Clinical Study Protocol

NCT Number: NCT06505031

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

Study Number: TAK-861-3002

Document Version and Date: Amendment 1, 29 Oct 2024

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TAKEDA PHARMACEUTICALS

PROTOCOL

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

A Study to Evaluate the Efficacy and Safety 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-861-3002		
Study Phase:	Phase 3		
IND Number:	154232	**EU CT Number:**	2024-511998-30
Clinicaltrials.gov:	NCT06505031		
Investigational Product:	TAK-861		
Date:	29 October 2024	**Version/Amendment Number:**	Amendment 1

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Amendment History:

Date	Amendment Number	Region
29 October 2024	Amendment 1 [a]	Global
29 February 2024	Initial protocol	Global

[a] Amendment 1 incorporates changes in Initial Protocol EU v1, dated 06 September 2024

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APPROVALS

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirem ents of this study protocol and also in accordance with the following:

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

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PPD, MD PPD, Clinical Science	Date	PPD, PhD PPD, Statistics and Quantitative Sciences	Date

PPD, PhD PPD, Quantitative Clinical Pharmacology	Date

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.

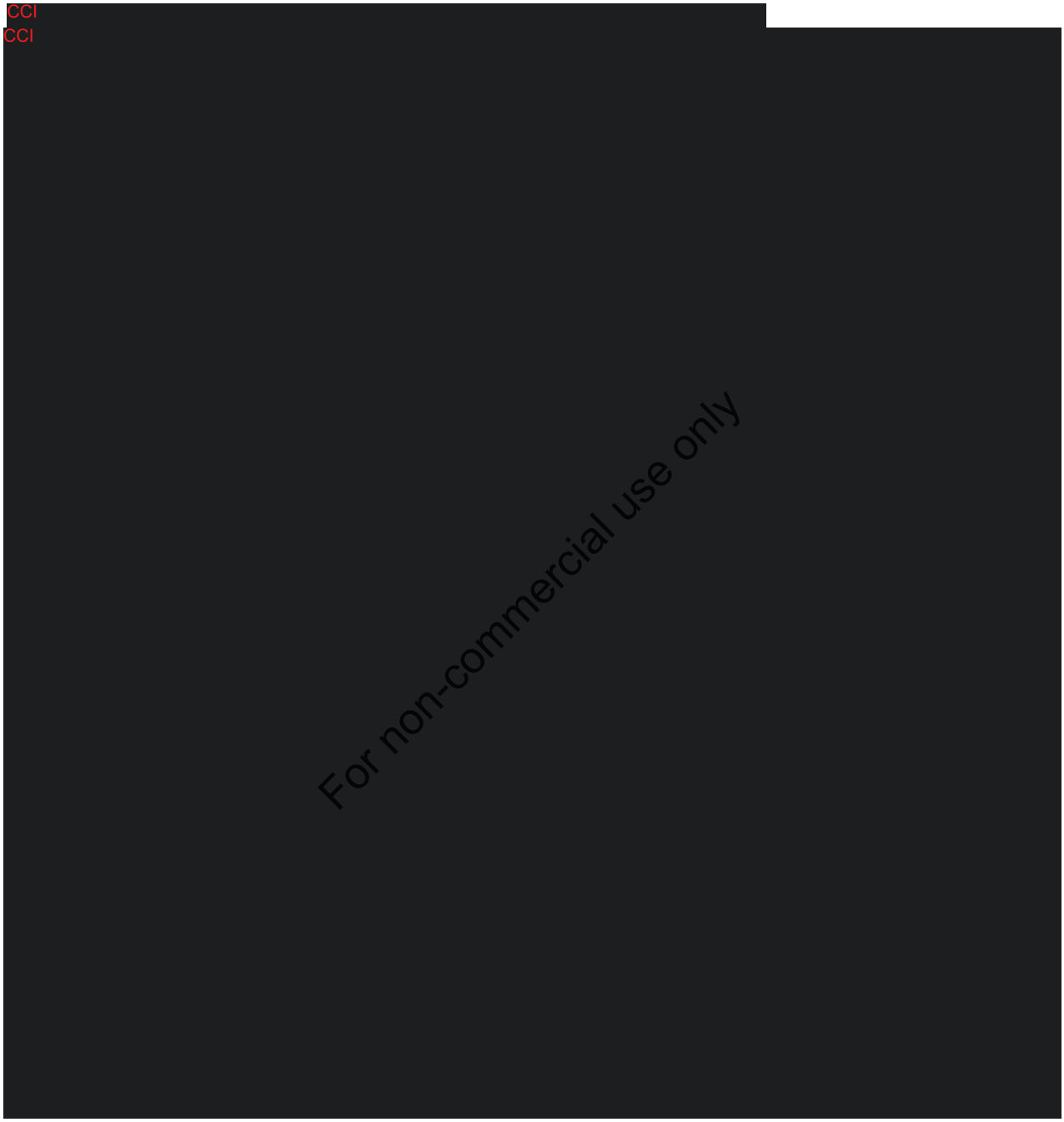
I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

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.

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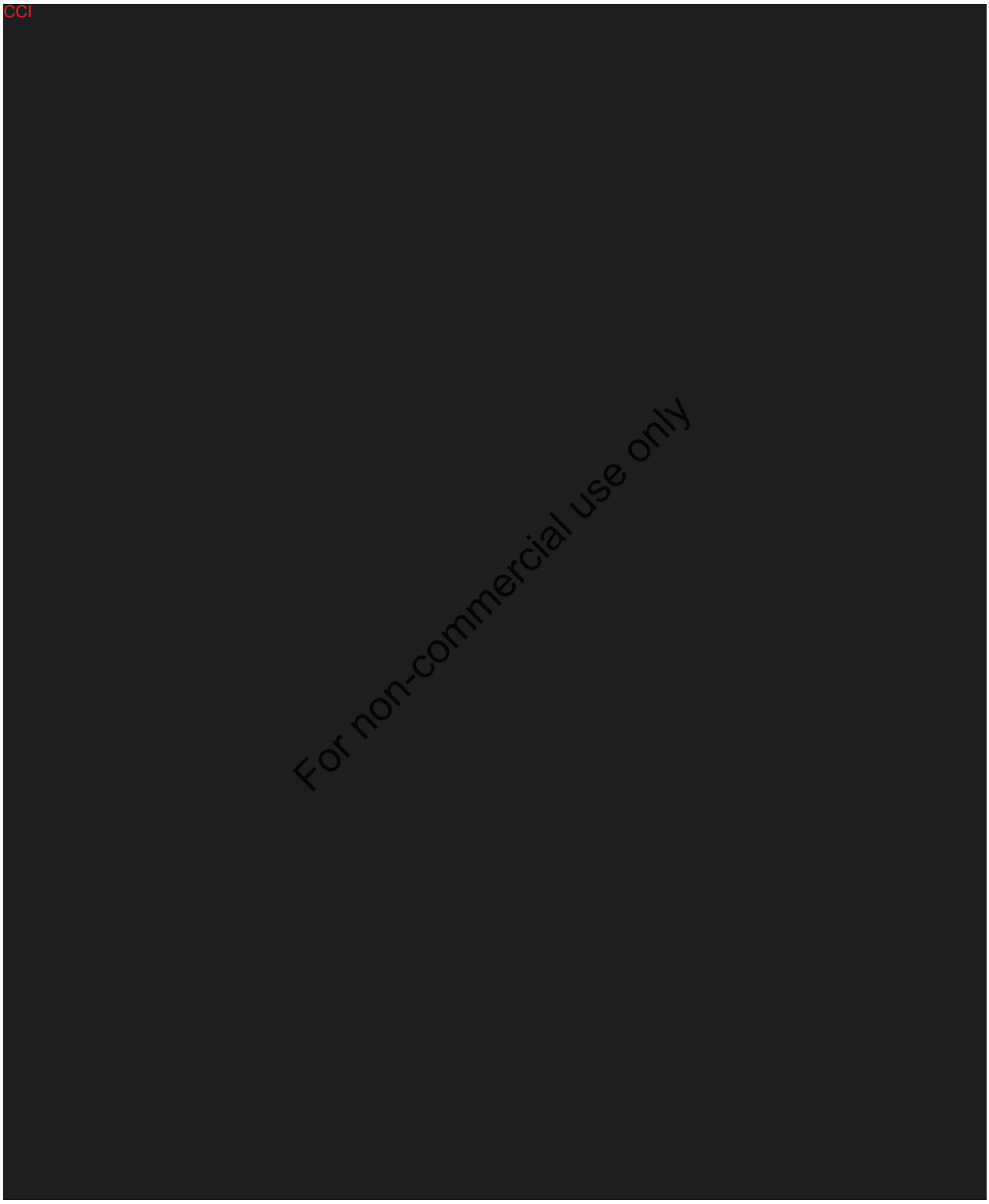
Signature of Investigator	Date
Investigator Name (print or type)	
Investigator's Title	
Location of Facility (City, State/Province)	
Location of Facility (Country)	

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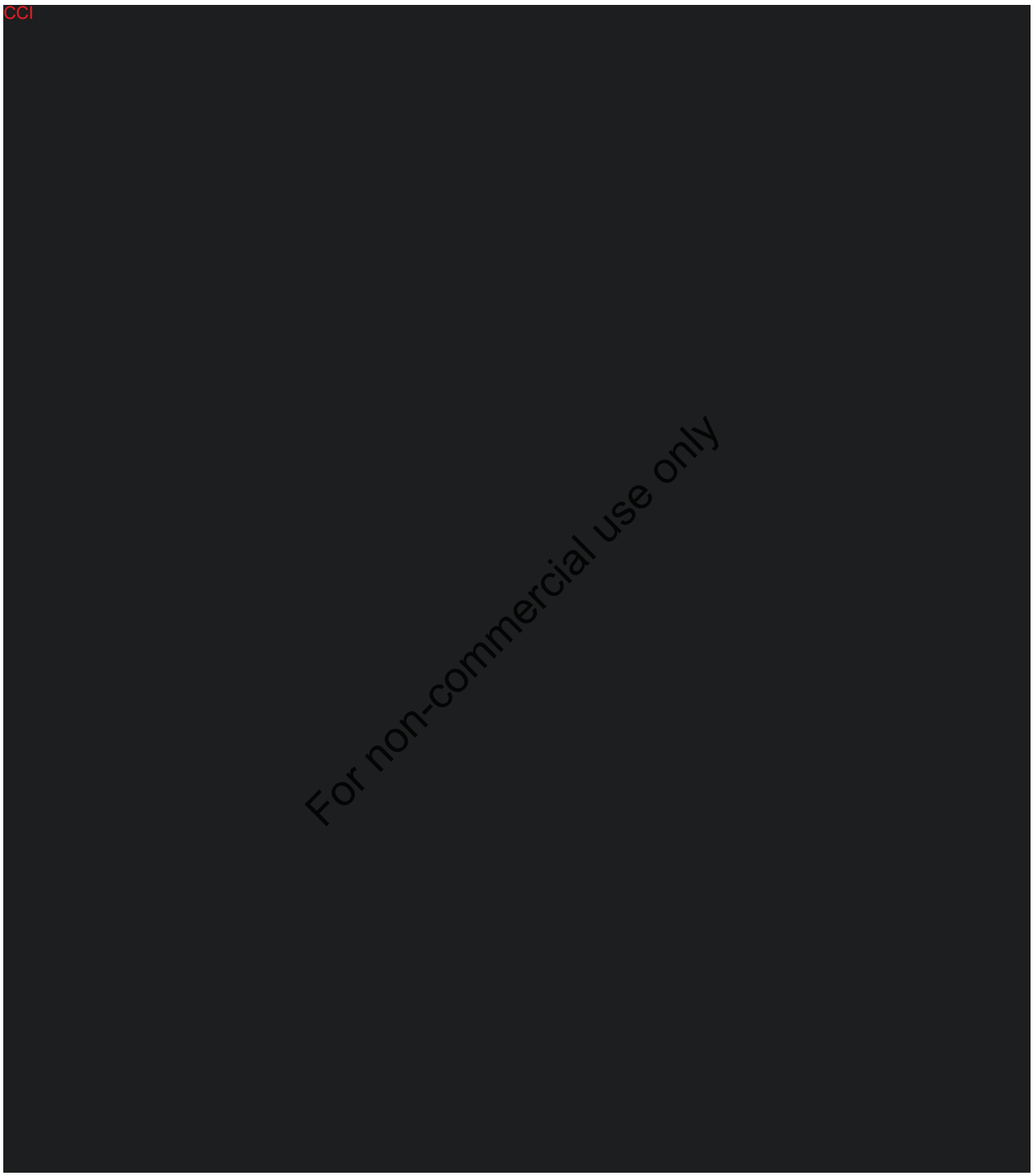


