A Double-Blind, Placebo-Controlled, Randomized-Withdrawal,;Multicenter Study of the Efficacy and Safety of Xyrem with an Open- Label Pharmacokinetic Evaluation and Safety Extension in Pediatric Subjects with Narcolepsy with Cataplexy

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Primary objectives are:1) To evaluate the efficacy of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy2) To evaluate the safety of Xyrem in the treatment of cataplexy in pediatric subjects with...

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

Summary

ID

NL-OMON45197

Source
ToetsingOnline

Brief title
Jazz 13-005

Condition

- Sleep disturbances (incl subtypes)

Synonym
Narcolepsy with cataplexy, Sleeping disorder with muscle relaxation

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Narcolepsy with cataplexy, Pediatric patients, Xyrem

Outcome measures

Primary outcome

For subjects who entered the Double-Blind Treatment Period prior to Amendment 4 becoming effective all efficacy assessments will be comparisons of the measurement made during, or at the end of, the last 2 weeks of the Stable-Dose Period compared with the 2 weeks of Double-Blind Treatment Period. These assessments will continue to be collected after Amendment 4 becomes effective.

Primary endpoint:

- Change in weekly number of cataplexy attacks.

Secondary outcome

Key secondary efficacy endpoints:

- Clinical Global Impression of Change (CGIc) for cataplexy severity

- Change in the Epworth Sleepiness Scale for Children and Adolescents (ESS [CHAD]) score

Other secondary endpoints:

- CGIc for narcolepsy overall

- Change in Quality of Life (QoL) (SF-10)

Exploratory endpoints:

- Change in weekly school attendance (if enrollment overlaps with school attendance period)

- Patient Global Impression of Change (PGIc) for narcolepsy overall

Safety assessments will include the following:

- Adverse event (AE) monitoring

- Vital signs

- Physical examinations (including weight and height)

- 12-lead ECG

- Polysomnography (PSG) parameters (including respiratory measures)

- Clinical laboratory tests (chemistry, hematology, and urinalysis)

- Assessments of growth and precocious puberty

- C-SSRS for emergent suicidality

- CDI 2:SR[S] for emergent or worsening depression

- MASC-10 for emergent or worsening anxiety

- Serum pregnancy tests (if applicable)

Exploratory endpoint:

- CO2 monitoring (end tidal CO2 [EtCO2] or transcutaneous CO2 [TcCO2]) in sites where monitoring is routinely performed and performance will not negatively

impact study participation or PSG data integrity

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.
The most common symptoms of narcolepsy are excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, sleep-related hallucinations, and disrupted nighttime sleep (DNS).

Narcolepsy effects include daily functioning and daily activities, psychosocial functioning, quality of life and work performance. The effects of narcolepsy on the lives of pediatric patients are less commonly described but equally burdensome: limitations on activities, poor performance in school, difficulty with peers and a variety of psychiatric and medical comorbidities including depression, obesity and precocious puberty.

Although the majority of adult patients with narcolepsy had symptoms develop before 15 years of age there are no approved treatments for pediatric narcolepsy/cataplexy. All treatments used for the treatment of adults are used to treat children with narcolepsy.
A need exists for safe and effective treatments for pediatric patients with narcolepsy/cataplexy.

Xyrem is currently marketed in the US, Canada, and 20 European countries. Xyrem has been used to treat narcolepsy symptoms in children and adolescents. Data from published studies in pediatric and adult patients indicate a similar safety profile and therapeutic response to Xyrem in the two age groups (<18 and *18 years).

The objective of this study is to generate efficacy, safety, and pharmacokinetics (PK) information on Xyrem in the pediatric population.

Study objective

Primary objectives are:
1) To evaluate the efficacy of Xyrem (sodium oxybate) oral solution in the treatment of cataplexy in pediatric subjects with narcolepsy
2) To evaluate the safety of Xyrem in the treatment of cataplexy in pediatric subjects with narcolepsy for up to one year (and potentially more than one year in some subjects participating in a continuation of the open-label safety

evaluation)

Secondary objectives are:
1) To evaluate the efficacy of Xyrem in the treatment of excessive daytime sleepiness (EDS) in pediatric subjects with narcolepsy with cataplexy
2) To characterize the pharmacokinetics (PK) of Xyrem in pediatric subjects (ages 7-17 years) with narcolepsy with cataplexy
3) To evaluate the safety of titrating Xyrem in pediatric subjects to an effective and tolerable dose

Study design

Under Amendment 5, this study is divided into two parts: Part 1 includes one year of treatment, and Part 2, the Open-Label Continuation Period, provides the opportunity to continue treatment for up to an additional 2 years.

