# A Double-Blind, Placebo-Controlled, Randomized-Withdrawal, Multicenter Study of the Efficacy and Safety of JZP-258 in Subjects with Narcolepsy with Cataplexy

Published: 16-08-2017
Last updated: 12-04-2024

Primary objective:To evaluate the efficacy of JZP-258 in the treatment of cataplexy in subjects with narcolepsyKey Secondary objective:To evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness (EDS) in...

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

## Summary

### ID

NL-OMON46347

**Source**
ToetsingOnline

**Brief title**
JZP-258 Efficacy Study

### Condition

- Sleep disturbances (incl subtypes)

**Synonym**
cataplexy, excessive daytime sleepiness

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Jazz Pharmaceuticals Ireland Limited
**Source(s) of monetary or material Support:** Industry;Jazz Pharmaceuticals

## Intervention

**Keyword:** Cataplexy, Excessive Daytime Sleepiness (EDS), Narcolepsy

## Outcome measures

### Primary outcome

Primary endpoint:
Change in weekly number of cataplexy attacks from the two weeks of the Stable-Dose Period to the two weeks of the Double-Blind Randomized-Withdrawal Period

### Secondary outcome

Key secondary endpoint:
Change in the Epworth Sleepiness Scale (ESS) score from the end of the Stable-Dose Period to the end of the Double-Blind Randomized-Withdrawal Period

Other secondary endpoints:
Patient Global Impression of Change (PGIc) for narcolepsy overall at the end of the Double-Blind Randomized-Withdrawal Period

Clinical Global Impression of Change (CGIc) for narcolepsy overall at the end of the Double-Blind Randomized-Withdrawal Period

Change in Quality of Life (QoL) (SF-36) at the end of the Double-Blind Randomized-Withdrawal Period

EuroQol 5 Dimensions Self-Report Questionnaire at the end of the Double-Blind Randomized-Withdrawal Period

# Study description

### Background summary

Narcolepsy is a life-long neurologic disease for which no cure has been identified. The worldwide prevalence of narcolepsy is estimated to be 0.02% to 0.067%. Narcolepsy has been defined as a rapid eye movement (REM) sleep

disorder resulting from the dysregulation of the sleep-wake cycle. It is characterized by pathological sleepiness, commonly termed excessive daytime sleepiness, or EDS, and includes disrupted nighttime sleep (DNS) and abnormal REM sleep manifestations, including cataplexy, sleep paralysis, and hypnagogic or hypnopompic hallucinations. At the moment only one treatment is approved for the treatment of cataplexy in narcolepsy: Xyrem (sodium oxybate). However, this treatment does has a downside. Due to the sodium in the formulation it adds a significant amount of sodium to the patient diet. This can pose a problem in a patient population that is not uncommon with a high incidence of cardiovascular morbidity. Jazz Pharmaceuticals has been developing an investigational formulation called JZP-258 combining four oxybate salts: sodium oxybate, potassium oxybate, calcium oxybate, and magnesium oxybate. JZP-258 could provide the known benefits of Xyrem treatment with an improved safety profile, particularly for patients with sodium-sensitive conditions but also for any patient concerned about salt intake. It could also enable patients with narcolepsy and cardiovascular, hypertensive, or renal conditions to continue on their Xyrem treatment or initiate oxybate treatment.

**Study objective**

Primary objective:
To evaluate the efficacy of JZP-258 in the treatment of cataplexy in subjects with narcolepsy

Key Secondary objective:
To evaluate the efficacy of JZP-258 in the treatment of excessive daytime sleepiness (EDS) in subjects with narcolepsy

Secondary objective:
To evaluate the safety of JZP-258 in the treatment of subjects with narcolepsy with cataplexy

Exploratory objective:
To characterize the conversion from non-Xyrem anticataplectic treatment regimens to JZP-258 in subjects with narcolepsy with cataplexy

**Study design**

This is a 2-part study consisting of the MAIN Study (a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of JZP-258) followed by a 24-week Open-Label Extension study.