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ADMINISTRATIVE INFORMATION

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 sponsored investigators will be provided with emergency medical contact information cards to be 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
SAE and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 001 224-554-1052 United States and Canada Email: PVSafetyAmericas@takeda.com Rest of the world Email: PharmacovigilanceMailbox@Takeda.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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Send it to the following email address:

ctmcomplaint@takeda.com

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1.0 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td colspan="2">Name of Sponsor(s):

Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington MA 02421
USA</td><td colspan="2">Compound:

TAK-861</td></tr>
<tr><td>Study Number:

TAK-861-3002</td><td>Phase:

3</td><td>IND No.:

154232</td><td>EU CT Number:

2024-511998-30</td></tr>
<tr><td colspan="4">Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-861 for the Treatment of Narcolepsy with Cataplexy (Narcolepsy Type 1)</td></tr>
<tr><td colspan="4">Short Title:

A Study to Evaluate the Efficacy and Safety of TAK-861 for the Treatment of Narcolepsy with Cataplexy</td></tr>
<tr><td colspan="4">Number of Participants (Total and per Treatment Arm):

A total of approximately 93 participants with randomization ratio CCI [redacted]</td></tr>
<tr><td colspan="4">Investigator(s): Multicenter global study</td></tr>
<tr><td colspan="4">Site(s) and Region(s): Up to 50 sites globally</td></tr>
<tr><td colspan="4">Study Period (Planned): CCI [redacted]</td></tr>
<tr><td colspan="4">Objectives and Endpoints:</td></tr>
<tr><td colspan="2">Objectives:</td><td colspan="2">Endpoints:</td></tr>
<tr><td colspan="4">Primary:</td></tr>
<tr><td colspan="2">Globally except in the European Union (EU) and European Economic Area (EEA):

• To assess the effect of TAK-861 on excessive daytime sleepiness (EDS) as measured by the Maintenance of Wakefulness Test (MWT).</td><td colspan="2">• Change from baseline to Week 12 in mean sleep latency from the 4 MWT wake trials.</td></tr>
<tr><td colspan="2">For the EU and EEA only:

• To assess the effect of TAK-861 on EDS as measured by the Epworth Sleepiness Scale (ESS) total score.</td><td colspan="2">• Change from baseline to Week 12 in ESS total score.</td></tr>
</table>

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Secondary:	
Globally except in the EU and EEA: • To assess the effect of TAK-861 on EDS as measured by the ESS total score.	• Change from baseline to Week 12 in ESS total score.
For the EU and EEA only: • To assess the effect of TAK-861 on EDS as measured by the MWT.	• Change from baseline to Week 12 in mean sleep latency from the 4 MWT wake trials.
• To assess the effect of TAK-861 on cataplexy as measured by the weekly cataplexy rate (WCR).	• WCR at Week 12.
• To assess the effect of TAK-861 on sustained attention as measured by the psychomotor vigilance test (PVT).	• Change from baseline to Week 12 in mean number of lapses on the PVT.
• To assess the effect of TAK-861 on overall narcolepsy symptoms measured by the Patient Global Impression of Change (PGI-C) scale.	• PGI-C score at Week 12.
• To assess the effect of TAK-861 on overall severity of narcolepsy symptoms measured by the Narcolepsy Severity Scale for Clinical Trials (NSS-CT).	• Change from baseline to Week 12 in NSS-CT total score.
• To assess the efficacy of TAK-861 on functional impacts of narcolepsy as assessed by the Functional Impacts of Narcolepsy Instrument (FINI).	• Change from baseline to Week 12 in FINI domain scores for: Tiredness, Cognitive Functioning, Cataplexy, Social Activities, Everyday Activities, and Everyday Responsibilities.
• To assess the effect of TAK-861 on quality of life of participants, as assessed by the Short Form-36 Survey (SF-36).	• Change from baseline to Week 12 in SF-36 mental and physical component summary scores.
• To evaluate the safety of TAK-861 as measured by treatment-emergent adverse event (TEAE) incidence.	• Occurrence of at least 1 TEAE during the study including the follow-up period, as applicable.
Estimands: CCI [redacted]	

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[redacted] CCI [redacted]

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Rationale:

This study is designed to evaluate the efficacy and safety of TAK-861 in participants with narcolepsy with cataplexy (narcolepsy type 1 [NT1]).

Narcolepsy is a rare, acquired, chronic neurologic disorder that alters the sleep-wake cycle. Five clinical features comprise the NT1 symptom pentad: EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed nighttime sleep. Narcolepsy with cataplexy, or NT1, has been defined by the International Classification of Sleep Disorders, 3rd Edition (ICSD-3) or ICSD-3 text revision (ICSD-3-TR) criteria as having low levels of orexin (OX) in the cerebrospinal fluid (CSF) (≤110 pg/mL, or less than one-third of normal levels), most likely due to a selective loss of hypothalamic OX-producing neurons. An OX type-2 receptor (OX2R) agonist is thus the first approach to directly address the loss of OX peptide in the brain 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 OX agonist has been well-tolerated and was associated with marked improvements in sleep latency in patients with NT1.

CCI

Overall, the available nonclinical information and available clinical safety and PK profiles from CCI and CCI (8 weeks of TAK-861 administered to patients with NT1) support this study.

The duration of the dosing (12 weeks) was chosen to allow sufficient 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 CCI the 84-day treatment period and 28-day follow-up period are of sufficient duration to characterize the potential effects of treatment.

Study Intervention, Dose, and Mode of Administration:

The following treatments will be included in this study; all treatments will be administered orally:

- TAK-861 CCI
- Matching placebo CCI

The study drug will be administered at approximately the same time each day for 12 weeks. On CCI , the CCI of TAK-861 or matched placebo will be administered CCI Participants will take CCI At home, the CCI should be taken CCI To maintain the blind, all participants will receive the same number of tablets and bottles.

Overall Design and Methodology:

This is a randomized, double-blind, placebo-controlled, multicenter, 12-week parallel-group study to evaluate the efficacy and safety of TAK-861.

Approximately 93 participants with NT1 will be randomized CCI to placebo or TAK-861. CCI

After providing informed consent, participants will complete a screening period of up to 50 days. The investigator may repeat screening assessments to ensure participant suitability, with permission of the sponsor or delegate. Participants will discontinue medications used to treat narcolepsy CCI Note that if tapering of any restricted medication is required, this tapering should be started early in the screening period, so the participant is no longer taking the medication by the study day indicated in the protocol.

Participants will be asked to complete an e-diary, starting no later than CCI . To be eligible for the study, participants must fill out self-reported cataplexy questions in the e-diary for at least CCI day period from CCI and have ≥4 partial and/or complete episodes of cataplexy/week (averaged over CCI

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CCI).

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After the Week 12 visit, participants who remained on study treatment throughout the treatment period will have the option to participate in a long-term extension (LTE) study under a separate protocol. Participants who immediately enroll in the LTE study will not have follow-up visits in this study.

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 study) will complete a first follow-up visit approximately 7 days after the final dose of study drug and a second follow-up visit approximately 28 days after the final dose of study drug. For participants who terminate the study early, every effort should be deployed to have them complete an early termination visit as soon as possible and a follow-up visit approximately 28 days after the last dose of study drug. Participants not participating in the LTE study can restart their restricted medications CCI 7 days after the last administration of study drug.

Inclusion and Exclusion Criteria:

Note that the site's investigator may determine if there is a need to repeat any screening assessments to ensure participant suitability. The sponsor (or designee) should be informed.

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 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.

   CCI

4. The participant has a body mass index within the range 18 to 40 kg/m^2 (inclusive).

Type of Participant and Disease Characteristics

5. The participant has an ICSD-3 or ICSD-3-TR diagnosis of NT1 supported by results from 1) Polysomnography (PSG) (with or without Multiple Sleep Latency Test [MSLT]), performed within the past CCI and meeting the minimal acceptable criteria for the proper performance of PSG/MSLT as outlined in the ICSD-3 or ICSD-3-TR, or 2) 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).

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[redacted]. CCI [redacted]

7. The participant has ≥4 partial or complete episodes of cataplexy/week (WCR), CCI [redacted]

8. The participant is positive for the human leukocyte antigen (HLA) genotype HLA-DQB1*06:02 (positive results for either homozygous or heterozygous alleles will be considered "positive" and acceptable) or results from radioimmunoassay 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 investigator 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, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead electrocardiogram (ECG), and vital sign measurements performed at the screening visit and before the first dose of study drug.

Contraception

10. The participant agrees to follow the contraceptive requirements detailed in the protocol.

Other

CCI CCI [redacted]

Exclusion Criteria

Medical Conditions

1. The participant has a current medical disorder, other than narcolepsy with cataplexy, associated with EDS. For example, the following are exclusionary:

   CCI CCI [redacted]

   [redacted]

2. The participant: (a) has a history of myocardial infarction; (b) has a history of clinically significant hepatic disease, thyroid disease, coronary artery disease, cardiac rhythm abnormality or heart failure; or (c) has any medical condition (such as unstable cardiovascular, pulmonary, renal or gastrointestinal disease, CCI [redacted]

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3. The participant has current or recent (within 6 months) gastrointestinal disease that is expected to influence the absorption of drugs. CCI

4. 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 carcinoma; these participants may be included after approval by the sponsor or designee).

5. The participant has a clinically significant history of head injury or head trauma.

6. The participant has a history of epilepsy, seizure, or convulsion (except for a single febrile seizure in childhood).

7. The participant has a history of cerebral ischemia, transient ischemic attack (<5 years from screening), intracranial aneurysm, or arteriovenous malformation.

8. The participant has 1 or more of the following psychiatric disorders:

CCI CCI

CCI CCI

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.

c) Current active major depressive episode (MDE) or an active MDE in the past 6 months.

d) Any current unstable psychiatric disorder.

CCI

9. 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.

10. The participant has a known hypersensitivity to any component of the formulation of TAK-861 or related compounds.

11. The participant has had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.

Prior/Concomitant Therapy

12. The participant is unable to refrain from or anticipates using excluded food products, beginning by CCI and continuing until 7 days after the last dose, or prohibited medications (including CCI) as described in the body of the protocol.

Prior Clinical Study Experience

13. The participant has participated in another investigational drug study, in which they received the investigational drug, within CCI The interval window from the previous study will be derived from the date of the last dose of

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investigational drug in the previous study to the screening visit of the current study. The participant must agree not to participate in any other interventional study while participating in TAK-861-3002.

Note: This does not apply to past participation in trials of approved drugs, for which rules are specified in the protocol.