Part 1
Part 1 of this study was initially designed as a double-blind, placebo-controlled, randomized-withdrawal, multicenter study of the efficacy and safety of Xyrem (sodium oxybate) oral solution. As a result of a preplanned interim analysis, which demonstrated positive efficacy results on the primary efficacy endpoint, the protocol was amended (Amendment 4) to replace placebo treatment in the Double-Blind Treatment Period with open-label Xyrem treatment. After Amendment 4 becoming effective, all subjects entering the Double-Blind Treatment Period will receive open-label Xyrem treatment. For administrative reasons, the term *Double-Blind Treatment Period* will continue to be used throughout the protocol. Following the double-blind treatment period (2 weeks), this study also includes an open-label safety extension allowing subjects to continue Xyrem treatment for up to one year in Part 1.

In addition, the PK of Xyrem will be evaluated in a subset of subjects (Not in The Netherlands).

Children and adolescents, diagnosed with narcolepsy with cataplexy who are currently treated with Xyrem or are Xyrem naïve, with or without concomitant stable stimulant use, are eligible to enter the study. For this study, a Xyrem naïve subject is defined as a subject who has never been treated with Xyrem or who was previously treated with Xyrem and discontinued Xyrem for at least one month prior to the Part 1 Screening visit for reasons other than lack of efficacy and/or tolerability issues (e.g., lost insurance coverage, could not afford Xyrem, changed prescribers).

All subjects will be evaluated for eligibility during the Part 1 Screening Period (up to 30 days [if needed, additional time may be granted with permission of the Medical Monitor]).

Following Part 1 screening, subjects who are Xyrem naïve will enter the

Open-Label Titration Period of up to 10 weeks. Once the Xyrem dose has been optimized per the Investigator*s judgment, these subjects may enter the open-label Stable-Dose Period with that dose.

Subjects who are on Xyrem at study entry will remain on their stable dose and regimen (i.e., two equally divided doses or two unequally divided doses) of Xyrem and enter the Stable-Dose Period following screening.

Subjects are eligible to enter the Double-Blind Treatment Period if the dose and regimen of Xyrem remains unchanged during the Stable-Dose Period and, in the judgment of the Investigator, no clinically significant worsening in narcolepsy symptoms or clinically significant adverse events due to Xyrem treatment have occurred. .

Subjects entering the Double-Blind Treatment Period prior to Amendment 4 becoming effective, had been randomized 1:1 to receive one of the following two treatments during the 2-week Double-Blind Treatment Period (randomized-withdrawal):
* Xyrem: Active Xyrem will be continued as a double-blind treatment at the stable dose taken and regimen used in the prior 2 weeks
* Xyrem placebo: Xyrem placebo will be initiated as a double-blind treatment at a volume and regimen equivalent to the Xyrem dose taken in the prior 2 weeks.

Subjects entering the Double-Blind Treatment Period after Amendment 4 becoming effective will receive open-label Xyrem treatment in this period.

Subjects who complete the entire Double-Blind Treatment Period will be eligible to continue in the Open-Label Safety Period. The Open-Label Safety Period will allow subjects to continue Xyrem treatment for up to one year in Part 1.

Part 2
Upon approval of Amendment 5, subjects who complete one year in the study (Part 1) will have the opportunity to continue open-label Xyrem treatment in Part 2 until the first occurrence of any of the following:
* Up to an additional 2 years
* Until the subject reaches 18 years of age
* Until up to 3 months after the US FDA decision on the addition of pediatric data to the Xyrem US prescribing information (PI)
Subjects who have already completed Part 1 may re-enroll in Part 2.

Intervention

Test product:
Xyrem (sodium oxybate) oral solution
Xyrem placebo (sodium citrate oral solution) - Placebo treatment only applicable to subjects who had already entered the Double-Blind Treatment prior to Amendment 4 becoming effective.

Flavorant that can be added to the water that is used as diluent will be provided, if available, for study drug preparation if flavored diluent is requested by the subject/parent/guardian for palatability.