Part 1 MAIN STUDY
The Main Study consists of the following periods, which are described further below:
* Screening Period for up to 30 days

* Optimized Treatment and Titration Period for 12 weeks
* Stable-Dose Period for 2 weeks
* Double-Blind Randomized-Withdrawal Period for 2 weeks
* Safety Follow-up Period

Subjects are eligible to enter the Main Study if they meet all eligibility criteria and their treatment status is:
* Currently treated with a stable dose of Xyrem (sodium oxybate) at least 2 months prior to screening
* Currently treated with a stable dose of Xyrem and an additional anticataplectic at least 2 months prior to screening
* Currently treated with an anticataplectic and not treated with Xyrem
* Not currently treated with any anticataplectic at Screening.

Part 2 OPEN-LABEL EXTENSION
Subjects who complete the double-blind treatment during the Main Study are eligible to enter a 24-week Open Label Extension which consists of the following:
* Open-Label Extension Period for 24 weeks
* Open-Label Safety Follow-up Period

During this period subjects will receive open-label JZP-258.
Subjects are eligible to enter the Open-Label Extension if they meet all eligibility criteria and their treatment status is:
* Completed double-blind treatment in the Main Study and rolling over into the Open-Label Extension
* Completed the Main Study and currently treated with Xyrem alone or Xyrem plus an additional anticataplectic
* Completed the Main Study and currently treated with a non-Xyrem anticataplectic or not receiving treatment

Open-Label Extension Period (24 weeks)
Subjects can enter the Open-Label Extension directly from the Main Study (enter at Visit 16) or after completion of the Main Study (enter at Visit 18).
* Rollover Subjects: those who enter the Open-Label Extension at Visit 16 (i.e., *rollover* directly from the Main Study (after a few additional procedures). Their Visit 16 has the dual purpose of being the last day of the Main Study and Day 1 for the Open-Label Extension.
* Re-entry Subjects: those who enter the Open-Label Extension following completion of the Main Study (i.e., require *re-entry* into the study). Their Open-Label Extension Day 1 is at Visit 19 and they undergo Open-Label screening at Visit 18

**Intervention**

Main Study: The trial consists of an open label and a double blind randomized phase.

In the open label phase:
subjects can be in four groups:
- on stable dose Xyrem --> straight conversion of dose Xyrem to dose JZP-258.
- on stable dose Xyrem and other anticataplectics --> straight conversion of dose Xyrem to dose JZP-258 and cross titration of other anitcataplectics with JZP-258.
- on other non Xyrem anticatapletics --> cross titration other catapletics with JZP-258.
- not on any anticatapletics --> titrate JZP-258.

After the titration a 2 week open-label stable-dose period follows.
After being titrated or converted all subjects should be on a tolerable and effective dose of JZP-258. if this dose remains stable in this period subjects are allowed to enter the double blind randomized phase.

After this phase a double blind randomized phase follows, in which subjects will be treated with either JZP-258 or placebo.
JZP-258 will be continued as a double-blind treatment at the stable dose taken in the prior 2 weeks.
Placebo will be initiated as a double-blind treatment at a volume equivalent to the JZP-258 dose taken in the prior 2 weeks.

Optional Open Label Extension:

Roll over subject (Visit 16- Day 1 of OLE) + assessments
Start w/dose not more than 1/2 that of dose from end of Stable Dose Period.
Titrated up to optimal dose per Investigator
(rate of 1 1.5 g/night/wk; not more than a total dose of 9 g/per night).

