*, 28(4), 586-604.
- [2] European Society of Hypertension Position Paper on Ambulatory Blood Pressure Monitoring, Eoin O'Brien, Jun 2013, *Journal of Hypertension*
- [3] Dauvilliers, Y., Barateau, L., Lopez, R., Rassu, A. L., Chenini, S., Beziat, S., & Jaussent, I. (2020). Narcolepsy Severity Scale: a reliable tool assessing symptom severity and consequences. *Sleep*, 43(6).
- [4] Report: Phase 2 Psychometric Validation of a PRO Measure for Narcolepsy Type 1 and Narcolepsy Type 2 (TK1037, 20 Dec 2022, COS for Takeda)
- [5] Report: The Functional Impacts of Narcolepsy Instrument (FINI) in Healthy Controls (TK1034AC, 23 May 2023, COS for Takeda)

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

- Updated the definition of full analysis set to include participants with at least one postdose efficacy measurement.
- Added multiplicity testing.

- Added baseline age to MMRM model for analysis of ESS and WCR and added prior use of narcolepsy medications as a baseline covariate to the MMRM model for the analysis of MWT, ESS, and WCR.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

Changes made from the previous version of the SAP that have a material impact to the planned statistical analysis methods are described below. In addition, there were textual changes purely to improve the flow, organization, and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
<ul style="list-style-type: none"> 6.5.2.2.2 Main Analytical Approach for WCR 	<p>The WCR will be analyzed by generalized estimating equations (GEE) using a log-link function featuring a Poisson distribution. The model will include fixed effects for visit, treatment, and treatment-by-visit interaction, and will be adjusted for baseline WCR, age, and prior use of narcolepsy medications. In case of overdispersion (the estimated scale parameter >2), a negative binomial regression will be used. An unstructured variance-covariance structure will be used initially in these models. Other variance-covariance structures will be evaluated if there are convergence issues with the model. If lack-of-convergence still exists,</p>	<p>The WCR will be analyzed by generalized estimating equations (GEE) featuring a negative binomial distribution. The model will include fixed effects for visit, treatment, and treatment-by-visit interaction, and will be adjusted for baseline WCR, age, and prior use of narcolepsy medications. An unstructured variance-covariance structure will be used initially in these models. If there are convergence issues with the model, an exchangeable variance-covariance structure will be used, followed by an independent structure. If lack-of-convergence still exists, the analysis will be done for Week 4 and Week 8 separately. The estimated incidence rate</p>	<p>Better analytical approach for the underlying data assumptions. Specific var/cov structures clarified</p>

	<p>the analysis will be done for Week 4 and Week 8 separately. The estimated incidence rate of weekly cataplexy for each treatment group and the associated SE and 95% CIs will be extracted from the model, along with the incidence rate ratio of weekly cataplexy (TAK-861 to placebo) for all TAK-861 treatment groups, and the associated SEs, 95% CIs, and two-sided p-values. The optional 4-week extension visits (week 10 and 12) and the 7-day follow-up visit will not be included in the GEE model.</p>	<p>of weekly cataplexy for each treatment group and the associated SE and 95% CIs will be extracted from the model, along with the incidence rate ratio of weekly cataplexy (TAK-861 to placebo) for all TAK-861 treatment groups, and the associated SEs, 95% CIs, and two-sided p-values. The optional 4-week extension visits (week 10 and 12) and the 7-day follow-up visit will not be included in the GEE model.</p>	
<ul style="list-style-type: none"> 6.9.1.1 PVT 	<p>For the change from time-matched baseline in the PVT endpoints, the normality assumption will be tested using the Shapiro-Wilk test. If there is no statistically significant departure from the normal distribution assumption, then the change from time-matched baseline will be analyzed with an MMRM model. The MMRM model will include fixed effects for the time-matched baseline value, treatment, visit (Week 4, Week 8), timepoint (morning and afternoon),</p>	<p>The number of lapses will be analyzed by generalized estimating equations (GEE) featuring a negative binomial distribution. The model will include fixed effects for visit, treatment, timepoint, treatment-by-timepoint, visit-by-timepoint, treatment-by-visit, and treatment-by-visit-by-timepoint interactions, and will be adjusted for time-matched baseline number of lapses. Subject will be the repeated factor and an unstructured variance-covariance structure will</p>	<p>The updated analytical approach better aligns with the underlying data assumptions and fit. Also clarified variance/covariance structures, and updated which endpoints are additionally tested non-parametrically.</p>