CCI [redacted]

Diagnostic Assessments

CCI CCI [redacted]

CCI [redacted]

15. The participant has a resting heart rate CCI [redacted] beats per minute during screening, confirmed on repeat testing within a maximum of C [redacted] minutes.
16. The participant's screening ECG reveals a QT interval with Fridericia correction method CCI [redacted] milliseconds (genetically male) or CCI [redacted] milliseconds (genetically female).
17. The participant has a positive test result for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, or HIV antibody/antigen at screening.

CCI CCI [redacted]

CCI CCI [redacted]

20. The participant has a positive pregnancy test result at screening or Day -2 or is breastfeeding.

CCI CCI [redacted]

22. 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 4 or 5 on the Columbia Suicide Severity Rating Scale within a year before randomization.

Other Exclusion Criteria

23. 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.
24. The participant consumes excessive amounts of caffeine, defined as greater than CCI [redacted]. (1 cup of coffee is approximately 120 mg.)

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25. The participant currently consumes alcohol exceeding CCI 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).

CCI

CCI

26. The participant has a nicotine dependence that is likely to affect sleep (eg, a participant who routinely awakens at night to smoke) CCI

CCI

CCI CCI

28. 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 treatment period.

29. The participant, in the opinion of the investigator or subinvestigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

30. The participant is considered to be vulnerable, as defined by local regulations and if exclusion is required by local regulations. Examples of vulnerable persons are persons under safeguard of justice, persons deprived of liberty by judicial or administrative decision, persons receiving psychiatric care without their consent, persons admitted to a health or social establishment for purposes other than research, persons of full age who are subject to a legal protection measure (guardianship or curatorship), and persons unable to express their consent.

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CCI [redacted]

Intervention Groups and Duration, Including Maximum Duration of Participant Involvement in the Study:

The total planned duration of study participation for each participant includes:

- Screening period: at least CCI [redacted] and up to 50 days.
- Treatment period: 12 weeks.
- Follow-up period: 0 or 4 weeks (0 if immediately enrolling in the LTE study).

Statistical Analysis:

Analysis Sets:

Safety set: The safety set will consist of all participants who received at least 1 dose of study drug. All participants will be analyzed according to the treatment they actually received.

Full analysis set: The full analysis set (FAS) will consist of all participants who were randomized. All participants in the FAS will be analyzed according to the treatment group to which they were randomized. The FAS will be used as the primary analysis population for efficacy.

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.

Efficacy:

The change from baseline in mean sleep latency will be analyzed CCI [redacted]. The estimated change from baseline in mean sleep latency for each treatment and the associated standard error (SE) and 95% confidence interval (CI) 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 analyzed CCI [redacted] The estimated change from baseline in mean ESS total score for each treatment and the associated SE and 95% CI will be extracted from the model, along with all estimated treatment differences from placebo and associated SEs, 95% CIs, and p-values.

The number of cataplexy attacks will be analyzed CCI [redacted] The estimated CCI [redacted] cataplexy for each treatment and the associated SE and 95% CI will be extracted from the model, along with the CCI [redacted] and the associated SE, 95% CIs, and p-values.

The mean number of lapses on PVT at baseline and post-randomization will be analyzed CCI [redacted]

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CCI . The estimated change from baseline in mean number of lapses CCI for each treatment and the associated SE and 95% CI will be derived CCI , along with all estimated treatment differences from placebo CCI for the TAK-861 treatment group, and the associated SEs, 95% CIs, and p-values.

The PGI-C CCI will be analyzed CCI for each treatment and the associated 95% CI will be extracted from the model, along with CCI , and the associated 95% CIs and p-values.

The change from baseline in NSS-CT total score, change from baseline in FINI domain scores, and change from baseline in SF-36 mental and physical component summary scores will all be analyzed CCI .

The details of the analytical methods for other efficacy endpoints will be described in the Statistical Analysis Plan (SAP).

Safety:

AEs will be coded using the Medical Dictionary for Regulatory Activities. 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, serious AEs, 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 markedly abnormal value criteria for safety laboratory tests, vital signs, and ECGs will be summarized by treatment group.

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CCI [redacted]

Data Monitoring/Other Committee: A TAK-861 program-level external data monitoring committee (DMC) will review unblinded safety data CCI [redacted], throughout the study.

CCI [redacted]

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1.2 Schema

Figure 1.a CCI



1.3 Schedule of Activities

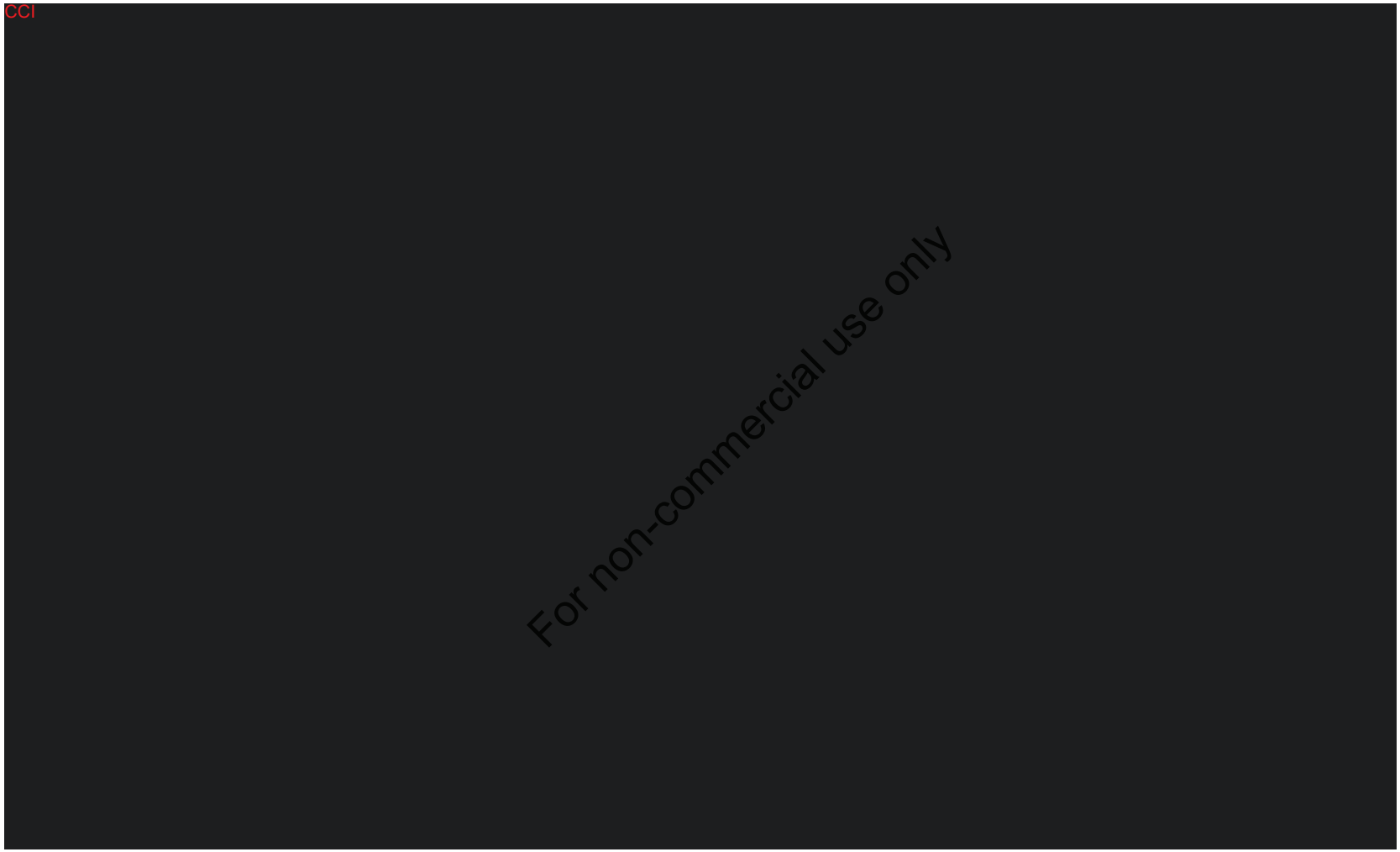
Table 1.a CCI

CCI

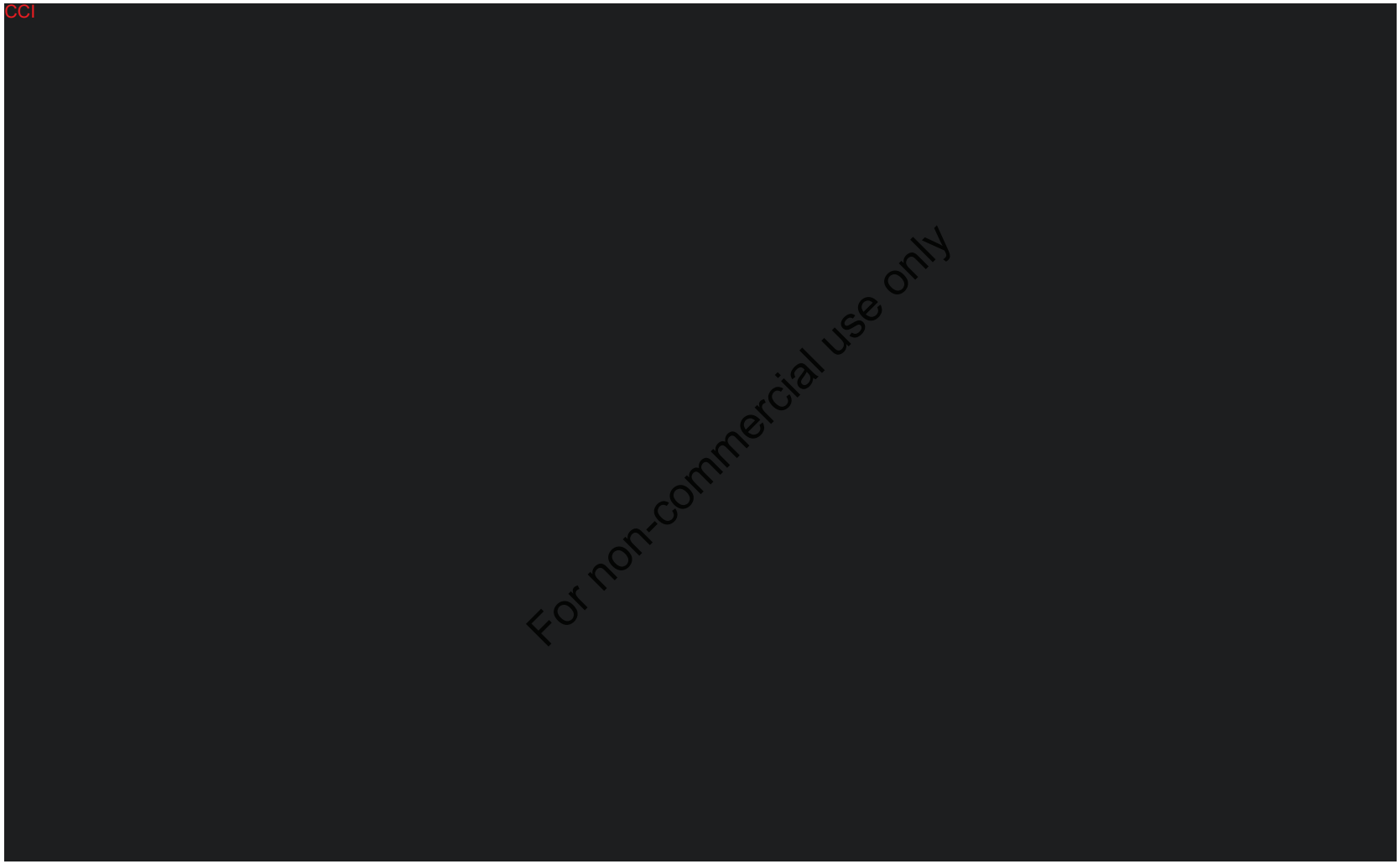
CCI

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CCI



CCI



CCI

[redacted]

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CCI

[redacted]

[redacted]

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[redacted]

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Table 1.b CCI [redacted]

CCI [redacted]

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CCI

[redacted]

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CCI

[redacted]

CCI



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2.0 INTRODUCTION

2.1 Study Rationale

This study is designed to evaluate the efficacy and safety of TAK-861 in participants with narcolepsy with cataplexy (narcolepsy type 1 [NT1]).