Re-Entry Subjects: (Visit 19- Day 1 of OLE)
Xyrem Alone +/- Additional Anticataplectic)
Switch from current Xyrem dose to JZP 258 on a g to g straight conversion
(If needed, titration at a rate of 1 1.5 g/ night/wk; not more than a total dose of 9 g/night)
Additional, non Xyrem anticataplectics must be tapered by Visit 30, during initial 12 weeks of OLE

Non-Xyrem Anticataplectic or Not Receiving Treatment
Initial JZP-258 dose of 4.5 g/night.
(Adjust at rate of 1-1.5 g/night/wk; not more than 9 g/night.

**Study burden and risks**

The experimental formulation JZP-258 is based upon the already approved drug

Xyrem, from which the active ingredient is sodium oxybate. Xyrem is already proven to be safe and effective as treatment, however it does add a significant amount of sodium to the patient diet. JZP-258 is formulated in such a way that it limits the intake of sodium by patients. The formulation of JZP-258 consists of four oxyybate salts (sodium oxybate, potassium oxybate, calcium oxybate, and magnesium oxybate), for which the daily intake is all within the Recommended Dietary Allowance (RDA). Therefore little risk for the patients participating in this trial is expected.

# Contacts

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US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Each subject must meet the following criteria to be enrolled in the study.
1. Male or female subjects between 18 and 70 years of age, inclusive at screening.

2. Have a primary diagnosis of narcolepsy with cataplexy that
meets ICSD-3 criteria or DSM-5 criteria, and currently untreated or treated with or without anticataplectics.
3. Have a history of having at least 14 cataplexy attacks in a
typical 2-week period and clinically significant symptoms of EDS prior to any narcolepsy treatment.
4. Treatment status (Pre-randomization Group) at study entry:
a) Have been taking Xyrem at unchanged doses (twice or thrice nightly dosing no higher than a total of 9 g/night), for the treatment of cataplexy in narcolepsy for at least
2 months prior to screening; or
b) Have been taking Xyrem at unchanged doses (twice or thrice nightly dosing no higher than a total of 9 g/night), and another anticataplectic (TCA, SNRI, SSRI, atomoxetine, or
other) for the treatment of cataplexy in narcolepsy for at least 2 months prior to screening; or
c) Treated with a non-Xyrem anticataplectic (TCA, SNRI, SSRI, atomoxetine, or other) and not treated with Xyrem; or
d) Not treated with any agent with anticataplectic properties.
5. If currently treated with Xyrem, must have documented clinical improvement of cataplexy and EDS per Investigator*s clinical judgment.
6. If applicable, treated with a stimulant or alerting agent at unchanged doses for at least 2 months prior to dosing or not treated with a stimulant or alerting agent.
7. Have used a medically acceptable method of contraception for at least 2 months prior to the first dose of study drug and consent to use a medically acceptable method of contraception
throughout the entire study period and for 90 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.
Open Label
1. Completion of the JZP-258 double-blind treatment and completion of Visit 16.
2. Is able, in the opinion of the investigator, to take JZP-258 for an additional 24 weeks.
3. Agrees to continue to use a medically acceptable method of contraception throughout the entire study period and for 90 days after the Open-Label Extension is completed.
4. Willing and able to comply with the study design schedule and other requirements.
5. Willing and able to provide written informed consent for Open-Label Extension.
6. If currently being treated with Xyrem, the subject's total twice nightly Xyrem dose must be no higher than 9 g/night.

## Exclusion criteria

Subjects who demonstrate any of the following will be excluded from
the study.
1. Narcolepsy secondary to another medical condition (e.g., CNS
injury or lesion).
2. Restless leg syndrome (RLS) requiring treatment other than
iron supplements.

