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 Narcolepsy

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

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

Summary

ID

NL-OMON43610

Source
ToetsingOnline

Brief title
TONES-002

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

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 narcolepsy 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

Narcolepsy is a life-long neurologic disease for which no cure has been identified. It affects an estimated 0.02% to 0.067% 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. 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 pharmacokinetic (PK) information in this population.

Study objective

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

Study design

This trial is a 12-week, randomized, double-blind, placebocontrolled, multicenter, 4-treatment parallel group study of the safety and efficacy of JZP-110 in the treatment of excessive sleepiness in adult subjects with narcolepsy as defined by The International Classification of Sleep Disorders, Third Edition (ICSD-3) or Diagnostic and Statistical Manual of Mental

Disorders, Fifth Edition (DSM-5). Following the successful completion of Screening and Baseline visits, stratified randomization on the basis of the presence or absence of cataplexy will occur. Subjects will be assigned to receive JZP110 75, 150, or 300 mg or placebo in a 1:1:1:1 ratio once daily over a 12-week Treatment Phase. Subjects randomized to the 150 mg dose will initially receive 75 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 150 mg starting on Day 4. Subjects randomized to the 300 mg dose will initially receive 150 mg from Day 1 through Day 3 of the first week of the Treatment Phase and will receive 300 mg starting on Day 4. Subjects randomized to the 75 mg group will not require titration. During the Treatment Phase, subjects will return to the investigative site to complete efficacy and safety assessments at the end of Weeks 1, 4, 8, and 12; the Week 1, 4, and 12 visits will include an overnight stay at the investigational site for nocturnal polysomnography (PSG) followed by a Maintenance of Wakefulness Test (MWT), and the Week 8 Visit will include 24-hour ambulatory blood pressure monitoring. Subjects will take their final dose of study drug at the Week 12 visit prior to the Week 12 visit assessments. Subjects will return at the end of Week 14 for follow-up assessments. Unless there are any outstanding safety issues that require follow-up, subjects will be discharged from the study at the Week 14 visit.

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. 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 75 - 77 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. Males and females between 18 and 75 years of age, inclusive.
2. Diagnosis of narcolepsy according to ICSD-3 or DSM-5 criteria.
3. Baseline mean sleep latency *25 minutes as documented by the mean of the first four trials of the
Baseline 5-trial MWT.
4. Baseline Epworth Sleepiness Scale (ESS) score *10.
5. Usual nightly total sleep time of at least 6 hours.
6. Body mass index from 18 to <45 kg/m2 .
7. 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.
8. Willing and able to comply with the study design schedule and other requirements.
9. 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. Moderate or severe obstructive sleep apnea (OSA) on the baseline PSG.
5. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy 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 any medications that could affect the evaluation of cataplexy 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 anti-cataplectic medications include selective serotonin reuptake inhibitors (SSRIs), serotoninnorepinephrine
reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), anti-convulsant agents, and sodium oxybate. These drugs will be discontinued if they are taken for the treatment of narcolepsy and discontinuation is deemed safe by the Investigator. Medications should be sufficiently washed out such that the subject has returned to his/her baseline level of cataplexy at least 7 days prior to the Baseline visit, in the opinion of the
Investigator.
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 previous clinical trial of JZP-110 (ADX-N05, R228060,
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):	19-05-2015
Enrollment:	5
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:	17-06-2015
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	EUCTR2014-005487-15-NL
CCMO	NL53351.058.15