A Twelve-Week, Double-Blind, Placebo-Controlled, Randomized, ParallelGroup, Multicenter Study of the Safety and Efficacy of JZP 110 [(R)-2- amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Obstructive Sleep Apnea (OSA)

Published: 19-06-2015
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To evaluate the efficacy of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

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

Summary

ID

NL-OMON44032

Source
ToetsingOnline

Brief title
TONES-003

Condition

- Sleep disturbances (incl subtypes)

Synonym
excessive sleepiness; sleep disorder

Research involving
Human

Sponsors and support

Primary sponsor: Jazz Pharmaceuticals Inc.
Source(s) of monetary or material Support: Jazz Pharmaceuticals Inc.

Intervention

Keyword: Excessive Sleepiness, JZP-110, Obstructive Sleep Apnea (OSA)

Outcome measures

Primary outcome

- MWT: Change in the mean sleep latency time (in minutes) as determined from the first four trials of a 40-minute MWT from Baseline to Week 12

- ESS: Change in ESS score from Baseline to Week 12

Secondary outcome

- PGIc: Percentage of subjects reported as improved (minimally, much, or very much) on the PGIc at Week 12

- Concentration data for JZP-110 will be tabulated by sampling time point, and will be included in a population PK analysis. The population PK model will be used to characterize JZP-110 PK profile in OSA patients, and to explore exposure-efficacy correlations.

- Safety and tolerability evaluations will consist of treatmentemergent adverse events (TEAEs) and changes in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, 24-hour ambulatory blood pressure monitoring, 12-lead ECGs, physical exams, and C-SSRS assessments

Study description

Background summary

OSA is diagnosed on the basis of the number of predominantly obstructive respiratory events that occur per hour of sleep during a nocturnal polysomnogram (PSG) or per hour of monitoring during an out of center sleep test (OCST. Essential features of OSA include repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep and excessive sleepiness that occurs during the day and is a complaint in many but not all cases. Most patients with OSA awaken in the morning feeling tired regardless of the duration of their time in bed. During the day, their sleepiness is most evident during relaxing or inactive situations; however, with extreme sleepiness, sleep may occur while actively conversing, eating, walking, or driving.
Positive airway pressure (PAP) applied through a nasal, oral, or oronasal interface during sleep is considered to be the reference- or gold-standard treatment for OSA. However, the effectiveness of PAP is limited by patient non-compliance or nonadherence to therapy. Non-compliance with PAP is a widely recognized problem that limits its effectiveness. In addition to PAP, there are alternative therapies that are used for the primary treatment of OSA when PAP therapy is refused or is unsuccessful.
Although PAP therapy is considered to be the international reference- or gold-standard
treatment for OSA, the effectiveness of PAP therapy to adequately treat objective and subjective sleepiness associated with OSA is less definitive. It has been concluded that although PAP has been shown to be effective in eliminating respiratory disturbances and reducing the apnea/hypopnea index (AHI), Level I and Level II evidence for CPAP improving objective measures of wakefulness in patients with OSA is equivocal. In addition, data from a multicenter study on the relationships between hours of PAP use and measures of sleepiness showed that subjective sleepiness did not resolve with PAP therapy in 34% of OSA subjects who had ESS scores >10 at baseline and that objective sleepiness did not resolve with PAP therapy in 65% of OSA subjects who had an MSLT sleep latency <7.5 minutes at baseline. Similarly, data from a multicenter study in France and from the French National Sleep Registry have estimated the prevalence of residual excessive sleepiness in OSA patients without major comorbidities who use CPAP to be 6 and 13%, respectively. These findings highlight the unmet medical need for therapies that reduce excessive sleepiness and increase the ability to stay awake during the day in OSA.
JZP-110 phase II studies found no unexpected drug-related toxicities and demonstrated that JZP-110 was safe and well tolerated in narcolepsy patients under the parameters tested. Taken together, these data suggest that JZP-110 might offer an important advance in the treatment of excessive sleepiness in OSA by increasing patients* ability to stay awake throughout the day.

Study objective

To evaluate the efficacy of JZP-110 administered once daily for up to 12 weeks in doses of 37.5, 75, 150, and 300 mg compared to placebo in the treatment of excessive sleepiness in adult subjects with OSA.

Study design

This trial is a 12 week, randomized, double-blind, placebocontrolled, multicenter, 5-arm parallel group study of safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with OSA. Following the successful completion of Screening and Baseline visits, stratified randomization on the basis of subjects* compliant or non-compliant use of their primary OSA therapy will be used to assign subjects in a 1:1:2:2:2 ratio to JZP-110 37.5, 75, 150, or 300 mg, or placebo.

Intervention

JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] will be supplied as 37.5, 75 mg, 150 mg, and 300 mg tablets that will be overencapsulated in identical opaque gelatin capsules. The doses of JZP-110 will be based on the free base of the molecule. Subjects will be instructed to take a single oral daily dose of study drug in the morning, on an empty stomach within one hour of awakening. Subjects will also be instructed to abstain from eating or drinking (except for water) for 30 minutes after taking the study drug.
Placebo tablets will also be overencapsulated in opaque gelatin capsules that will be identical to those used for the active JZP-110 treatments. Mode of administration will be the same as for the test product above.