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	<p>treatment-by-visit interaction, treatment-by-timepoint interaction, visit-by-timepoint interaction and the 3-way interaction of treatment, visit, and timepoint. Both visit and timepoint are repeated factors.</p> <p>Kronecker product</p> <p>UN@UN will be used for the covariance structure.</p> <p>Other Kronecker product structures such as UN@AR(1), and UN@CS will also be used if there are convergence issues. If the model does not converge then the change from time-matched baseline will be analyzed with an MMRM model at each visit (Week 4, Week 8).</p> <p>Otherwise, the normality assumption will be tested on the square root transformation of the actual values at post baseline visits. If there is no statistically significant departure from the normal distribution assumption, the square root transformed values will be analyzed as the response variable in an MMRM model with the same specification as described above. The LS means and 95% confidence intervals will</p>	<p>be used in the model. If lack-of-convergence exists, an exchangeable variance-covariance structure will be used, then an independent variance-covariance structure, and if lack of convergence still exists the analysis will be done for Week 4 and Week 8 separately. The estimated number of lapses for each treatment group and the associated SE and 95% CI will be extracted from the model, along with the ratio of number of lapses between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values. The mean reaction time will be analyzed by generalized estimating equations (GEE) using a log-link function featuring a gamma distribution. The model will include fixed effects for visit, treatment, timepoint, treatment-by-timepoint, visit-by-timepoint, treatment-by-visit, and treatment-by-visit-by-timepoint interactions, and will be adjusted for time-matched baseline mean reaction time. Subject will be the repeated factor and an unstructured variance-</p>	
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	<p>be transformed back to the original scale.</p> <p>Number of lapses may be evaluated by a (zero inflated) negative binomial model, if appropriate. If the normality assumptions do not hold after square root transformation, Friedman's test will be performed to compare the population distributions of the treatments</p>	<p>covariance structure will be used in the model. If lack-of-convergence exists, an exchangeable variance-covariance structure will be used, then an independent variance-covariance structure, and if lack of convergence still exists the analysis will be done for Week 4 and Week 8 separately. The estimated mean reaction time for each treatment group and the associated SE and 95% CI will be extracted from the model, along with the ratio of mean reaction times between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values.</p> <p>The mean inverse reaction time (1/RT) will be analyzed with an MMRM model. The MMRM model will include fixed effects for the time-matched baseline value, treatment, visit (Week 4, Week 8), timepoint (morning and afternoon), treatment-by-visit interaction, treatment-by-timepoint interaction, visit-by-timepoint interaction and the 3-way interaction of treatment, visit, and timepoint. Both</p>	
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		<p>visit and timepoint are repeated factors.</p> <p>Kronecker product UN@UN will be used for the covariance structure. Other Kronecker product structures such as UN@AR(1), and UN@CS will also be used if there are convergence issues. If the model does not converge then the mean 1/RT will be analyzed with an MMRM model at each visit (Week 4, Week 8). The estimated mean 1/RT for each treatment group and the associated SE and 95% CIs will be extracted from the model, along with the difference in mean 1/RTs between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values. For mean inverse reaction time, Friedman's test will be performed to compare the population distributions of the treatments.</p>	
<ul style="list-style-type: none"> 6.9.1.2 CPAL/ONB/iDSST-s 	<p>The normality assumption for each endpoint will be tested using the Shapiro-Wilk test for the change from baseline. If there is no statistically significant departure from the normal distribution assumption,</p>	<p>CPAL number of errors will be analyzed using a GEE model featuring a negative binomial distribution. The model will include fixed effects for visit, treatment and treatment-by-visit</p>	<p>The updated analytical approach better aligns with the underlying data assumptions and fit. Also clarified variance/covariance structures, and updated which endpoints are additionally tested non-parametrically.</p>

