A Phase 1, Open-Label, Single Ascending Dose Study to Evaluate the Pharmacokinetics and Safety of Solriamfetol in Pediatric Subjects with Narcolepsy

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PRIMARY OBJECTIVE To characterize the pharmacokinetics (PK) of single doses of solriamfetolin pediatric subjects with narcolepsy.SECONDARY OBJECTIVE To assess the safety and tolerability of single doses of solriamfetol inpediatric subjects with...

Ethical review	Not approved
Status	Will not start
Health condition type	Sleep disturbances (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON49961

Source
ToetsingOnline

Brief title
JZP865-101

Condition

- Sleep disturbances (incl subtypes)

Synonym
Excessive daytime sleepiness

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Excessive Daytime Sleepiness (EDS), Narcolepsy, Pediatric Subjects, Phase 1

Outcome measures

Primary outcome

PRIMARY OBJECTIVE To characterize the pharmacokinetics (PK) of single doses of

solriamfetol

in pediatric subjects with narcolepsy.

Secondary outcome

SECONDARY OBJECTIVE To assess the safety and tolerability of single doses of

solriamfetol in

pediatric subjects with narcolepsy.

Study description

Background summary

Narcolepsy is a life-long neurologic disease for which no cure has been identified. Narcolepsy is commonly diagnosed in adulthood; however, onset typically occurs in childhood or adolescence. The diagnostic criteria (International Classification of Sleep Disorders-3 [ICSD-3]; Sateia 2014) for pediatric patients with narcolepsy (Type 1 and Type 2) are the same as those used for adult patients. For example, in the multiple sleep latency test (MSLT), which is part of the diagnostic criteria in both children and adults, the criteria for a diagnosis of narcolepsy in children is the same as those for adults: both requiring a mean sleep latency < 8 minutes and * 2 Sleep-onset rapid eye movement periods (SOREMPs). Children and adolescents with narcolepsy have been reported to meet these criteria in 92% to 100% of cases across several studies in pediatric narcolepsy. In addition, the mean number of SOREMPs in the MSLT was approximately 3 across studies in 150 children and

adolescents, a value similar to that seen in adult MSLT studies (Challamel 1994; Guilleminault and Pelayo 1998). Consistent with findings in adults, the average sleep latency on the MSLT in children and adolescents is reported to be < 5 minutes in multiple pediatric studies (Dauvilliers 2001; Huang and Guilleminault 2009; Aran 2010; Han 2011; Jambhekar 2011; Lecendreux 2012; Mansukhani and Kotagal 2012; Partinen 2012; Nevsimalova 2013; Poli 2013). The signs and symptoms of narcolepsy in children are the same as those in adults. The pentad of narcolepsy symptoms seen in adults (excessive daytime sleepiness [EDS], cataplexy, hynogogic or hypnopompic hallucinations, sleep paralysis, and disturbed nocturnal sleep), which are currently described in ICSD-3 for the diagnosis of narcolepsy (Sateia 2014), are seen in children and adolescents with similar frequencies to that of adults. All patients have EDS and many have some or all of the other 4 core symptoms. Children are similar to adults in that the development of symptoms may progress over time. These data indicate the strong similarity in narcolepsy presentation between these 2 populations.

The solriamfetol clinical program that led to its approval in the US and on which the MAA was submitted to the CHMP comprised 18 completed studies in adults. To date, no PK studies have been conducted with solriamfetol in pediatric subjects. This phase 1, multi-center, open-label, 3-period, fixed-sequence, single ascending dose study is designed to characterize the PK in pediatric subjects, evaluate the safety profile, and to inform dose selection for future pediatric studies.
Dose selection for this study is based on population PK simulations from adult PK data and the calculated safety margins from the juvenile toxicology study. For further details on dose selection, please refer to Section 1.2.4.
Solriamfetol has a systemic elimination half-life of 5.0 to 7.6 hours in adults; therefore, the washout periods of 14 ± 2 days separating consecutive dosing Periods are long enough for drug elimination and also for keeping the blood volume collection within acceptable limits.
No control/placebo group is necessary in this phase 1 open-label study to evaluate the PK of solriamfetol.
This study was designed in accordance with:
* Regulation (EU) No 536/2014 *Ethical considerations for clinical trials on medicinal products conducted with minors.*
* The ethical principles given in these guidances, which have their origins in the Declaration of Helsinki.
* Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.
* EU Paediatric Regulation 1901/2006 (as amended by Regulation 1902/2006).

Study objective

PRIMARY OBJECTIVE To characterize the pharmacokinetics (PK) of single doses of solriamfetol
in pediatric subjects with narcolepsy.

SECONDARY OBJECTIVE To assess the safety and tolerability of single doses of solriamfetol in
pediatric subjects with narcolepsy.