Narcolepsy is a rare, acquired, chronic neurologic disorder that alters the sleep-wake cycle. Five clinical features comprise the NT1 symptom pentad: excessive daytime sleepiness (EDS), cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disturbed nighttime sleep (DNS). Narcolepsy with cataplexy, or NT1, has been defined by International Classification of Sleep Disorders, 3rd Edition (ICSD-3) or ICSD-3 text revision (ICSD-3-TR) criteria as having low levels of orexin (OX) in the cerebrospinal fluid (CSF) (≤110 pg/mL, or less than one-third of normal levels), most likely due to a selective loss of hypothalamic OX-producing neurons. An OX type 2 receptor (OX2R) agonist is thus the first approach to directly address the loss of OX peptide in the brain 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 OX agonist has been well-tolerated and was associated with marked improvements in sleep latency in patients with NT1 (Evans et al. 2022).

The available nonclinical information and available clinical safety and pharmacokinetic (PK) profiles from CCI [redacted] and CCI [redacted] (8 weeks of TAK-861 administered to patients with NT1) support this study (see Section 2.2 for additional details).

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

For additional information, see the investigator's brochure (IB).

2.2 Background

As stated above, narcolepsy is a rare neurologic disorder comprised of 5 clinical features (ie, the NT1 pentad). 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 rapid eye movement (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 uncinate events typically occurring during at the transitions into and out of sleep), and sleep paralysis (similar to cataplexy, ie, acute onset of muscle atonia accompanied by a somatic feeling of general paralysis, usually occurring during the transition from wakefulness into sleep) (Abad and Guilleminault 2017; Thorpy and Dauvilliers 2015). DNS is a common narcolepsy-related symptom, with difficulty maintaining continuous sleep. Together, these

5 clinical features (EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and DNS) comprise the narcolepsy symptom pentad (Abad and Guilleminault 2017; Thorpy and Dauvilliers 2015). It has been estimated that only 20% to 30% of patients have all components of the pentad at any one time (Billiard et al. 1983).

NT1, has been defined by ICSD-3 or ICSD-3-TR 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 the laboratory's normal levels), The loss of OX-producing neurons is reflected by low levels of OX in the CSF. 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 (De la Herran-Arita and Garcia-Garcia 2014; Krahn et al. 2002).

The orexinergic system is a major wake-promoting system of the brain. It is comprised of wake-promoting OX (also known as hypocretin) neurons, localized in a specific region of the lateral hypothalamus, which have excitatory projections to wide areas of the neuraxis including the cerebral cortex and other wake-promoting nuclei (cholinergic neurons of the basal forebrain, tuberomammillary nucleus, locus coeruleus, ventral tegmental area, and dorsal raphe nucleus). The orexinergic system is also involved in several other functions, such as feeding, reward, and sympathetic activity.

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Two orexinergic neuropeptides, OX-A and OX-B, have been identified to date. The OXs exert effects via 2 types of G-Protein-Coupled-Receptors, the OX type 1 receptor (OX1R) and the OX2R. OX-A has a high affinity to OX1R and OX2R, and OX-B has a high affinity to OX2R. The 2 OX receptors have a distinct distribution within various brain structures and monoaminergic arousal networks – the locus coeruleus contains only OX1R, and the tuberomammillary nucleus contains only OX2R; both receptor types occur in the dorsal raphe nucleus and ventral tegmental area (Tsujino and Sakurai 2013).

Because partial or complete OX deficiency plays an important role in the development of EDS, OX replacement therapy may 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 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 IB.

2.2.2 Summary of Effects in Humans

TAK-861 has been studied across a range of doses in [redacted]

For additional information on the studies summarized below, refer to the TAK-861 IB.

CCI [redacted]

[redacted]

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CCI [redacted]

TAK-861-1002

The phase 1 study TAK-861-1002 was a randomized, double-blind, placebo-controlled, 3-period crossover study designed to evaluate the safety, tolerability, PD, and PK of TAK-861 during an acute sleep phase delay paradigm in healthy adult male participants. 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 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 (KSS) 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 KSS 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 TAK-861 was well tolerated with no severe or serious TEAEs, no TEAEs leading to discontinuation, and no clinically relevant MAV for clinical laboratory parameters. All TEAEs were mild in intensity, except for 1 moderate TEAE of blood creatine phosphokinase increased that occurred predose in the second treatment period and was considered by the investigator to be not related to the study drug. 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.

CCI [redacted]

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CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

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[redacted] There were no deaths, study-drug related serious TEAEs, or discontinuations due to TEAEs. The most commonly reported TEAEs were insomnia, urinary events (micturition urgency, pollakiuria), and salivary hypersecretion; the majority of these were mild or moderate in intensity and none required medical intervention. Most of these events were mild or moderate in intensity, started on Day 1, and resolved during study treatment.

CCI [redacted] The safety data showed that TAK-861 was well tolerated with no severe or serious TEAEs. The most commonly reported AEs were urinary events (micturition urgency, pollakiuria) and insomnia; all were mild or moderate in intensity and none required medical intervention.

2.3 Benefit-Risk Assessment

Refer to the latest version of TAK-861 IB for the overall benefit-risk assessment and the most current information regarding drug metabolism, PK, efficacy, and safety of TAK-861.

This is a randomized, double-blind, placebo-controlled, multicenter, 12-week parallel-group study to evaluate the efficacy and safety of TAK-861.

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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.

Available nonclinical and clinical data have provided evidence of wake-promoting and cataplexy-reducing effects of TAK-861 (TAK-861 IB). CCI [redacted]

2.3.2 Potential Risks

Based on nonclinical data and clinical results for TAK-861, clinical data for the 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 investigational product are:

- Increases in blood pressure (BP) and heart rate (HR).
- Insomnia.
- Urinary events (eg, increased frequency of urination and micturition urgency).

The following mitigation measures are in place to address potential risks:

- For increases in BP and HR: Appropriate selection of the study population (exclusion criteria cutoffs for BP/HR measurements); monitoring of vital signs and electrocardiogram (ECG) assessments throughout the study; and discontinuation and stopping criteria established based on BP/HR measurements.
- For insomnia: CCI [redacted] and routine adverse event (AE) monitoring.
- For urinary events: Routine AE monitoring.

Stopping rules for individual participants and the overall study have been established and are noted in Section 7.0.

CCI [redacted]

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Finally, there is minimal risk associated with the procedures planned for this study. Potential risks related to 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 supports a favorable benefit-risk ratio for this study with TAK-861.

3.0 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1 Objectives and Endpoints

The following are the objectives and endpoints of this study:

Objectives:	Endpoints:
Primary:	
Globally except in the European Union (EU) and European Economic Area (EEA): • To assess the effect of TAK-861 on EDS as measured by the MWT.	• Change from baseline to Week 12 in mean sleep latency from the 4 MWT wake trials.
For the EU/EEA only: • To assess the effect of TAK-861 on EDS as measured by the ESS total score.	• Change from baseline to Week 12 in ESS total score.
Secondary:	
Globally except in the EU and EEA: • To assess the effect of TAK-861 on EDS as measured by the ESS total score.	• Change from baseline to Week 12 in ESS total score.
For the EU/EEA only: • To assess the effect of TAK-861 on EDS as measured by the MWT.	• Change from baseline to Week 12 in mean sleep latency from the 4 MWT wake trials.
• To assess the effect of TAK-861 on cataplexy as measured by the WCR.	• WCR at Week 12.
• To assess the effect of TAK-861 on sustained attention as measured by the psychomotor vigilance test (PVT).	• Change from baseline to Week 12 in mean number of lapses on the PVT.
• To assess the effect of TAK-861 on overall narcolepsy symptoms measured by the Patient Global Impression of Change (PGI-C) scale.	• PGI-C score at Week 12.
• To assess the effect of TAK-861 on overall severity of narcolepsy symptoms measured by the Narcolepsy Severity Scale for Clinical Trials (NSS-CT).	• Change from baseline to Week 12 in NSS-CT total score.
• To assess the efficacy of TAK-861 on functional impacts of narcolepsy as assessed by the Functional Impacts of Narcolepsy Instrument (FINI).	• Change from baseline to Week 12 in FINI domain scores for: Tiredness, Cognitive Functioning, Cataplexy, Social Activities, Everyday Activities, and Everyday Responsibilities.

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Objectives:	Endpoints:
• To assess the effect of TAK-861 on quality of life of participants, as assessed by the Short Form-36 Survey (SF-36).	• Change from baseline to Week 12 in SF-36 mental and physical component summary scores.
• To evaluate the safety of TAK-861 as measured by TEAE incidence.	• Occurrence of at least 1 TEAE during the study including the follow-up period, as applicable.
Additional/Exploratory:	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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Objectives:	Endpoints:
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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Objectives:	Endpoints:
[redacted]	[redacted]

3.2 Estimands

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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	CCI [redacted]
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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4.0 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter, 12-week parallel-group study to evaluate the efficacy and safety of TAK-861.

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Approximately 93 participants with NT1 will be randomized CCI to placebo or TAK-861. CCI

After providing informed consent, participants will complete a screening period of up to 50 days. The screening window may be extended on a case-by-case basis after consultation with and approval from the sponsor or designee for a reason such as an unexpected schedule change, or to perform a CCI or other assessments to confirm eligibility. The investigator may repeat screening assessments to ensure participant suitability, with permission of the sponsor or delegate. Participants will discontinue medications used to treat narcolepsy CCI as described in Section 6.8.1. Note that if tapering of any restricted medication is required, this tapering should be started early in the screening period, so the participant is no longer taking the medication by study day specified in Section 6.8.1.

Participants will be asked to complete an e-diary, starting no later than CCI. To be eligible for the study, participants must fill out self-reported cataplexy questions in the e-diary for at least CCI day period from CCI and have ≥4 partial and/or complete episodes of cataplexy/week (averaged over CCI).

CCI

After the Week 12 visit, participants who remained on study treatment throughout the treatment period will have the option to participate in an LTE study under a separate protocol. Participants who immediately enroll in the LTE study will not have follow-up visits in this study.

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 study) will complete a first follow-up visit approximately 7 days after the final dose of study drug and a second follow-up visit approximately 28 days after the final dose of study drug. For participants who terminate the study early, every effort should be deployed to have them complete an early termination visit as soon as possible and a follow-up visit approximately 28 days after the last dose of study drug. Participants not participating in the LTE study can restart their restricted medications CCI 7 days after the last administration of study drug.

For a schematic of the study design, see Section 1.2, Figure 1.a. For the Schedule of Activities (SoA), see Section 1.3 (Table 1.a and Table 1.b).

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.

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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 and safety of TAK-861 in participants with NT1. Approximately 93 (male and female) participants with NT1 will be randomized CCI to placebo or TAK-861 CCI (see dose rationale in Section 4.3). CCI [redacted]. This study is designed to evaluate the efficacy and safety of TAK-861 in participants with NT1.

