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

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PART A and PART DTo assess the safety and tolerability of TAK-994 following multiple oral doses in subjects with narcolepsy with or without cataplexy (NT1 or NT2).PART B and PART C To assess the efficacy of TAK-994 on reducing excessive daytime…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sleep disturbances (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON51104

Source
ToetsingOnline

Brief title
TAK-994-1501

Condition

- Sleep disturbances (incl subtypes)

Synonym
Extreme sleepiness, Narcolepsy

Research involving
Human

Sponsors and support

Primary sponsor: Takeda Development Center Americas, Inc.
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Cataplexy, Narcolepsy, TAK-994

Outcome measures

Primary outcome

PART A and PART D-Primary Endpoints

The primary endpoints assessing safety and tolerability are:

Number of subjects with at least 1 treatment-emergent AE (TEAE) during the

study.

Number of subjects with at least 1 markedly abnormal value (MAV) for post dose

laboratory values during the study.

Number of subjects with at least 1 MAV for vital signs during the study.

Number of subjects with at least 1 MAV for ECGs during the study.

PART B and PART C-Primary Endpoints:

The primary endpoints assessing efficacy is:

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

Secondary outcome

PART A and PART D

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

Day 1: maximum observed concentration [Cmax], time to reach Cmax [tmax], area under the concentration-time curve [AUC] from time 0 to time of the last quantifiable concentration [AUClast]

Day 28: Cmax, tmax, area under the concentration-time curve during a dosing interval, where * is the length of the dosing interval [AUC*]

Secondary Endpoints-PART B and PART C:

The secondary endpoints assessing efficacy are:

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

WCR at Week 8.

The secondary endpoints assessing safety are:

Number of subjects with at least 1 TEAE during the study.

Number of subjects with at least 1 MAV for post dose laboratory values during the study.

Number of subjects with at least 1 MAV for vital signs during the study.

Number of subjects with at least 1 MAV for ECGs during the study.

Study description

Background summary

The orexinergic (OX) system is a major wake-promoting system of the brain. The OX system acts to coordinate and synchronize the wake-promoting centers of the brain.
Narcolepsy has been classified on the basis of the presence or absence of cataplexy and on levels associated with demonstrably absent or low levels of OX in the cerebrospinal fluid (CSF). Narcolepsy Type 1 (NT1) is characterized by

Excessive Daytime Sleepines (EDS) and the presence of cataplexy. CSF levels of OX are absent or less than one-third of normal (typically <110 pg/mL). In contrast, patients with Narcolepsy Type 2 (NT2) do not have cataplexy, and CSF levels of OX are greater than one-third the normal value. Approximately 70% of those with narcolepsy are classified as having NT1.
Based on the aforementioned data demonstrating that partial or complete OX deficiency plays an important role in the development of EDS, OX replacement therapy is expected to improve EDS through a pathophysiology-directed mechanism of action. A novel drug that acts to help address the deficiency of OX may address the spectrum of narcolepsy symptoms and may have greater efficacy than currently approved drugs for EDS and cataplexy.
TAK-994 is a first-in-class, orally available, highly selective OXR agonist being developed by Takeda for the treatment of narcolepsy with or without cataplexy (NT1 or NT2).
In non-clinical pharmacology studies, TAK-994 showed strong wakefulness promoting effects in wild type animals who have normal OX levels. The primary potential risk from nonclinical safety data, is increased BP and is considered limited to the mode of action.
TAK-994 has previously been studied in healthy subjects and showed no major safety concerns.

Study objective

PART A and PART D
To assess the safety and tolerability of TAK-994 following multiple oral doses in subjects with narcolepsy with or without cataplexy (NT1 or NT2).
PART B and PART C
To assess the efficacy of TAK-994 on reducing excessive daytime sleepiness as measured by prolongation of sleep onset in MWT procedure.

Study design

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

Intervention

Part A:
Part A subjects will receive TAK-994 or matching placebo twice daily (BID) (with randomization ratio of 2:1).