Study design

This is a phase 1, multi-center, open-label, 3-period, fixed-sequence, single ascending dose study to evaluate the PK and safety of solriamfetol in pediatric subjects (6 to < 18 years old) with narcolepsy.
Twelve pediatric subjects who have satisfied all eligibility criteria, 6 subjects in each age group, are planned to be dosed. An attempt will be made to enroll an equal number of male and female subjects in each group. Additionally, an attempt will be made to enroll at least 2 subjects below the age of 9.
The study consists of a Screening Period, which is followed by 3 Pharmacokinetic/Safety Periods, and the End of Study Period.
Screening Period (up to 28 days)
All subjects will undergo screening evaluations to determine their eligibility within 28 days before dosing. Prior to conducting any studyrelated screening procedures, all subjects will provide written assent and their parent(s) or guardian(s) will give written informed consent.
Pharmacokinetic/Safety Periods (approximately 4 weeks)
Each subject in Group 1 (adolescents 12 to < 18 years old) is planned to receive 3 single oral doses of solriamfetol (ie, 75, 150, and 300 mg) during 3 separate Periods 1, 2, and 3, respectively, in an ascending manner. Each subject in Group 2 (children 6 to < 12 years old) is planned to receive 3 single oral doses of solriamfetol (ie, 37.5, 75, and 150 mg) during 3 separate Periods 1, 2, and 3, respectively, in an ascending manner. Periods 1, 2, and 3 will be separated by washout periods of 14 ± 2 days.
Dosing in Group 2 will not start until dosing in Group 1 has been complete and all the safety, tolerability, and PK data from all subjects/doses in Group 1 have been reviewed by the principal investigators (or designee) and Jazz medical/clinical staff. In the event of observing intolerance or unexpectedly high exposures relative to the predicted PK exposures at 75 or 150 mg in subjects in Group 1, that dose and any higher dose if applicable will not be administered in Group 2.
Within Group 1 and Group 2, each subject will be allowed to dose escalate from Period 1 to Period 2 and from Period 2 to Period 3 independently of other subjects in the same group. Within each age group, however, not more than 2 subjects can receive the same dose at the same time. A safety evaluation for each subject will be performed by the principal investigator (or designee) and Jazz medical/ clinical staff before the next higher dose can be received.
End of Study Period (approximately 1 week)
At the End-of-Study, which will occur 7 ± 2 days after the last dose was received at Period 3, subjects will return as outpatients to complete the

End of Study assessments. Subjects who discontinue early should also return as outpatients to undergo End of Study assessments 7 ± 2 days after receiving their last dose.

Intervention

Each subject in each age group will receive 3 single oral doses of solriamfetol (if tolerated) during 3 separate periods, in an ascending manner (Table 1). Dosing in Group 2 (children 6 to < 12 years old) will not start until the dosing in Group 1 (adolescents 12 to < 18 years old) is complete.
Within Group 1 and Group 2, each subject will be allowed to dose escalate from Period 1 to Period 2 and from Period 2 to Period 3 independently of other subjects in the same group. Within each age group, however, not more than 2 subjects can receive the same dose at the same time. A safety evaluation for each subject will be performed by the principal investigator (or designee) and Jazz medical/clinical staff before the next higher dose can be received for each subject.
In performing these safety evaluations as each subject dose escalates from a lower to a higher dose, the principal investigator (or designee) and Jazz medical/clinical staff will review each subject*s safety data in alignment with the known safety profile of solriamfetol. The safety data will include, but not be limited to, vital signs, ECGs, C-SSRS, and AEs. Once each safety review has concluded that adequate safety and tolerability have been demonstrated, each subject will be permitted to proceed to the next higher dose.
Once the last subject in Group 1 has completed the last study period, PK will be assessed for all subjects in this group. The safety, tolerability, and PK data from all subjects/doses in Group 1 will be reviewed by the principal investigators (or designees) and Jazz medical/clinical staff before dosing can begin in Group 2.
Within Group 1, dosing will be terminated at any dose, and any higher dose if applicable, if 3 or more subjects at that dose:
* Had a drug-related serious adverse event (SAE), or
* Had a drug-related nonserious adverse event (AE) of severe intensity requiring medical intervention.
If dosing is terminated for the 75 mg dose in Group 1, subjects in Group 2 will still receive the 37.5 mg dose. If dosing in Group 1 is terminated at 150 mg, subjects in Group 2 could still receive the 37.5 and 75 mg doses.
Furthermore, in the event of observing unexpectedly high exposures relative to the predicted PK exposures at 75 mg in subjects in Group 1, the 75 and 150 mg doses will not be administered in Group 2. If unexpectedly high exposures relative to the predicted PK exposures are only observed at the 150 mg dose in subjects in Group 1, the 150 mg dose will not be administered in Group 2.
Within Group 2, dosing will be terminated at any dose, and any higher dose if applicable, if 3 or more subjects at that dose:
* Had a drug-related SAE, or
* Had a drug-related nonserious AE of severe intensity requiring medical intervention.