This study compares TAK-861 with placebo. CCI [redacted].The use of placebo (matching TAK-861) is justified since the placebo-controlled study is the most efficient study design, providing the highest likelihood of conclusively detecting a true treatment difference if one exists and requiring a smaller sample size than studies with active controls. Interpretation of drug effects on safety is also more straight-forward in placebo-controlled studies. Placebo-controlled studies have commonly been used in drug approvals of other drugs to treat narcolepsy (Dauvilliers et al. 2013; US Xyrem Multicenter Study Group 2002). Narcolepsy is generally not associated with disease-specific fatal outcomes, and the treatment duration of 12 weeks proposed in this study is not expected to result in additional risks of serious or irreversible harm from withdrawal of prior treatments and exposure to placebo. However, reversible worsening of narcolepsy symptoms, including excessive daytime sleepiness and cataplexy, may occur after discontinuation of prior narcolepsy medications. Worsening of narcolepsy symptoms may result in poor school and work performance, social interactions, and quality of life and may increase risk of motor vehicle accidents and depression, including suicidal ideation. Safety measures such as driving restrictions, discontinuation criteria, adverse event monitoring, and C-SSRS monitoring are implemented in this study to mitigate these risks. Participants can voluntarily withdraw or be withdrawn by the investigator at any time to restart other treatments. After completing this study, participants will have the option to participate in an LTE study, in which all participants receive active treatment.

The duration of the dosing (12 weeks) was chosen to allow sufficient 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 mean plasma half-life of TAK-861 of CCI [redacted], the 84-day treatment period and 28-day follow-up period are of sufficient duration to characterize the potential effects of treatment.

CCI [redacted]

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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 clinical investigation are included.

CCI [redacted]

CCI [redacted]

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 CSSRS CCI [redacted] The CSSRS will be administered at least CCI [redacted], and during the first follow-up visit in this study (if applicable) as indicated in the SoA CCI [redacted] (Posner et al. 2007a; Posner et al. 2007b).

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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 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, and cataplexy, measured by WCR. The functional impacts of narcolepsy (eg, narcolepsy-specific quality of life) will also be assessed as secondary endpoints across the 6 domains of the FINI.

Further, several efficacy endpoints including CCI [redacted], will be evaluated.

4.2.4 Participant Input Into Design

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

4.3 Justification for Dose

This study will evaluate[redacted].

This proposed dosing level is based on the efficacy and safety findings from the phase 2 study [redacted] in participants with NT1. Following 8 weeks of treatment, all TAK-861 dosing levels [redacted] (see Section 2.2.2; or refer to the IB for details).

A population PK model was developed to characterize TAK-861 PK in participants with NT1 and subsequently investigate exposure-response relationships for MWT, ESS, and WCR and selected safety/tolerability measures.

[redacted]

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[redacted]

The most commonly reported TEAEs were insomnia, urinary events (micturition urgency, pollakiuria), and salivary hypersecretion. These events were dose-dependent ranging from[redacted] for insomnia events, [redacted] for urinary events, and [redacted] for salivary hypersecretion, with [redacted] leading to the highest incidences compared to placebo. Most of these events were mild or moderate in intensity, started on [redacted] and resolved during the treatment period. There were no discontinuations due to TEAEs. [redacted]

[redacted]

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.

A participant's duration of participation to complete the study will range CCI [redacted] only for participants not immediately rolling over to the LTE).

5.0 STUDY POPULATION

All entry criteria, including test results, must be confirmed before randomization. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

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.

Note that the site's investigator may determine if there is a need to repeat any screening assessments to ensure participant suitability. The sponsor (or designee) should be informed.

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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.
2. The participant has provided informed consent (that is, in writing, documented via a signed and dated ICF) 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.

   CCI [redacted]

4. The participant has a body mass index (BMI) within the range 18 to 40 kg/m^2 (inclusive).

Type of Participant and Disease Characteristics

5. The participant has an ICSD-3 or ICSD-3-TR diagnosis of NT1 supported by results from 1) PSG (with or without MSLT), performed within the past CCI [redacted] and meeting the minimal acceptable criteria for the proper performance of PSG/MSLT as outlined in the ICSD-3 or ICSD-3-TR(see Appendix 3), or 2) 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).

CCI

CCI CCI

7. The participant has ≥4 partial or complete episodes of cataplexy/week (WCR), CCI

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 radioimmunoassay 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 investigator 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, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12-lead ECG, and vital sign measurements performed at the screening visit and before the first dose of study drug.

Contraception

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

Other

CCI

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. For example, the following are exclusionary:

   CCI CCI

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CCI [redacted]

2. The participant: (a) has a history of myocardial infarction; (b) has a history of clinically significant hepatic disease, thyroid disease, coronary artery disease, cardiac rhythm abnormality or heart failure; or (c) has any medical condition (such as unstable cardiovascular, pulmonary, renal or gastrointestinal disease, CCI [redacted] that would preclude enrollment in the view of the investigator.
3. The participant has current or recent (within 6 months) gastrointestinal disease that is expected to influence the absorption of drugs. CCI [redacted]
4. 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 carcinoma; these participants may be included after approval by the sponsor or designee).
5. The participant has a clinically significant history of head injury or head trauma.
6. The participant has a history of epilepsy, seizure, or convulsion (except for a single febrile seizure in childhood).
7. The participant has a history of cerebral ischemia, transient ischemic attack (<5 years from screening), intracranial aneurysm, or arteriovenous malformation.
8. The participant has 1 or more of the following psychiatric disorders:

CCI [redacted]

c) Current active major depressive episode (MDE) or an active MDE in the past 6 months.

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d) Any current unstable psychiatric disorder.

CCI [redacted]

9. 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.
10. The participant has a known hypersensitivity to any component of the formulation of TAK-861 or related compounds.
11. The participant has had major surgery or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks before the screening visit.

Prior/Concomitant Therapy

12. The participant is unable to refrain from or anticipates using excluded food products, beginning by CCI [redacted] and continuing until CCI [redacted], or prohibited medications (including CCI [redacted]) as described in Section 5.3.1 and 6.8.1.

Prior Clinical Study Experience

13. The participant has participated in another investigational drug study, in which they received the investigational drug, within CCI [redacted] The interval window from the previous study will be derived from the date of the last dose of investigational drug in the previous study to the screening visit of the current study. The participant must agree not to participate in any other interventional study while participating in TAK-861-3002.

    Note: This does not apply to past participation in trials of approved drugs, for which rules are specified in the protocol.

CCI [redacted]

Diagnostic Assessments

CCI [redacted]

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15. The participant has a resting HR CCI beats per minute during screening, confirmed on repeat testing within a maximum of CCI minutes.
16. The participant's screening ECG reveals a QT interval with Fridericia correction method (QTcF) >450 milliseconds (genetically male) or CCI milliseconds (genetically female).
17. The participant has a positive test result for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C virus antibody, or HIV antibody/antigen at screening.

CCI

20. The participant has a positive pregnancy test result at screening or Day -2 or is breastfeeding.

CCI

22. 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 4 or 5 on the CSSRS within a year before randomization.

Other Exclusion Criteria

23. 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.
24. The participant consumes excessive amounts of caffeine, defined as greater than CCI . (1 cup of coffee is approximately 120 mg.)
25. The participant currently consumes alcohol exceeding CCI 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).

CCI

26. The participant has a nicotine dependence that is likely to affect sleep (eg, a participant who routinely awakens at night to smoke) CCI

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CCI [redacted]

CCI [redacted]

28. 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 treatment period.

29. The participant, in the opinion of the investigator or subinvestigator, is unlikely to comply with the protocol or is unsuitable for any other reason.

30. The participant is considered to be vulnerable, as defined by local regulations and if exclusion is required by local regulations. Examples of vulnerable persons are persons under safeguard of justice, persons deprived of liberty by judicial or administrative decision, persons receiving psychiatric care without their consent, persons admitted to a health or social establishment for purposes other than research, persons of full age who are subject to a legal protection measure (guardianship or curatorship), and persons unable to express their consent.

CCI [redacted]

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CCI [redacted]

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

CCI [redacted]

On days of CCI [redacted] MWT (Table 1.a and Table 1.b), participants will follow the procedures outlined in the CCI [redacted] MWT manual. Caffeine will not be allowed on these days. At all other times, caffeinated beverages (including caffeinated tea) or other xanthine-containing products will be limited to amounts of no more than CCI [redacted] of caffeine/xanthine CCI [redacted].

Participants may smoke nicotine during the study outside the confines of the center CCI [redacted]

For a comprehensive list of prohibited medications, see Section 6.8.1 and Table 6.b.

Information on when to take the study drug in relation to mealtimes is provided in Section 6.2.4.

5.3.2 Activity

CCI [redacted]

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5.3.3 Contraception and Breastfeeding

5.3.3.1 Contraception for Participants Capable of Producing Viable Ova and/or Becoming Pregnant

Please refer to Section 10.4.2 for contraception requirements.

5.4 Screening

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The site investigator 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:

- 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).

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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 number, 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 do not meet eligibility criteria 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:

- [redacted]
- [redacted]
- [redacted]
- Coronavirus disease 2019 (COVID-19) infection.
- Quarantine requirement.
- Site closure.
- Pretreatment AE before randomization/treatment.

5.6 Enrollment

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

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

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6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Study Intervention(s) Administered

In this study, the interventions include:

- TAK-861 [redacted]
- Matching placebo [redacted]

To maintain the blind, all participants will receive the same number of tablets and bottles.

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.

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6.2 Preparation, Handling, Storage, and Accountability

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

6.2.1 Accountability Throughout the Study

The investigator or designee must ensure that the sponsor-supplied study drug 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 drug (Section 6.1), the investigator or designee must maintain 100% accountability for all sponsor-supplied study interventions that the site receives and dispenses during his or her 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-approved drug accountability log.
- Based on entries in the log, it must be possible to reconcile study drugs delivered with those used and returned.
- All study drugs 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.

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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

Starting on the morning of Day 1, the study drug will be administered at approximately the same time each day for 12 weeks.

On clinic Days CCI [redacted] of TAK-861 or matched placebo will be administered in CCI [redacted] with 240 mL of water after an overnight fast of at least 8 hours; CCI [redacted]. Participants may consume water ad libitum. CCI [redacted]

CCI [redacted]

CCI [redacted]

On other clinic days and while at home, participants will be instructed to take CCI [redacted] TAK-861/matched placebo CCI [redacted], with a large glass of water (approximately 240 mL total). CCI [redacted]. Participants are encouraged to take study drug at approximately the same time each day.

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.

Additional steps may be taken to ensure participants understand the dosing instructions and that they follow the correct TAK-861 dosing level, 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.

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6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization

A designated vendor will generate the randomization schedule using the permuted block method with the requisite stratification factors CCI [redacted] and randomization ratio for the IRT system. Randomization will be conducted through the IRT system, accessed by the investigator or designee. Details are included 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. In case of emergency, the investigator may unblind the study drug without notifying the sponsor first.

For unblinding a participant's intervention assignment, the investigator can independently obtain the study drug assignment by accessing the IRT, which will be programmed with blind-breaking instructions.

The date and time for the unblinding must be recorded in the IRT. The date and reason for unblinding must be recorded on the eCRF.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant whose study drug assignment was revealed should be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from the sponsor's medical monitor for the participant to continue in the study. The investigator must inform the sponsor that the participant's study drug assignment was unblinded; however, they are not required to reveal to the sponsor the participant's study drug assignment.

The sponsor's safety staff may unblind the study drug assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to investigators in accordance with local regulations and/or sponsor policy.

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6.4 Study Intervention 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 the eCRF. The study participant identification will follow the standard operating procedure of the site and the pharmacy manual.

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

CCI [redacted]

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

After the completion of the CCI [redacted] in the current study, participants who remained on study treatment throughout the treatment period 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 must be documented on the eCRF (also see Section 10.3.5.3 for special situation reporting). Because these events are not, in and of themselves, AEs, they should be reported regardless of whether any 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. The investigator should take into consideration the medication pharmacokinetics (eg, half-life), medication dose, and relevant participant clinical factors to determine the medication taper plan, such that the medication can be safely stopped at the start of the restriction period.