Refer to 'Study design' for dosing information.

Study burden and risks

Narcolepsy is a life-long neurologic disease for which no cure has been identified. The symptoms of narcolepsy effects daily functioning, daily activities, psychosocial functioning and the quality of life: excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, sleep-related hallucinations, and disrupted nighttime sleep (DNS).
There are no approved treatments for pediatric narcolepsy/cataplexy. All treatments used for the treatment of adults are used to treat children with narcolepsy. A need exists for safe and effective treatments for pediatric patients with narcolepsy/cataplexy.
Xyrem is currently marketed and has been already used to treat narcolepsy symptoms in children and adolescents. The objective of this study is to generate efficacy, safety, and pharmacokinetics (PK) information on Xyrem in the pediatric population.
This study design ensures that all subjects are able to receive Xyrem treatment and minimizes the duration of placebo exposure. Placebo is the only control group used. In this year-long study, the maximal time that any pediatric subject will receive placebo is only 2 weeks.

As a result of a preplanned interim analysis, which demonstrated positive efficacy results on the primary efficacy endpoint, the protocol has been amended (Amendment 4) to replace the placebo treatment in the Double-Blind Treatment Period with open-label Xyrem treatmentWhen Amendment 4 becomes effective all subjects entering the Double-Blind Treatment Period will receive open-label Xyrem treatment.

It is expected that the potential benefits of participating in the trial outweigh the risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Male or female subjects aged 7-16 years at Visit 2 for subjects on Xyrem at study entry and at Visit 1.1 for Xyrem-naïve subjects (to ensure subjects are <18 years of age at the end of the study).;2. Have a primary diagnosis of narcolepsy with cataplexy that meets International Classification of Sleep Disorders (ICSD)-2 or ICSD-3 criteria, whichever was in effect at the time of the diagnosis or, with the permission of the Medical Monitor, completes a Multiple Sleep Latency Test (MSLT) during Screening to confirm the diagnosis of Type 1 narcolepsy by ICSD-3 criteria (ie., the subject meets all other ICSD-3 criteria for Type 1 narcolepsy).;3. Be positive for the Human Leukocyte Antigen (HLA) DQB1:0602 haplotype, determined prior to the study or as part of the study screening procedures, or have cerebrospinal fluid (CSF) hypocretin level *110 pg/ml determined prior to the study. In the absence of both, be evaluated by a panel of narcolepsy experts to confirm the diagnosis of narcolepsy with cataplexy in accordance with ICSD-3.;4. Have given documented assent indicating that he/she was aware of the investigational nature of the study and the required procedures and restrictions before participation in any protocol-related activities.;5. Have parent(s)/guardian(s) who have given informed consent for his/her/their child*s participation in the study.;6. 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 .;7. Be willing to spend the required number of nights (2 to 3) in a sleep laboratory for PSG evaluations.;8. If currently treated with Xyrem, must have been taking unchanged doses (twice nightly dosing no higher than 9 g/night) of Xyrem, and stimulants, if applicable, for the

treatment of narcolepsy symptoms for at least 2 months prior to screening. ;9. If currently treated with Xyrem, must have demonstrated clinical improvement of cataplexy per investigator*s clinical judgment.;10. Have agreed to abstain from caffeinated products during PSG and PK nights. ;11. Any female subject of child-bearing potential must be willing to use a method of contraception, deemed medically acceptable by the Investigator, or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination.;12. Any male subject who is sexually active with a female partner must be willing to use a method of contraception, deemed medically acceptable by the Investigator, or agree to abstain from sexual intercourse for the duration of the study and for 30 days after study termination.;Subjects who have completed Part 1 of the study are eligible to re-enroll in Part 2 regardless of their current Xyrem treatment status if they meet Inclusion Criteria 4, 5, 11, and 12 and the following criteria at the Part 2 Screening visit (Visit 17) and the first drug-dispensing visit (Visit 18):
- Are less than 18 years of age
- If currently being treated with Xyrem, the subject is on a stable dose
- If currently being treated with Xyrem, the subject's total twice nightly Xyrem dose must be no higher than 9 g/night