3. Succinic semi-aldehyde dehydrogenase deficiency (SSADH).
4. Uncontrolled hypothyroidism.
5. History of seizures, excluding early childhood nonpathological febrile seizures.
6. History of head trauma associated with loss of consciousness in the past 5 years or if the event occurred more than 5 years prior to screening and the subject has sequelae due to the event.
7. Evidence of untreated or inadequately treated sleep-disordered breathing including:
a. Presence of clinically significant and untreated obstructive or central sleep apnea as determined by the Investigator or documented previously;
or documentation of one of the following:
b. Apnea index (AI) >10 if on OSA treatment or untreated;
or
c. Clinically significant hypoventilation; or
d. Noncompliance with primary OSA therapy. (Compliance defined as positive airway pressure use of *4 hours per night on *70% of nights [*5 of 7 nights/week], historical report [with Investigator concurrence] of use of an oral appliance on *70% of nights [*5 of 7 nights/week], or receipt of an effective surgical intervention for OSA symptoms.)
8. Parasomnias (e.g., sleep walking, REM Sleep Behavior Disorder, etc.) felt by the investigator to negatively affect the conduct of the study. Parasomnia events associated with physical injury to the subject (or others) shall be discussed with the Medical Monitor.
9. Meets criteria for current major depression by clinical interview.
10. Any other clinically relevant medical, behavioral, or psychiatric disorder other than narcolepsy that is associated with excessive sleepiness.
11. History or presence of bipolar disorder, bipolar related disorders, schizophrenia, schizophrenia spectrum disorders, or other psychotic disorders according to DSM-5 criteria.
12. History or presence of any unstable or clinically significant medical condition, behavioral or psychiatric disorder (including active suicidal ideation), or history or presence of another neurological disorder or surgical history that might affect the subject*s safety and/or interfere with the conduct of the study in the opinion of the Investigator.
13. A current electrocardiogram (ECG) with clinically significant deviation(s) from normal, or clinically significant physical examination findings, as determined by the Investigator at screening.

14. Any current clinically significant laboratory abnormality as determined by the Investigator at screening.
15. Is a female subject who is pregnant, nursing, or lactating.
16. A positive urine drug screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse including alcohol abuse, or unwillingness to refrain from consuming alcohol during the study (if the subject takes prescribed amphetamines, a positive result for amphetamines will not exclude the subject).
17. Treatment with any central nervous system sedating agents, including but not limited to benzodiazepines, nonbenzodiazepine anxiolytics/ hypnotics/sedatives, neuroleptics, opioids, barbiturates, phenytoin, ethosuximide, or the monocarboxylate transporter (MCT) inhibitor valproate, within 2 weeks prior to enrollment (Day 1) (discontinuation for the purpose of study enrollment is permitted only if considered safe by the Investigator and approved by the Medical Monitor).
18. Treatment with an antidepressant for cataplexy, if the withdrawal of the antidepressant during cross-titration with JZP-258 might be unsafe due to prior history of depression.
19. Current treatment with oral isotretinoin.
20. Received any investigational drug within 30 days or 5 halflives (whichever is longer) before the Screening Visit.
21. Allergy or sensitivity to malic acid, sucralose or ingredients in the study drug formulation or placebo.
22. Unsafe for the subject to receive placebo treatment for 2 weeks, in the opinion of the Investigator.
Open Label
1. Meet Exclusion Criteria 1 through 19 from the Main Study at Visits 18 and 19.
2. Received any investigational drug (with the exception of JZP 258) within 30 days or 5 half-lives (whichever is longer) before the screening visit.
3. Allergy or sensitivity to malic acid, sucralose or ingredients in the study drug formulation.

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Other |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |

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| Control: | Placebo |
| Primary purpose: | Treatment |

### Recruitment

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 24-10-2018 |
| Enrollment: | 14 |
| Type: | Actual |

### Medical products/devices used

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| Product type: | Medicine |
| Brand name: | JZP-258, 500mg/ml oral solution |
| Generic name: | Oxybate mixed salt solution |

## Ethics review

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|---|---|
| Approved WMO Date: | 16-08-2017 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 15-01-2018 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 19-03-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 28-06-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 09-08-2018 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 04-09-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 06-09-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 22-08-2019 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# 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 | EUCTR2016-00426-20-NL |
| ClinicalTrials.gov | NCT03030599 |
| CCMO | NL62769.028.17 |