Administration of any medication or supplement used for the treatment of narcolepsy with cataplexy (NT1) must be discontinued. CCI [redacted]

Hormonal contraceptives are not prohibited. Participants may receive the COVID-19 vaccination; however, vaccinations CCI [redacted] before checking-in 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.

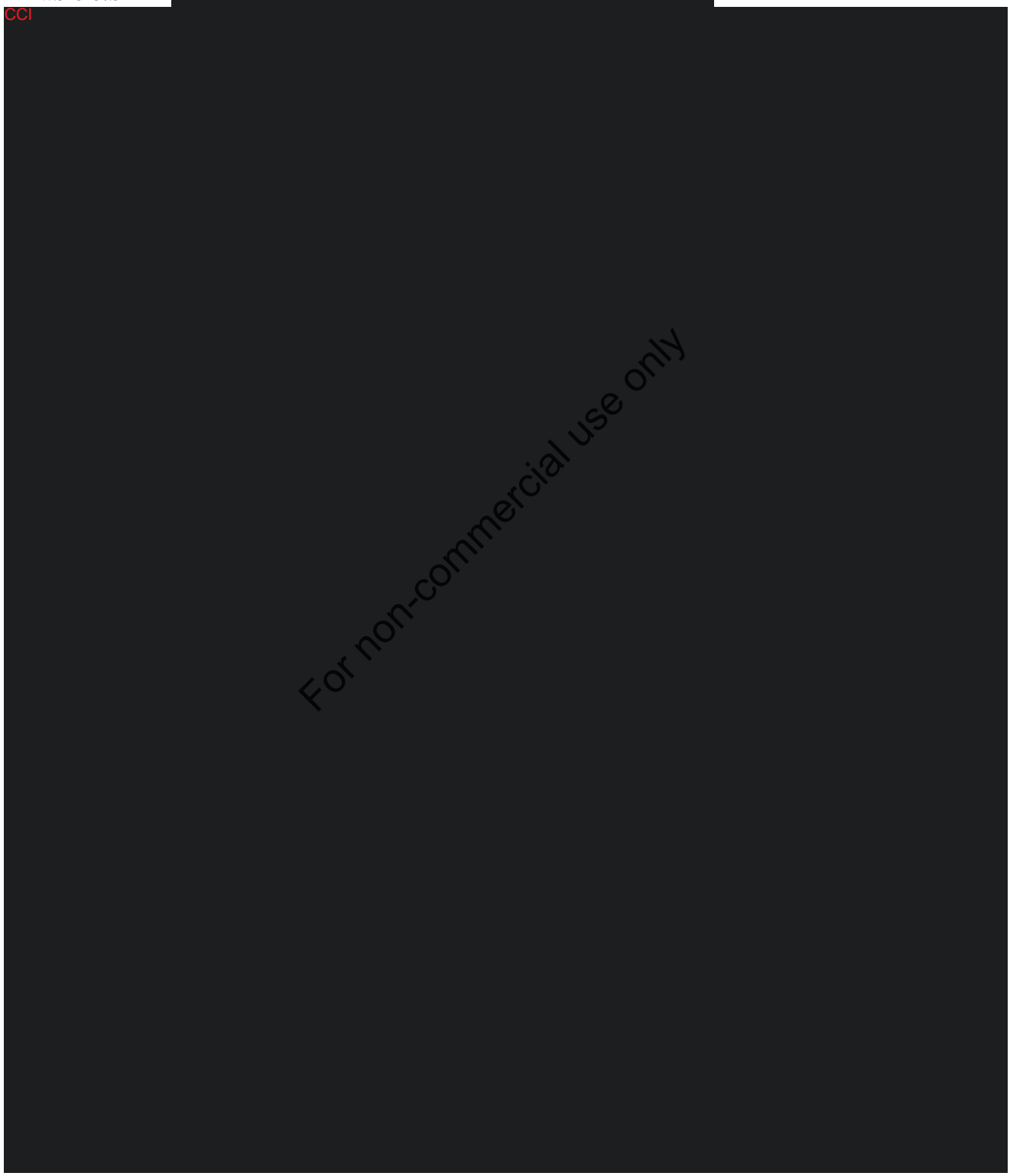
Table 6.b CCI [redacted]

CCI [redacted]

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Table 6.b CCI

CCI



For non-commercial use only

Table 6.b CCI

CCI

[redacted]

CCI

[redacted]

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

Restart of medications CCI [redacted] may occur after completion of all the assessments on follow-up visit CCI [redacted], unless an investigator feels an earlier restart is warranted. Earlier medication restart should be discussed on a case-by-case basis with the sponsor.

7.0 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. The primary reason for discontinuation of study drug or withdrawal of the participant from the study 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 as per the investigator's clinical judgment, or the participant is unwilling to continue because of the AE. Participants who discontinue the study due to an AE should be followed up as described in Section 8.3.9.3.

[redacted] CCI

- Suicidality: Study drug should be discontinued for participants at imminent risk of suicide per the CSSRS (endorsement of Item 4 with the investigator's clinical judgement or Item 5) or per the investigator's clinical judgment.

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[redacted] CCI [redacted]

- Death.
- Pregnancy.
- **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 withdrawal by participant 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.

CCI [redacted]

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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 primary reason for discontinuation or withdrawal of the participant from the study should be determined by the investigator and recorded in the eCRF using the categories listed in Section 7.1.

CCI [redacted]

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.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Written 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.

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Table 8.a CCI

CCI [redacted]

8.1 Demographics, Medical History, and Medication History

8.1.1 Demographics

Participant demographic information will be collected prior to the participant receiving 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. CCI [redacted]

Note: as permitted by country- or site-specific guidelines or regulations, race and ethnicity data collected in this study will be used to understand how similar the enrolled study population is to the general population of people with NT1 and to help researchers understand if the efficacy and/or safety of TAK-861 could be different for people of different races or ethnicities.

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.

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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 CCI [redacted]

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 and ICSD-3-TR criteria for NT1 are provided in Appendix 3.

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8.1.4.2 PSG[redacted]

[redacted]

The PSG[redacted] should be conducted in accordance with American Academy of Sleep Medicine recommended protocols.

8.1.4.3 HLA Genotyping

HLA DQB1*06:02 typing will be obtained from participants during screening unless previous HLA results are reviewed and accepted by the investigator 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 biomarker in the appropriate clinical setting.

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8.1.4.4 [redacted]

[redacted]

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.
  - 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 investigator 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 CSSRS (at applicable visits), and an assessment of clinical symptoms.
    - 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.

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- 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.
- 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. Should a 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.

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8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Table 1.a).

8.2.1 MWT

The MWT is a validated, objective measure that evaluates a person's ability to remain awake under soporific conditions for a defined period of time. 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 MWT, that includes four 40minute wake trials, will be done on each day specified in the SoA. Sleep latency in each wake trial will be recorded. Participants will be required to stay awake in between the 4 MWT wake trials.

During each MWT wake trial, 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. Wake trials 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 CCI

[redacted]

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.

- Duration of test: CCI

8.2.2.2.2 CCI

[redacted]

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CCI

8.2.2.2.3 CCI

8.2.2.2.4 CCI

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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 indicated in the SoA. Participants will be asked to evaluate their subjective sleepiness based on recalling their most recent daily life experiences.

8.2.2.3.2 CCI [redacted]

[redacted]

8.2.2.3.3 Patient Global Impression Scales

The Patient Global Impression rating scales capture global effect of TAK-861 on daytime sleepiness, and overall narcolepsy symptoms as perceived by the participant.

CCI [redacted] The PGI-C measures change due to treatment relative to baseline on a 7-point scale ranging from "very much improved" to "very much worse".

Instructions will be provided to the participant to help ensure consistency in the tests.

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8.2.2.3.4 CCI [redacted]

[redacted]

8.2.2.3.5 FINI

The FINI is a fit-for-purpose CCI [redacted] item instrument developed CCI [redacted] to ensure easy to interpret concepts that are meaningful to narcolepsy patients. The FINI measures the functional

impacts of narcolepsy across 6 domains: CCI [redacted]

8.2.2.3.6 NSS-CT

The NSS-CT is a 15-item self-administered questionnaire (total 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).

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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.

When scores for all 8 scales are available, 2 summary measures known as component scores are derived: the Physical Health Component Score and the Mental Health Component Score. Similar to each scale, the component scores are also positively scored so that higher scores represent better health-related quality-of-life.

8.2.2.3.8 CCI

8.2.2.3.9 CCI

8.2.2.3.10 CCI

8.2.2.3.11 CCI

8.2.2.3.12 CCI

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8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Physical Examinations

A baseline physical examination (defined as the assessment before first dose of study drug) 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.

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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 sign measurements will be avoided CCI minutes before and CCI minutes after a blood draw.

Prior to measuring vital signs, the participant should be resting for a minimum of CCI minutes sitting with back supported.

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

For BP assessment, the same method (ie, the same size cuff, manual or automated, sitting) must be used for all measurements for each individual participant and should be the same for all participants at the study site. [redacted] If systolic BP [redacted] mm Hg or diastolic BP [redacted] mm Hg, BP must be repeated in approximately 15 minutes and criteria for Discontinuation of Study Intervention (Section 7.1) must be assessed.

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.

[redacted]

8.3.2.1 [redacted]

[redacted]

8.3.3 Weight, Height, and BMI

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

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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).

8.3.4 Electrocardiograms

Participants should be resting in a supine position for at least [redacted] minutes before each ECG measurement. The investigator 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 one 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 [redacted] hour before dosing of study drug. If a participant has an [redacted] compared with a predose baseline measurement or if the [redacted] in a male or [redacted] milliseconds in a female, the ECG will be repeated within [redacted] minutes. [redacted] If the average QTcF interval increase from baseline for any postdose time point [redacted] milliseconds or if [redacted] in a male or [redacted] milliseconds in a female, the participant will continue to be monitored by repeat 12-lead ECGs every [redacted] minutes for at least [redacted] hours or until the QTcF interval no longer meet the above thresholds. If prolongation of the QTcF interval according to the stated thresholds persists, a consultation with a cardiologist may be appropriate, and the sponsor should be notified.

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If the QTcF interval is [redacted] 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 [redacted] 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.

8.3.5 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 (Table 1.a and Table 1.b). Details about these procedures and required safety monitoring will be given in the laboratory manual.

All study-required laboratory tests collected at the site should be performed by a central laboratory if possible. Visits consisting of only blood chemistry may be completed using a local lab. A local laboratory may be used for other special circumstances (sponsor should be

informed). Dipstick tests are allowed for urine drug screening and pregnancy tests (other than the serum pregnancy test at screening).

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 CCI [redacted] 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.

CCI [redacted].

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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8.3.6 Pregnancy Testing

A serum human chorionic gonadotropin (β-hCG) pregnancy test will be performed at screening for all participants of childbearing potential. Urine pregnancy test will be performed on all participants of childbearing potential at time points specified 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.

8.3.7 Suicidal Ideation and Behavior Risk Monitoring

Two versions of CSSRS will be used to assess suicidal ideation in this study: the Screening/Baseline CSSRS Lifetime and the Since-Last-Visit CSSRS. CCI [redacted]

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

8.3.8 Other

Not applicable.

8.3.9 Adverse Events, Serious Adverse Events, 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).

8.3.9.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until the final follow-up visit or enrollment in the LTE study, as 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.

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8.3.9.2 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.

8.3.9.3 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.

8.3.9.4 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 towards 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.

8.3.9.5 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 CCI after the last dose of study drug. Collection of pregnancy data from a participant's partner requires the participant's and 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. Although the investigator is not obligated to actively seek poststudy pregnancy-related SAE information from former study participants or their partners, he or she may learn of an SAE through spontaneous reporting.