Table 1 Treatment and dosing schedule
Age Group Period 1 Period 2 Period 3
Group 1,
12 to < 18 years old
(N = 6) 75 mg 150 mg 300 mg
Group 2,
6 to < 12 years old
(N = 6) 37.5 mg 75 mg 150 mg

The washout period (ie, 14 ± 2 days) was selected in consideration of keeping the blood volume collection within the acceptable limits as advised by the applicable guidance (eg, the European Commission*s recommendations *Ethical considerations for clinical trials on medicinal products conducted with minors*, 2017 or according to IRB/EC guidelines). For example, the 2017 guidance specifies that the volume of blood taken on any 1 occasion should not exceed 1% of the total blood volume and the blood volume taken in any 4-week period should not exceed 3% of the total blood volume.
Subjects will check into the study site the evening of Day -1 (Period 1) and will remain at the study site for approximately 10 hours after receiving their dose on Day 1 for PK and safety assessments. Subjects will receive a single dose of solriamfetol as a tablet with 240 mL of water in the morning approximately 2 hours after completing a light breakfast, which will be provided at the study site. The contents of the light breakfast should be of the same or similar content on each day blood is drawn for PK assessment.
All subjects will return to the study site 2 additional times (Period 2 and Period 3) for PK and safety assessments (see Appendix A). At these visits, subjects will receive the next higher dose of solriamfetol, provided that the prior dose was well tolerated as established by the principal investigator (or designee) and Jazz medical/clinical staff.
During Periods 1, 2, and 3, blood samples for PK analyses will be collected at predose and at 1, 2, 3, 6, 8, and 10 hours following administration of the single dose of solriamfetol. An indwelling catheter may be used to facilitate the collection of the blood samples.

Study burden and risks

Solriamfetol has a large adult clinical safety database comprised of healthy subjects and subjects with OSA, narcolepsy, or MDD with a consistent safety profile across conditions. The robust wake promoting efficacy of solriamfetol has been demonstrated among subjects with OSA or narcolepsy.
This study will be conducted in pediatric subjects with narcolepsy. Benefits to the subjects include a physical examination, clinical safety assessments, and comprehensive laboratory evaluations. The subjects will also have the opportunity, if eligible, to participate in future efficacy and/or long-term solriamfetol safety studies as approved under the pediatric investigational plan. However, subjects likely will not benefit from taking solriamfetol directly in the current study as they will be receiving a single dose rather

than maintenance dosing.
Risks to the subjects include those related to solriamfetol and to blood collection. The risks to subjects are expected to be similar to those seen in prior clinical studies, which are summarized in Section 1.2.1.2. Adverse events following a single dose have generally been transient and mild to moderate.

Contacts

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Jazz Pharmaceuticals

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Jazz Pharmaceuticals

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Palo Alto 94304
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Each subject must meet the following criteria to be enrolled in the study.
1. Male and female subjects 6 to < 18 years old at Screening, depending on Group.
2. Minimum body weight of 22 kg.

3. Subjects with diagnosis of narcolepsy according to International Classification of Sleep Disorders-3 (ICSD-3) criteria, or, with the permission of the medical monitor, completed a Multiple Sleep Latency Test (MSLT) during Screening to confirm the diagnosis of narcolepsy by ICSD-3 criteria (ie, the subject met all other ICSD-3 criteria for narcolepsy).
4. Subjects with documented written assent per institutional review board (IRB) / ethics committee (EC) requirements indicating that he/she is aware of the investigational nature of the study and the required procedures and restrictions before participation in any protocol-related activities.
5. Parent(s)/guardian(s) must give their written informed consent for his/her/their child*s participation in the study.
6. Female subjects of childbearing potential (ie, fertile, following menarche) and male subjects who have female partners of childbearing potential must agree to use medically acceptable methods of contraception with their partners from Screening, throughout the study, and for 30 days after the last dose of solriamfetol. Medically acceptable methods of contraception that may be used by the subject include abstinence (when this is in line with the preferred and usual lifestyle of the subject), progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, and a combination of a male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, single barrier methods (male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide), and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Female condom and male condom should not be used together.
7. Subjects must agree to abstain from alcohol and nicotine-containing products; including tobacco (eg, cigarettes, cigars, chewing tobacco, snuff), e-cigarettes, and nicotine lozenge/gum/patch within 3 days prior to each dosing in Periods 1, 2, and 3 through discharge from that period.
8. Subjects must agree to discontinue use of over-the-counter (OTC) or prescription stimulants (eg, pseudoephedrine, methylphenidate, amphetamines, modafinil, armodafinil, and pitolisant) the day before dosing and on each day when receiving a dose of solriamfetol.
9. Subjects must have sufficient blood volume for PK sampling based on body weight in accordance with applicable guidance (eg, European Commission*s recommendations document *Ethical considerations for clinical trials on medicinal products conducted with minors* 2017, or according to the IRB/EC guidelines).
10. Subjects must be willing and able to comply with the study schedule, all study procedures, and other requirements.

