A Long-Term, Safety and Maintenance of Efficacy Study of JZP110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] in the Treatment of Excessive Sleepiness in Subjects with Narcolepsy or Obstructive Sleep Apnea

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To evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg

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

Summary

ID

NL-OMON45139

Source
ToetsingOnline

Brief title
TONES 005

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, Narcolepsy, Obstructive Sleep Apnea

Outcome measures

Primary outcome

- Safety and tolerability evaluations will consist of treatmentemergent adverse events (TEAEs) and changes in clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), physical exams, and the C-SSRS assessments.

- Efficacy endpoints (ESS, PGIc, CGIc) will be summarized by treatment using descriptive statistics. ESS data will be compared to baseline data from this study for subjects in Group B and to baseline data from the previous trial that the subject had participated in for Group A. The outcome measures in the FOSQ-10, SF-36v2, and EQ-5D-5L will be summarized and displayed graphically. No adjustment of significance level for multiple testing will be employed.

Secondary outcome

The outcome measures associated with the WPAI:SHP and the Resource Utilization Questionnaire will be summarized by final dose and time point and displayed graphically. For subjects who participated in Study 14-002 or 14-003, the WPAI:SHP measures may also be summarized by the previous treatment group. Where applicable, the changes in the WPAI:SHP

measures from prior study baseline and from the endpoint of the prior study will be examined. Standard unit costs will be applied to the resources identified with the Resource Utilization Questionnaire (as well as to any hospitalizations reported as SAEs) in order to calculate the mean/median healthcare costs over the one-year period.

Study description

Background summary

Narcolepsy is a life-long neurologic disease for which no cure has been identified. It affects an estimated 0.02% to0.067% of the population worldwide, approximately 1 in 2000 individuals in the United States and 4.7 of 10,000 (0.047 %) individuals in the general population of five European countries (United Kingdom [UK], Germany, Italy, Portugal, and Spain). The symptomatology of this condition is well described in the literature, with consensus on the five core symptoms of narcolepsy: excessive daytime sleepiness, cataplexy, sleep paralysis, sleep-related (hypnagogic and hypnopompic) hallucinations, and disrupted nighttime sleep (DNS) with excessive daytime sleepiness and cataplexy being the most common symptoms. Currently approved medications to improve wakefulness and to treat excessive daytime sleepiness in narcolepsy include dextroamphetamine (Dexedrine®), methylphenidate (Ritalin®), sodium oxybate (Xyrem®), modafinil (Provigil®), and armodafinil (Nuvigil®). Each of these medications has limitations, including those related to efficacy and safety. Dextroamphetamine and methylphenidate are C-II stimulant medications with high potential for abuse. Sodium oxybate is a C-III CNS depressant that requires twice nightly dosing. Modafinil and armodafinil do not appear to adequately promote
wakefulness throughout the day with once daily dosing.

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 studies found no unexpected drug-related toxicities and demonstrated that JZP-110 was safe and well tolerated in narcolepsy patients under the parameters tested. As a result of the findings of significant decreases in excessive sleepiness (lower ESS scores) and significant increases in the ability to stay awake throughout the day (higher MWT sleep latencies) when adult patients with narcolepsy were treated with JZP-110, as well as the urgent clinical need reported by patients for therapies that better treat the excessive sleepiness that significantly impacts their daily lives, Jazz Pharmaceuticals is conducting this study with JZP-110 to generate efficacy, safety and information in this population.

Study objective

To evaluate the safety and tolerability of JZP-110 administered once daily for up to 52 weeks in doses of 75, 150, and 300 mg

Study design

This is a Phase 3 study to assess the long-term safety and maintenance of

efficacy of JZP-110 under open-label and double-blind, placebo-controlled conditions, in subjects who have completed Study 14-002, 14-003, 14-004, 15-004, 15- 005, ADX-N05 201, or ADX-N05 202. The study will consist of a 2-week Titration Phase for all subjects, a 38-week Maintenance Phase for subjects who completed Study 14-002 or 14-003 or a 50-week Maintenance Phase for subjects who completed Study 14-004, 15-004, 15-005, ADX-N05 201, or ADX-N05 202, and a 2-week Safety Follow-up period

Intervention

JZP-110 [(R)-2-amino-3-phenylpropylcarbamate hydrochloride] will be supplied as 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.

Study burden and risks

Patients are asked to undergo procedures described in the flowchart on pages 72 - 73 of the study protocol. These procedures include physical examination, vital signs, urine pregnancy tests (female;chidbearing patients, ECG, 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 theelectrodes from the ECG 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. Subject meets one of the following:
a. Completed Study 14-002 or 14-003 (Group A)
b. Completed Study 14-004, 15-004, 15-005, ADX-N05 201 or ADX-N05 202 (Group B)
2. Subject is able, in the opinion of the investigator, to take JZP-110 for 40 weeks if continuing from 14-002 or 14-003 or for 52 weeks if the subject completed 14-004, 15-004, 15-005, ADX-N05 201, or ADXN05 202, and is able to complete all tests and visits described in this protocol.
3. Usual nightly total sleep time of at least 6 hours.
4. Body mass index from 18 to <45 kg/m2
5. 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.
6. Willing and able to comply with the study design schedule and other requirements.
7. Willing and able to provide written informed consent.

Exclusion criteria

1. Female subjects who are pregnant, nursing, or lactating.
2. Usual bedtime later than 1 AM (0100 hours).
3. Occupation requiring nighttime or variable shift work.
4. Experienced any serious adverse event (SAE) in a previous study that was deemed related to JZP-110 or experienced an AE in a previous study that might prevent him/her from safely participating in and completing the current study.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy or 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. 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 or safety 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 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 criterion 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 AICD or medication therapy, uncontrolled hypertension, or systolic blood *155 mmHg or diastolic blood pressure *95 mmHg at screening or Baseline for Group B subjects according to protocol specifications; or any history of cardiovascular disease or 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 the Baseline Visit or anticipated excessive use during the study defined as >600 mg/day of caffeine.
15. Use of a monoamine oxidase inhibitor (MAOI) in the past 14 days or five half-lives of the drug (whichever is longer) prior to the Baseline Visit, or plans to use an MAOI during the study.
16. Received an investigational drug other than JZP-110 in the past 30 days or five half-lives (whichever is longer) before the Baseline Visit, or plans to use an investigational drug (other than the study drug) during the study.
17. Current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria.
18. Nicotine dependence that has an effect on sleep (e.g., a subject who routinely awakens at night to smoke).
19. Current, past (within the past 2 years), or seeking treatment for a substance related disorder.

20. 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.
21. History of phenylketonuria (PKU) or history of hypersensitivity to phenylalanine-derived products.
22. Group A: Planned use of any over-the-counter (OTC) or prescription medications that could affect the evaluation of excessive sleepiness at any time during the study.
Group B: 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. 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. 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

Study design

Design

Study phase:	3
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):	07-12-2016
Enrollment:	15
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:	22-06-2015
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:	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:	16-08-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-09-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-05-2017
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-10-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-11-2017
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	EUCTR2014-005489-31-NL
CCMO	NL53470.058.15