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

8.3.9.6 Adverse Events of Special Interest

See Section 10.3.3.2.

8.4 Pharmacokinetics

8.4.1 Pharmacokinetic Sample Collection and Analysis

Blood samples CCI for plasma TAK-861 concentration will be collected according to the SoA CCI

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.

CCI

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

8.5 Genetics

8.5.1 CCI

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CCI [redacted]

8.5.2 HLA Genotyping

See Section 8.1.4.3.

8.6 Immunogenicity Assessments

Not applicable.

8.7 Health Economics/Medical Resource Utilization and Health Economics

Not applicable.

9.0 STATISTICAL CONSIDERATIONS

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

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9.1 Statistical Hypotheses

9.1.1 CCI [redacted]

[redacted]

9.1.2 CCI [redacted]

[redacted]

CCI

[redacted]

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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. All participants will be analyzed according to the treatment they actually received.

9.2.2 Full Analysis Set

The full analysis set (FAS) will consist of all participants who were randomized. All participants in the FAS will be analyzed according to the treatment group to which they were randomized. The FAS will be used as the primary analysis population for efficacy.

9.2.3 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.

9.3 Efficacy Analyses

9.3.1 Primary Efficacy Endpoint

The mean sleep latency from the 4 MWT wake trials will be calculated for each participant. CCI [redacted] The estimated change from baseline in mean sleep latency for each treatment and the associated standard error (SE) and 95% confidence interval (CI) will be extracted from the model, along with all estimated treatment differences from placebo and associated SEs, 95% CIs, and p-values.

For the EU/EEA only:

The change from baseline in ESS total score will also be analyzed CCI [redacted] The estimated change from baseline in mean ESS total score for each treatment and the associated SE and 95% CI will be extracted from the model, along with all estimated treatment differences from placebo and associated SEs, 95% CIs, and p-values.

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9.3.2 Secondary Efficacy Endpoints

The secondary endpoint of ESS total score will be analyzed as described above.

The secondary endpoint of MWT (for the EU/EEA only) will be analyzed as described above.

The number of cataplexy attacks will be analyzed CCI [redacted] The estimated CCI [redacted] weekly cataplexy for each treatment and the associated SE and 95% CI will be extracted from the model, along with CCI [redacted], and the associated SEs, 95% CIs, and p-values.

The mean number of lapses on PVT CCI [redacted] The estimated changes from baseline in mean number of lapses CCI [redacted] for each treatment and the associated SE and 95% CI will be derived CCI [redacted], along with all estimated treatment differences from placebo CCI [redacted] for the TAK-861 treatment group, and the associated SEs, 95% CIs, and p-values.

The PGI-C CCI [redacted] for each treatment and the associated 95% CI will be extracted from the model, along with CCI [redacted] to placebo, and the associated 95% CIs and p-values.

The change from baseline in NSS-CT total score, change from baseline in FINI domain scores, and change from baseline in SF-36 mental and physical component summary scores will all be analyzed CCI [redacted]

The details of the analytical methods for other secondary efficacy endpoints will be described in the SAP. CCI [redacted]

9.3.3 CCI [redacted]

[redacted]

9.3.4 CCI [redacted]

[redacted]

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CCI [redacted]

Figure 9.a CCI [redacted]

CCI [redacted]

CCI [redacted]

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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

The details of the analytical methods to support the evaluation of additional/exploratory endpoints will be documented in the SAP.

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, standard deviation [SD], coefficient of variation, median, minimum, maximum, and geometric mean), as deemed appropriate.

CCI [redacted]

9.5.2 Exposure-Response Analyses

CCI [redacted] The objectives and details of these analyses (if performed) will be described in a separate analysis plan, and the results of these analyses will be reported separately.

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9.6 Interim/Intermediate Analysis

CCI [redacted]

9.7 CCI [redacted]

[redacted]

CCI [redacted]

10.0 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, , the European Union (EU) Clinical Trials Regulation (CTR) No 536/2014, as well as all applicable national and local laws and regulations.

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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 subinvestigators 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 subinvestigator 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 subinvestigator should declare all institutional affiliations on the curricula 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 informed consent from all participants before any study-related procedures including screening assessments.

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 and responsibilities.

After the participant has received and read (or been read) the participant information, they will be requested to sign and date the ICF or a certified translation if applicable.

A copy of the informed consent 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 consent 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 investigator provides the sponsor with a copy of the consent 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 facing information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

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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.

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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 study 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.

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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.

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10.1.4.2 Serious Data Breach Prevention and Reporting

The sponsor will notify the concerned EU Member States of a serious breach of EU CTR or the applicable protocol version through the EU portal not later than 7 days after becoming aware of the breach. In this instance a "serious breach" is one likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of trial data. All parties involved in the conduct of the clinical trial must immediately report any events they encounter that might meet the definition of a serious breach to the contact point designated in the Site Manual.

If a serious data breach affecting personal data is detected, the sponsor or its designee and the investigator (as applicable) will take appropriate corrective and preventive actions in response. These actions will be documented, and the relevant regulatory agency(ies) will be notified as appropriate. Where appropriate, the relevant individuals materially affected by the breach would also be notified; in the case of study participants, this would be done through the investigator.

10.1.4.3 Inspection Reporting

The sponsor will submit all inspection reports of third country authorities concerning the clinical trial, to the Member States concerned, through the EU portal.

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

A TAK-861 program-level external data monitoring committee (DMC) will review unblinded safety data CCI throughout the study.

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10.1.6 Dissemination of Clinical Study Data

10.1.6.1 Study Results Disclosure

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

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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 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. 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(s).

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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 or designee 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 or designee 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, and 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 consent 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.

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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, CCI [redacted] MWT, CCI , ECG, and CCI data are 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 investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date. In CCI , 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.

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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 CCI .

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 ICFs (including consent to use digital tools and applications, if applicable), participant authorization forms regarding the use of personal health information (if separate from the ICFs), 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.

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Data collected are stored in the trial master file for the life of the product plus 30 years unless longer retention is required by local laws. 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 CCI 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 ICFs, participant authorization forms regarding the use of personal health information (if separate from the ICFs), 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.

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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 study 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 ensure 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 European Union (EU) (EU) Clinical Trial Regulation (CTR) No 536/2014.

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 or CCI 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.

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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.

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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 CTR No 536/2014, 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 subinvestigators, 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.

- 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 (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.

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10.1.11.2 Investigator Responsibilities

The investigator must perform the study in accordance with ICH GCP Guideline E6, EU CTR No 536/2014, other applicable regulatory requirements and guidelines, and rules considering the rights, safety, and well-being of human participants.

The investigator and any subinvestigators 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 subinvestigators 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 subinvestigators 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).

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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 Primary/Coordinating Investigator

The primary/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 EU CTR No 536/2014 and ICH Guidance E3 (1995).

10.2 Clinical Laboratory Tests

Table 10.a lists the tests that will be performed for each laboratory specimen. All study-required laboratory tests collected at the site should be performed by a central laboratory if possible. Visits consisting of only blood chemistry may be completed using a local lab. A local laboratory may be used for other special circumstances (sponsor should be informed). Dipstick tests are allowed for urine drug screening and pregnancy tests (other than the serum pregnancy test at screening).

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

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Table 10.a Protocol-Required Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet count Hemoglobin Hematocrit	RBC count		WBC count with absolute differential Neutrophils Lymphocytes Monocytes Eosinophils Basophils
CCI [redacted]	CCI [redacted] [b] CCI [redacted] [c]			
Clinical Chemistry	BUN Creatinine Creatine kinase Triglycerides Lipid panel (HDL, LDL, total cholesterol)	Potassium Sodium Chloride Calcium Glucose Bicarbonate	AST ALT Alkaline phosphatase CCI [redacted]	Total bilirubin [a] Total protein Albumin
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			

Table 10.a Protocol-Required Laboratory Tests

Laboratory Tests	Parameters
Other Screening Tests	If menopause is suspected: FSH
	Serology (hepatitis B surface antigen, hepatitis B core antibody, HCV antibody, and HIV antibody/antigen)
	Alcohol screen
	Drug screen

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; FSH: follicle stimulating hormone; CCI [redacted]; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HDL: high density lipoprotein; HIV: human immunodeficiency virus; CCI [redacted]; LDL: low density lipoprotein; CCI [redacted] CCI [redacted]; RBC: red blood cell; ULN: upper limit of normal; WBC: white blood cell.

[redacted] CCI [redacted]

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 blood chemistry panel), physical examination, vital sign, or ECG values that were not present at the pretreatment evaluation observed closest to the start of study intervention, 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 CCI [redacted]

[redacted]

CCI [redacted]

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

10.3.1 Definition of AE

AE Definition
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. 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. 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 retests] for verification, evaluation, or monitoring of an abnormality is not considered a therapeutic intervention.)
Events Meeting the AE Definition
• 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, blood 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.

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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 consent) 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.

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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:
• Results in death
• Is life threatening Note: The term *life threatening* in the definition of *serious* 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.

SAE Definition
• Requires inpatient hospitalization or prolongation of existing hospitalization 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. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• Results in persistent or significant disability/incapacity Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. 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.
• 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. [redacted] CCI [redacted]

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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 consent.
- 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.

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10.3.3.2 AEs of Special Interest

An AE of special interest (serious or nonserious) 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 to characterize and understand them.

Based on 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 AEs of special interest for the study drug:

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

[redacted] CCI [redacted]

BP and HR are monitored throughout the study at clinic visits, including measurement every 4 weeks during the treatment period. The participant should promptly discontinue study drug if they meet the BP/HR specific study drug discontinuation criteria as specified in Section 7.1.

CCI [redacted]

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

CCI [redacted]

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.

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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.

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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.

Assessment of Intensity	
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:	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. 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.
Not related:	An AE that does *not* 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.
The investigator will also consult the IB and/or product information, for marketed products, in their assessment. 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. 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	

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Assessment of Causality
SAE data. The causality assessment is one of the criteria used when determining regulatory reporting requirements. 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.

10.3.4.4 Action Taken

Action Taken Concerning Intervention(s)
The investigator must make note of the action taken concerning the study drug: • 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). 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.

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10.3.4.5 Outcome

Outcome
The investigator must make note of the outcome of any AEs that occur during the course of the study • Recovered/resolved: The participant returned to first assessment status with respect to the AE. • Recovered/resolved with sequelae: The participant recovered from an acute AE but was left with permanent/significant impairment.

Outcome
• 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 other than this particular AE. • 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. • Fatal: The AE is considered to be the cause of death or contributed to the participant's death. • Unknown: The course of the AE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study.

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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. CCI [redacted] 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 located in Section 6 of 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 a 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.

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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 CCI

[redacted]

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 all regions included in the study. SUSARs will be submitted to the regulatory authorities (including submission in the EU through Eudravigilance Clinical Trial Module in E2B) as an expedited report within 7 days for fatal and life-threatening 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 expedited reports for other safety issues that might materially alter the current benefit-risk assessment of a study drug, or that would be sufficient to consider changes in the study drug administration or in the overall conduct of the study. Such reports will be submitted via EU portal to the member states within 7 days.

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

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10.3.5.3 Special Situation Reporting

Abuse, misuse, medication error, overdose and other uses not foreseen in the protocol must be reported to sponsor within 7 days of awareness on a paper Special Situation Reporting form.

Definitions:

- Abuse: Persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful physical or psychological effects.
- Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indications(s) or within the legal status of its supply.
- Medication error: An unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor-quality administration) of a medicinal product while in the control of a health care provider, patient, or consumer, which leads to harm or has the potential to lead to harm.
- Overdose: An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at doses above that is assigned to that individual subject according to the study protocol.