Exclusion criteria

Inclusion Criteria

Each subject must meet the following criteria to be enrolled in the study.
1. Male and female subjects 6 to < 18 years old at Screening, depending on Group.
2. Minimum body weight of 22 kg.
3. Subjects with diagnosis of narcolepsy according to International Classification of Sleep Disorders-3 (ICSD-3) criteria, or, with the permission of the medical monitor, completed a Multiple Sleep Latency Test (MSLT) during Screening to confirm the diagnosis of narcolepsy by ICSD-3 criteria (ie, the subject met all other ICSD-3 criteria for narcolepsy).
4. Subjects with documented written assent per institutional review board (IRB) / ethics committee (EC) requirements indicating that he/she is aware of the investigational nature of the study and the required procedures and restrictions before participation in any protocol-related activities.
5. Parent(s)/guardian(s) must give their written informed consent for his/her/their child*s participation in the study.
6. Female subjects of childbearing potential (ie, fertile, following menarche) and male subjects who have female partners of childbearing potential must agree to use medically acceptable methods of contraception with their partners from Screening, throughout the study, and for 30 days after the last dose of solriamfetol. Medically acceptable methods of contraception that may be used by the subject include abstinence (when this is in line with the preferred and usual lifestyle of the subject), progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, and a combination of a male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, single barrier methods (male or female condom with or without spermicide; cap, diaphragm, or sponge with spermicide), and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Female condom and male condom should not be used together.
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9. Subjects must have sufficient blood volume for PK sampling based on body weight in accordance with applicable guidance (eg, European Commission*s recommendations document *Ethical considerations for clinical trials on medicinal products conducted with minors* 2017, or according to the IRB/EC guidelines).
10. Subjects must be willing and able to comply with the study schedule, all study procedures, and other requirements.
Exclusion Criteria
Subjects who demonstrate any of the following will be excluded from the study.

1. Subjects with any significant abnormality in the physical or psychological finding, or clinical laboratory results that could interfere with the study conduct or the ability of the subject to complete the study based on the judgement of the investigator, or place the subject at risk during the trial or compromise the study objectives.
2. Subjects with clinically significant disorders other than narcolepsy, including but not limited to, endocrine, neoplastic, gastrointestinal, hematological, hepatic, immunologic, metabolic, neurological (other than narcolepsy/cataplexy), pulmonary, renal disease, behavioral, or psychiatric disorder, which could interfere with the study conduct or the ability of the subject to complete the study based on the judgement of the investigator, or place the subject at risk during the study or compromise the study objectives.
3. Subjects with uncontrolled hypertension, uncontrolled cardiac arrhythmias, or systolic blood pressure and/or diastolic blood pressure values greater than the 95th percentile for sex, age, and height, any clinically significant electrocardiogram (ECG) abnormality in the opinion of the Investigator, or any history of cardiovascular disease or any significant cardiovascular condition that in the Investigator*s opinion may jeopardize a subject*s safety in the study.
4. Subjects with an estimated creatinine clearance (CrCL) < 90 mL/min.
5. Female subjects who are pregnant, nursing, or lactating.
6. Subjects with self-reported consumption of more than 200 mg of caffeine per day (for example, more than 12 oz [approximately 355 mL] of coffee).
7. Subjects with hemoglobin less than normal range for age and gender at Screening.
8. Subjects who are positive for urine drug screening for opiates, barbiturates, amphetamine, tetrahydrocannabinol (THC), benzodiazepines, or cocaine unless the subject is receiving prescribed drugs.
9. Subjects who are positive for the alcohol breath test.
10. Subjects who donated blood within 1 month before the start of the study.
11. Subjects who received any investigational drug within 30 days or 5 half-lives (whichever is longer) before Screening.
12. Subjects who are receiving monoamine oxidase inhibitors.
13. Subjects with allergy to any components of topical, local anesthetics that might be used for blood collection (not applicable if numbing agents will not be used).
14. Subjects with history or presence of phenylketonuria or hypersensitivity or idiosyncratic reaction to phenylalanine-derived products, or any excipient in the formulated drug products.
15. Subjects with current suicidal risk as determined from history, or Columbia Suicide Severity Rating Scale (C SSRS), or history of suicide attempt.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	JZP865-101 Solriamfetol
Generic name:	Sunosi

Ethics review

Approved WMO

Date:	04-06-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Not approved

Date:	09-09-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2019-003008-11-NL
CCMO	NL73669.000.20