Part B:.
Part B will have 4 parallel arms with subjects randomized to 1 of 3 different TAK-994 dose levels (dose 1, 2 or 3) or placebo in 1:1:1:1 ratio.

Part C (China-specific): art C subjects will receive TAK-994 BID or matching placebo at a ratio of 2:1.

Part D:
Part D subjects will be randomized in a ratio of 2:1 to receive TAK-994 BID or matching placebo.

Study burden and risks

Burden:
For part B the participation in the study will last for up to 110 days (56 days treatment). During the study, there will be certain visits which involve an overnight stay at the hospital. This will occur at least 3 and up to 5 times (at least 6 nights and up to 8 nights).
For part D the participation will last for up to 82 days (28 days treatment). During the study, there will be certain visits which involve an overnight stay at the hospital. This will occur at least 3 and up to 5 times (at least 6 nights and up to 8 nights).
Part A and part C are not applicable for the Netherlands.

Subjects will need to fast at certain periods during the study, they need to complete questionnaires, wear an accelerometer and complete an e-diary for the study period, wear an Ambulatory Blood Pressure Monitoring device on certain days and they will have a nocturnal polysomnography (nPSG) and a Maintenance of Wakefulness Test (MWT) on various timepoints during the study. Furthermore, a Multi Sleep Latency Test (MSLT) can be performed as a pre-screening assessment in case not performed within the last 10 years.
Also venapunctures will be done at various days, and for part B there is an optional CSF collection.
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Risks:
No serious adverse events were reported in previous studies; the adverse events observed in study participants to date varied from mild to moderate mostly included Dizziness, Headache, Paresthesia (tingling or pricking), Nausea, Urinary urgency (urgent need to pee), Increased sweating, Muscle weakness, Frequent peeing, Urinary incontinence/incontinence (loss of bladder control), Dysuria (painful urination), Excessively cautious (state of excessive attention), Pain in the back and lower back, Insomnia (inability to sleep), Euphoric mood (excitement and intense feelings), Increases in liver enzyme, Heart rate increased and Blood pressure increased

Risk-benefit analyses
Patients with Narcolepsy are deficient or low in OX and hence are the first individuals who would most benefit from treatment with an OXR agonist. This study has been designed to mitigate potential safety risks based on clinical and nonclinical findings. The principal mitigation strategy for these risks includes appropriate selection of the study population; intermittent use

of the inpatient clinical research unit setting; and appropriate specified monitoring procedures;
Overall, there is manageable risk associated with the proposed study. Review of data supports a favorable benefit/risk ratio for this study of TAK-994. To date, the observed nonclinical and clinical safety data for TAK-994, including mild and manageable AEs, are acceptable considering its potential clinical benefit.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligible for randomization on Day 1, subjects must:
Be male or female, aged 18 to 65 years (inclusive), at the time of informed consent.

Be judged in good health by the investigator based on clinical evaluations including laboratory safety tests.

Have a body mass index *17.0 and *40.0 kg/m2 at the screening visit).

Have a diagnosis of NT1 (Parts A, B, and C) or NT2 (Part D) (as per International Classification of Sleep Disorders-3rd Edition) made by PSG/ multiple sleep latency test (MSLT) performed within the past 10 years meeting the minimal acceptable criteria for the proper performance of the PSG/MSLT as outlined by ICSD-3. Note: If there is a potential subject with a diagnosis of NT1 or NT2 whose diagnostic nPSG/MSLT was performed more than 10 years ago or is not available, special exemptions, ie, ability of the site to repeat the diagnostic PSG/MSLT will be considered on a case-by-case basis after discussions between the investigator and the sponsor or designee.

Have *10 ESS score at Day -1.

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

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

For Parts A, B, and C during the screening period, the subject must have *4 partial or complete episodes of cataplexy/week (WCR), averaged over 2 weeks (14 consecutive days) minimum. WCR recording taken during the following period will be considered for study eligibility: after the patient has stopped taking anticataplexy medications for at least 7 days (minimum 7-day washout) and completed before study Day -2.