Study burden and risks

Patients are asked to undergo procedures described in the flowchart on pages 78 - 80 of the study protocol. These procedures
include physical examination, vital signs, urine pregnancy tests (female;chidbearing patients, ECG, overnight sleep tests (PSG/MWT), completing questionnaire, diaries and adminsitration of study drug (oral). Additionally, fertile patients who are
sexually active must agree to use an effective form of contraception with their sexual partners throughout participation in the study.
Patients are also asked to inform their study doctor on their medication use and change in health status.
JZP-110 has been studied in healthy adults, patients with major depressive disorder and in patients with narcolepsy. In these
studies of JZP-110, most side effects have been mild to moderate in severity; however, one patient with major depressive disorder
experienced a heart attack which was severe. The most frequently reported side

effects associated with the use of JZP-110 in
narcolepsy trials at the same doses (need to qualify the mg of 150 and 300)
that will be studied in this trial have included: Anxiety,
Chest discomfort, Diarrhea, Difficulty sleeping (insomnia), Excessive grinding
of the teeth and/or clenching of the jaw, Irritability,
Headache, Loss of appetite for food (anorexia), Nausea, Rapid, strong, or
irregular heartbeat (palpitations).
Patients may have pain, swelling, or bruising or possible infection during
blood draws. Additionally, the adhesive used for the
electrodes from the ECG and the PSG may irritate patient's skin

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

1. Male or female between 18 and 75 years of age, inclusive.
2. Diagnosis of OSA according to ICSD-3 criteria.
3. Subject report (with clinician concurrence) of at least minimal use of a primary therapy for OSA or an attempt to use a primary therapy for OSA as follows:
a. Use of a primary therapy for OSA (i.e., positive airway pressure or oral appliance) on at least 1 night/week, or
b. History of at least 1 month of an attempt to use one or more primary OSA therapies with at least one documented adjustment that was made in an attempt to optimize the primary OSA therapy, or
c. History of a surgical intervention intended to treat OSA symptoms.
4. Subject report (with clinician concurrence) of a stable level of compliance with a primary OSA therapy for at least 1 month prior to Baseline as follows:
a. A stable level of use of a primary OSA therapy, or
b. A lack of use of a primary OSA therapy following a history of attempted use, or
c. A history of a surgical intervention intended o treat OSA symptoms.
5. Baseline Epworth Sleepiness Scale (ESS) score *10.
6. Baseline mean sleep latency *30 minutes as documented by the mean of the first four trials of the
MWT.
7. Usual nightly total sleep time of at least 6 hours.
8. Body mass index from 18 to <45 kg/m2 .
9. Consent to use a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug, throughout the entire study period, and for 30 days after the study is completed.
10. Willing and able to comply with the study design schedule and other requirements.
11. Willing and able to provide written informed consent.

Exclusion criteria

1. Unwilling to attempt to use one or more primary OSA therapies.
2. Female subjects who are pregnant, nursing, or lactating.
3. Usual bedtime later than 1 AM (0100 hours).
4. Occupation requiring nighttime shift work or variable shift work.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness.
6. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia
spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
7. History or presence of any acutely unstable medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or surgical history that could affect the safety of the subject or interfere with study efficacy, safety, PK assessments, or the ability of the subject to complete the trial per the judgment of the Investigator.

8. History of bariatric surgery within the past year or a history of any gastric bypass procedure.
9. Presence of renal impairment or calculated creatinine clearance <60 mL/min.
10. Clinically significant ECG abnormality, in the opinion of the Investigator.
11. This criteria has been removed.
12. Presence of significant cardiovascular disease including but not limited to: myocardial infarction within the past year, unstable angina pectoris, symptomatic congestive heart failure (ACC/AHA stage C or D), revascularization procedures within the past year, ventricular cardiac arrhythmias requiring automatic implantable cardioverter defibrillatory (AICD) or medication therapy, uncontrolled hypertension, systolic blood pressure *155 mmHg or diastolic blood pressure *95 mmHg (at screening, or consistently across Baseline measures according to protocol specifications), or any history of cardiovascular disease or any significant cardiovascular condition that in the investigator's opinion may jeopardize subject safety in the study.
13. Laboratory value(s) outside the laboratory reference range that are considered to be clinically significant by the Investigator (clinical chemistry, hematology, and urinalysis); NOTE: Screening labs may be repeated once.
14. Excessive caffeine use one week prior to Baseline assessments or anticipated excessive use during the study defined as >600 mg/day of caffeine.
15. Use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of
excessive sleepiness within a time period prior to the Baseline Visit corresponding to at least five half-lives of the drug(s) or planned use of such drug(s) at some point throughout the duration of the study. Examples of excluded medications include OTC sleep aids or stimulants (e.g., pseudoephedrine), methylphenidate, amphetamines, modafinil, armodafinil, sodium oxybate, pemoline, trazodone, hypnotics, benzodiazepines, barbiturates, and opioids. Medications should be discontinued such that the subject has returned to his/her baseline level of daytime sleepiness at least 7 days prior to the Baseline visit, in the opinion of the Investigator.
16. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives (whichever is longer) prior to the Baseline Visit, or plans to use an MAOI during the study.
17. Received an investigational drug in the past 30 days or five half-lives (whichever is longer) prior to the Baseline Visit, or plans to use an investigational drug (other than the study drug) during the study.
18. Previous exposure to or participation in a clinical trial of JZP-110 (ADX-N05, R228060, or YKP10A).
19. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria.
20. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
21. Current, past (within the past 2 years), or seeking treatment for a substance related disorder.
22. Urine drug screen positive for an illicit drug of abuse (including cannabinoids) at screening or at any point throughout the duration of the study, except for a prescribed drug (e.g., amphetamine) at screening.
23. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-03-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	JZP-110
Generic name:	(R)-2-amino-3-phenylpropylcarbamate hydrochloride

Ethics review

Approved WMO Date:	19-06-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-01-2016
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-02-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-05-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2014-005514-31-NL
CCMO	NL53408.058.15