10.4 Contraceptive and Barrier Guidance

10.4.1 Definitions

10.4.1.1 Women of Childbearing Potential

For the purpose of this study, a person of female birth sex is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

10.4.1.2 Fertile Men

For the purpose of this study, a person of male birth sex is considered a fertile man after puberty unless permanently sterile by bilateral orchidectomy.

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10.4.2 Contraception Guidance

For WOCBP, the use of highly effective or acceptable contraception (Table 10.b) is required from signing of the informed consent (CCI depending on the type of contraception used) until CCI after last dose. For male participants, there are no contraceptive requirements. However, contraceptive use (for all participants) must 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.

Note that hormonal contraception must be combined with a barrier method due to possible interaction with TAK-861, which may reduce the efficacy of hormonal contraceptive methods.

Unacceptable contraception methods are shown in Table 10.c.

Table 10.b Acceptable Contraception Methods Guidance for This Study

Highly Effective Contraceptives (Failure rate of <1% per year when used consistently and correctly)	Acceptable Contraceptives (Failure rate of >1% per year when used consistently and correctly)
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (must be combined with barrier contraception) [a, b] – Oral – Intravaginal – Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation (must be combined with barrier contraception) [a, b] – Oral – Injectable – Implantable • IUD • IUS • Bilateral tubal occlusion • Vasectomized partner (highly effective provided that partner is the sole sexual partner of the WOCBP study participant and the vasectomized partner has received medical assessment of the surgical success) • Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of the risk associated with the study intervention[s]. Reliability of abstinence should be evaluated in relation to study duration and the preferred and usual lifestyle of the study participant.)	• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action (must be combined with barrier contraception) [a, b] • Male or female condom with or without spermicide [c] • Cap, diaphragm or sponge with spermicide [c] • •

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IUD: Intrauterine device; IUS: Intrauterine hormone-releasing system, WOCBP: women of childbearing potential
[a] Hormonal contraceptive use must be stable for CCI
[b] Hormonal contraception may be susceptible to interaction with TAK-861, which may reduce the efficacy of the contraceptive method. Therefore, it should be combined with a barrier method of contraception during the treatment period and for at least CCI after the last dose of study intervention.
[c] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Table 10.c Unacceptable Contraception Methods

Methods that are unacceptable
• Periodic abstinence (calendar, symptothermal, postovulation methods) only
• Withdrawal (*coitus interruptus*) only
• Spermicides only
• Lactational amenorrhea method only
• Use of both female condom and male condom together at the same time

In addition, female participants must be advised not to donate ova from signing of the ICF to [redacted] PLUS 30 days after the last dose of study drug (ie, a total of [redacted]). Male participants must be advised not to donate sperm from signing of the ICF to 5 half-lives [redacted] after the last dose of study drug (ie, a total of [redacted]).

10.4.3 Pregnancy

If any participant is found to be pregnant during the study, the participant should be withdrawn from study treatment.

If a participant's partner becomes pregnant during the study or within [redacted] 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) 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 at the first well baby visit.

10.5 [redacted]

[redacted].

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CCI

[redacted]

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CCI [redacted]

Table 10.d CCI [redacted]

CCI [redacted]

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10.6 Country-Specific Requirements

Not applicable.

10.7 Abbreviations and Definitions

10.7.1 Abbreviations

CCI [redacted]	[redacted]
AE	adverse event
CCI [redacted]	[redacted]
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curves
CCI [redacted]	[redacted]
[redacted]	[redacted]
BMI	body mass index
BP	blood pressure
CCI [redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CCI [redacted]	[redacted]
CRO	contract research organization
CSF	cerebrospinal fluid
CSSRS	Columbia Suicide Severity Rating Scale
CTR	Clinical Trials Regulation
CYP	cytochrome P450
DBP	diastolic blood pressure
DMC	data monitoring committee
DNS	disturbed nighttime sleep
CCI [redacted]	[redacted]
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic patient-reported diary
EDS	excessive daytime sleepiness
EEA	European Economic Area
ESS	Epworth Sleepiness Scale
EU	European Union
FINI	Functional Impacts of Narcolepsy Instrument
GCP	Good Clinical Practice

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CCI	[redacted]
HLA	human leukocyte antigen
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSD-3	International Classification of Sleep Disorders, Third Edition
ICSD-TR	International Classification of Sleep Disorders, Third Edition, Text Revision
CCI	[redacted]
IEC	independent ethics committee
CCI	[redacted]
IRB	institutional review board
IRT	interactive response technology
CCI	[redacted]
[redacted]	[redacted]
LS	least square
LTE	long-term extension
MAR	missing at random
MAV	markedly abnormal value
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
CCI	[redacted]
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
CCI	[redacted]
NSS-CT	Narcolepsy Severity Scale for Clinical Trials
NT1	narcolepsy type 1
NT2	narcolepsy type 2
CCI	[redacted]
OX	orexin
OX1R	orexin type-1 receptor
OX2R	orexin type-2 receptor
CCI	[redacted]
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
CCI	[redacted]

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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
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF-36	Short Form-36
SoA	schedule of activities
SOREMP	sleep onset rapid eye movement period
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
CCI	[redacted]
ULN	upper limit of normal
CCI	[redacted]
WCR	weekly cataplexy rate
CCI [redacted]	[redacted]

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10.8 Protocol Amendment History

Date	Document	Global/Country/Site Specific
29 October 2024	Amendment 1[a]	Global
29 February 2024	Original Protocol	Global

[a] Amendment 1 incorporates changes in Initial Protocol EU v1 dated 6 September 2024.

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Appendix 1: CCI [redacted]

[redacted]

[redacted]

[redacted]

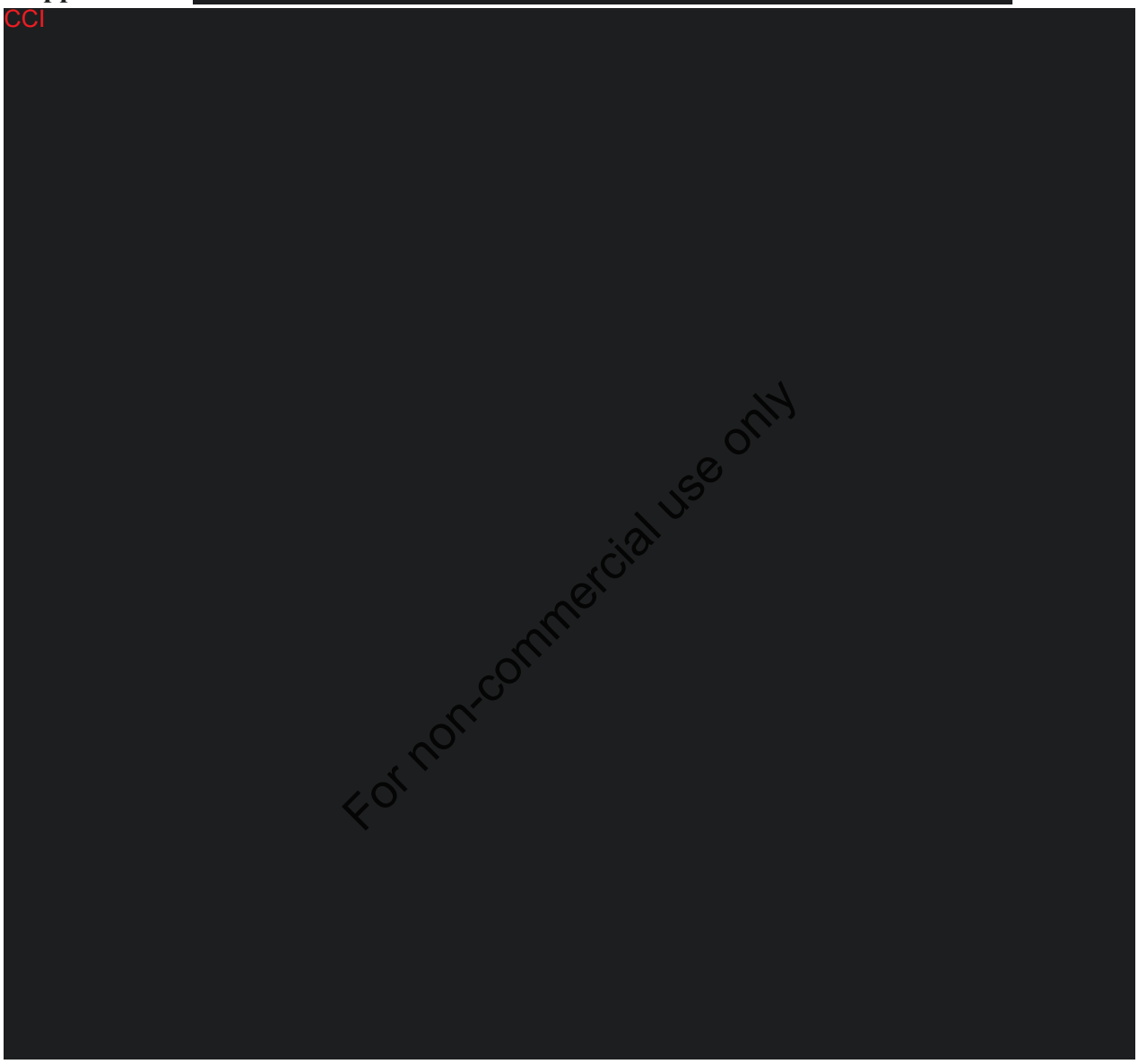
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Appendix 2: CCI

CCI



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Appendix 3: ICSD-3(-TR) Criteria for NT1

ICSD-3 Diagnostic Criteria

Criteria a and b must be met:

a) The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.[1]

b) The presence of 1 or both of the following:

   1. Cataplexy (as defined under Essential Features) and a mean sleep latency of ≤ 8 minutes and 2 or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.[2]
   2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/ml or <1/3 of mean values obtained in normal participants with the same standardized assay.

Notes

1. In young children, narcolepsy may sometimes present as excessively long night sleep or as resumption of previously discontinued daytime napping.
2. If NT1 is strongly suspected clinically but the MSLT criteria of b1 are not met, a possible strategy is to repeat the MSLT.

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ICSD-3 TR Diagnostic Criteria

Criteria a, b, and c must be met.

a) The participant has daily periods of irrepressible need to sleep or daytime lapses into sleep.

b) The presence of one or both of the following:

   1. Cataplexy (as defined under Essential Features)[1] and either:
      a. Mean sleep latency of ≤8 minutes and 2 or more SOREMPs on an MSLT performed in accordance with current recommended protocols[2] or:
      b. A SOREMP (within 15 minutes of sleep onset) on nocturnal polysomnogram.
   2. CSF hypocretin-1 concentration, measured by radioimmunoassay, is ≤110 pg/mL (using a Stanford reference sample) or less than one-third of mean values obtained in normal participants with the same standardized assay.[3]

c) The symptoms and signs are not better explained by chronic insufficient sleep, a circadian rhythm sleep-wake disorder or other current sleep disorder, medical disorder, mental disorder, or medication/substance use or withdrawal.

Notes

1. Typical cataplexy is most strongly associated with NT1. Although some patients with NT1/hypocretin deficiency may present with atypical cataplexy features, presentations that include only atypical cataplexy should raise a higher index of doubt regarding a diagnosis of NT1. Clinical judgment is required.
2. See references - AASM Recommended Protocols for the MSLT and MWT in Adults. Sleep logs are required, accompanied by actigraphy, whenever possible, before in-laboratory sleep testing to evaluate for insufficient sleep and circadian rhythm disturbances.
3. If hypocretin deficiency is verified, the diagnosis of NT1 should be made regardless of other comorbidities that could potentially be related to clinical symptoms, given the definitive nature of this finding.

Further guidance is provided in the ICSD-3 or ICSD-3-TR guidelines.

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