Be willing to discontinue all medications used for the treatment of NT1 or NT2.

BP <140 mmHg (systolic) and <90 mmHg (diastolic). The subject may have a history of hypertension and be on antihypertensive medication treatment as long as the BP meets these criteria. BP measurements should be obtained after the subject has been resting for a minimum of 10 minutes and will be repeated 3 times. The median BP obtained will be used.

Exclusion criteria

A subject must be excluded from participating in the study if the subject:
Has a positive pregnancy test or is a lactating/nursing female subject.

Has a known hypersensitivity to any component of the formulation of TAK-994 or related compounds.

Has a risk of suicide according to endorsement of Item 4 or 5 of the screening/baseline visit Columbia Suicide Severity Rating Scale and/or has made a suicide attempt in the previous 12 months.

Has a screening ECG with a QT interval with Fridericia's correction method >450 ms (men) or >470 ms (women).

Has a resting pulse rate outside of the range of 40 to 100 beats per minute, confirmed on repeat testing within a maximum of 30 minutes.

Has renal creatinine clearance *50 mL/min.

Has LFTs (alanine aminotransferase, aspartate aminotransferase) higher than 1.5× ULN at screening.

Is an excessive (>600 mg/day) caffeine user 1 week before the study screening.

Has a history of cancer (does not apply to carcinoma in situ that has been resolved without further treatment or basal cell skin cancer); these subjects may be included after approval by the sponsor or designee.

Has past or current epilepsy or seizure, except for febrile seizure in

childhood.

Has a lifetime history of major psychiatric disorder (such as bipolar disorder or schizophrenia), a current active major depressive disorder (MDD), or has had active MDD in the past 6 months.

Has a clinically significant history of head injury or head trauma per the judgment of the investigator.

Has a history of cerebral ischemia, transient ischemic attack, intracranial aneurysm, or arteriovenous malformation; known coronary artery disease, a history of myocardial
infarction, angina, cardiac rhythm abnormality, or heart failure.

Has current or recent (within 6 months) gastrointestinal disease expected to influence the absorption of drugs.

Subjects on fluoxetine (any dose) or on *300 mg per day of venlafaxine will be excluded due to the drug's long elimination half-life or clinically significant tapering/washout difficulties. See Section 7.3 for a complete list of medications that are not allowed during the treatment period and the guidelines for washout for stimulant, anticataplexy, antidepressant medications and sodium, and/or multisalt oxybate, when applicable.

Be unwilling to abstain from driving and operating dangerous or hazardous machinery during study participation, starting from when narcolepsy medications are discontinued and extending until after the follow-up visit (Day 35 ±2 days or Day 63 ±2 days as applicable).

Has a medical disorder (including moderate to severe sleep apnea syndrome with or without treatment with mandibular advanced device hypoglossal nerve stimulation and/or positive airway pressure therapy), other than narcolepsy, associated with excessive daytime sleepiness, or has any other medical condition (eg, anxiety, depression, epilepsy, heart disease, or significant hepatic, pulmonary, or renal disease) that requires the subject to take excluded medications or at the time of screening the subject is being treated with nasal /oro-nasal positive airway pressure for any reason.

Has a usual bedtime later than 2400 (12:00 AM, midnight) or an occupation requiring nighttime shift work or variable shift work within the past 6 months or travel within more than 3 times zones, within 14 days before Study Day -2.

The subject has a nicotine dependence that is likely to have an effect on sleep (eg, a subject who routinely awakens at night to smoke) and/or an unwillingness to discontinue all smoking and nicotine use during the confinement portions of the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-07-2021
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	N/A
Generic name:	TAK-994

Ethics review

Approved WMO Date:	22-03-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

(Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-000777-24-NL
ClinicalTrials.gov	NCT04096560
CCMO	NL76214.056.21