Exclusion criteria

1. Not able to understand assent or follow study instructions, in the investigator's opinion.;2. Parent(s)/guardian(s) unable to comply with the study requirements, in the investigator's opinion.;3. Previously treated with Xyrem and discontinued because of lack of efficacy and/or tolerability issues.;4. Narcolepsy secondary to another medical condition, e.g., CNS injury or lesion.;5. Restless leg syndrome requiring treatment other than iron supplements.;6. Succinic semi-aldehyde dehydrogenase deficiency.;7. Uncontrolled hypothyroidism.;8. History of seizure disorders.;9. History of head trauma associated with loss of consciousness.;10. Evidence of sleep-disordered breathing including:
a. Presence of clinically significant obstructive or central sleep apnea as determined by the investigator or documented previously; or
b. Obstructive AHI >5 for subjects 7-11 years of age or obstructive AHI>10 for subjects 12-17 years of age; or
c. Oxygen saturation nadir *85% at night; or
d. Clinically significant hypoventilation.;11. Oxygen saturation level <95% for at least 5 minutes on room air as measured by pulse oximetry while fully awake during daytime monitoring, or subjects with known or suspected respiratory difficulty, or any condition that may compromise a subject*s breathing. If oxygen saturation values lower than 95% are observed at study sites at high geographic elevations and are acceptable to the investigator, enrollment of the subject requires permission from the Medical Monitor.;12. Past or current major thought disorder, e.g., schizophrenia, paranoia, mania, etc.;13. Recent history of clinically significant parasomnia (e.g., sleep walking, REM behavior disorder, etc.) that would negatively affect the conduct of the study.;14. Current suicidal risk as determined from history or Columbia Suicide Severity Rating
Scale or history of suicide attempt.;15. If the T-score is at or above 65 on the Children*s Depression Inventory 2nd Edition Self-Report Short Version (CDI 2:SR[S]), an evaluation of

depression by the Investigator (if qualified as a mental health professional) or by the Investigator in consultation with a mental health professional must be performed to exclude a clinically significant depression.;16. Other documented clinically significant condition (including unstable medical and/or psychiatric conditions, chronic disease other than narcolepsy with cataplexy, porphyria, or history or presence of another neurological disorder) that might affect the subject*s safety and/or interfere with the conduct of the study in the investigator's opinion.;17. An ECG with clinically significant deviation(s) from normal, or clinically significant physical examination findings, as determined by the investigator.;18. Any clinically significant lab abnormality as determined by the investigator.;19. A positive pregnancy test result at screening (pregnancy tests will be performed for any female subject who has reached menarche).;20. 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).;21. Treatment with benzodiazepines, non-benzodiazepine anxiolytics/ hypnotics/sedatives, neuroleptics, opioids, barbiturates, diclofenac, valproate, phenytoin, ethosuximide within 2 weeks prior to enrollment (discontinuation for the purpose of study enrollment is permitted only if considered safe by the investigator and approved by the Medical Monitor).;22. Treatment with any other medications that have anticataplectic effect (e.g., serotonin*norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs], or tricyclic antidepressants [TCAs]) within 1 month before Screening;23. Current treatment with oral isotretinoin;24. Inability to fast for 2 hours before the first dose through 4 hours after the last dose of Xyrem on PSG and PK nights;25. Lack of parental (or legal guardian) commitment to ensuring home situation is safe for Xyrem use, in the opinion of investigator.;26. Received any investigational drug within 30 days or 5 half-lives (whichever is longer) before screening.;27. Allergy to any components of topical, local anesthetics that might be used for blood collection (not applicable if numbing agents will not be used).;28. Allergy or sensitivity to malic acid, sucralose, or ingredients in the study drug formulation and/or the flavorant, if used;Subjects will be excluded from re-enrolling in Part 2 if they meet Exclusion criteria: 1-10, 12, 17, 19-22, 24, 26-29 or any of the following criteria at the Part 2 Screening visit (Visit 17) and the first drug-dispensing visit (Visit18):
- Have not completed Part 1
- If they are 18 years of age
- If they have suicidal risk or clinically significant depression independent of narcolepsy symptoms as determined by the investigator

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-08-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Xyrem
Generic name:	gamma hydroxy butyrate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	18-12-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	12-03-2015
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	12-10-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	23-03-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	14-06-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	12-06-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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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	EUCTR2014-001389-93-NL
ClinicalTrials.gov	NCT02221869
CCMO	NL50646.058.14