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	<p>then the change from baseline will be analyzed with an MMRM model. For number of errors from CPAL and number of correct responses from iDSST-s, the normality assumption will be tested on the square root transformation of the actual values at the post baseline visits. If there is no statistically significant departure from the normal distribution assumption, the square root transformed values will be analyzed with an MMRM model. The LS means and 95% confidence intervals will be transformed back to the original scale. Number of errors from CPAL, and the number of correct responses from iDSST-s, may be evaluated by a (zero inflated) negative binomial model, if appropriate. If the normality assumptions do not hold after square root transformation, Friedman's test will be performed to compare the population distributions across the treatment groups.</p>	<p>interaction, and will be adjusted for baseline number of errors. Subject will be the repeated factor and an unstructured variance-covariance structure will be used in the model. If lack-of-convergence exists, an exchangeable variance-covariance structure will be used, then an independent variance-covariance structure, and if lack of convergence still exists the analysis will be done for Week 4 and Week 8 separately. The estimated number of errors for each treatment group and the associated SE and 95% CI will be extracted from the model, along with the ratio of number of errors between all TAK-861 treatment groups and placebo, and the associated SEs, 95% CIs, and two-sided p-values. The iDSST-s number of correct responses will be analyzed using the same model as CPAL number of errors.</p> <p>ONB speed of performance, ONB accuracy of performance, and iDSST-s speed of performance will all be analyzed using an</p>	
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		<p>MMRM model specified in Section 6.1.2. For ONB speed of performance, the model will provide estimated speed of performance and the associated SE and 95% CI for correct responses for each treatment group, as well as difference in speed of performance between TAK-861 and placebo, along with the associated SEs, 95% CIs, and two-sided p-values. For ONB accuracy of performance, the model will provide estimated accuracy of performance and the associated SE and 95% CI for each treatment group, as well as difference in accuracy of performance between TAK-861 and placebo, along with the associated SEs, 95% CIs, and two-sided p-values. For iDSST-s speed of performance, the model will provide estimated speed of performance for each treatment group and the associated SE and 95% CI, as well as difference in speed of performance for correct responses between TAK-861 and placebo, along with the associated SEs, 95% CIs, and two-sided p-values.</p>	
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		For ONB speed of performance, ONB accuracy of performance, and iDSST-s speed of performance, Friedman's test will be performed to compare the population distribution across the treatment groups.	
<ul style="list-style-type: none"> 6.9.4 Narcolepsy Symptoms (eDiary) 	The number of naps will be analyzed with a GEE model using a log-link function featuring a Poisson distribution similar to WCR.	The number of naps will be analyzed with a GEE model featuring a negative binomial distribution similar to WCR.	The updated analytical approach better aligns with the underlying data assumptions and fit.
<ul style="list-style-type: none"> 6.9.4 Narcolepsy Symptoms (eDiary) 		Removed Kruskal-Wallis test for Narcolepsy Symptoms and Cataplexy-Free Days	Aligned with the analytical needs for this study
<ul style="list-style-type: none"> 6.9.4 Narcolepsy Symptoms (eDiary) 	<p>For number of naps, weekly episodes (WE) at baseline will be based on the number of episodes averaged over 2 weeks minimum, and for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:</p> $WE = ((\text{number of episodes over a 2 week period}) / (\text{number of non-missing diary days in the 2 week period})) * 7$ <p>Weekly episodes for number of naps in the 7-day post last dose follow-up visit is calculated as follows:</p> $WE = ((\text{number of episodes over the follow-up period}) / (\text{number of non-missing diary days in the follow-up period})) * 7$	Added clarifying language about calculation of weekly episodes for diary symptoms	Clarifying language

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	<p>For all other endpoints, Weekly episodes (WE) at baseline will be based on the number of episodes averaged over 2 weeks minimum, and for postdose visits (Week 2, Week 4, Week 6, and Week 8) will be calculated as follows:</p> $WE = ((\text{number of nights with an episodes over a 2 week period}) / (\text{number of non-missing diary days in the 2 week period})) * 7$ <p>Weekly episodes for all other endpoints for the 7-day post last dose follow-up visit is calculated as follows:</p> $WE = ((\text{number of nights with an episodes over the follow-up period}) / (\text{number of non-missing diary days in the follow-up period})) * 7$		
<ul style="list-style-type: none"> 6.4.2 Concomitant Medications 	<p>Concomitant medications are defined as any medications that started prior to the first dose of study drug and are ongoing at the time of the first dose or started after the first dose of study drug but before the date of last TAK-861 dose.</p>	Added bold text	<p>This definition better avoids capturing the incorrect impression that patients were taking prohibited medication during study, as some began medication</p>
<ul style="list-style-type: none"> 6.5.2.2.2 Main Analytical Approach for WCR 	<p>WCR will be summarized by treatment group and TAK-861 overall at baseline and postdose visits (Week 2, Week 4, Week 6, Week 8, Week 10 (optional), Week 12 (optional) and 7-day follow-up visit),</p>	Remove language in bold	<p>More parsimonious summary of cataplexy-free days</p>

	including change/percent change from baseline.		
<ul style="list-style-type: none"> 6.6.3.4 ECG 	The number and percentage of participants meeting each markedly abnormal criteria and any MAV criteria will be summarized over all postdose visits, at Week 2, Week4, Week 8, Week 12 (optional 4-week extension) and at the 7-day follow-up visit by treatment group, TAK-861 overall, and total.	Remove language in bold	More parsimonious summary of ECG MAVs

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Refer to programming specifications.

9.2.2 Definition of Baseline

The definition of baseline is addressed in the specific section of the SAP.

9.2.3 Definition of Visit Windows

Refer to programming specifications.