A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

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Primary ObjectiveThe primary objective of the study is:• To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating EDS in both NT1 and NT2 subjects as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT)...

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

Summary

ID

NL-OMON45892

Source
ToetsingOnline

Brief title
REST-ON

Condition

- Sleep disturbances (incl subtypes)

Synonym
Narcolepsy - sleeping disorder

Research involving
Human

Sponsors and support

Primary sponsor: Flamel Ireland Limited (trading under the business name Avadel Ireland)
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Cataplexy, Excessive Daytime Sleepiness, Narcolepsy, Sodium Oxybate

Outcome measures

Primary outcome

The primary criteria that efficacy determination will be based on include:

• Longer MWT sleep latency

• Improvement in CGI sleepiness scores

• Fewer cataplexy attacks as recorded by Sleep and Symptom Daily Diary

Secondary outcome

Secondary Endpoint:

The secondary criterion that efficacy determination will be based on is fewer

PSG transitions from N1, N2, N3, and REM sleep to wake sleep and N1 sleep and

from N2, N3, and REM sleep to N1.

Tertiary Endpoints:

The tertiary criteria that efficacy determination will be based on include:

• Lower ESS scores

• Reduction in the number of arousals in both NT1 and NT2 subjects obtained

from a PSG as defined by the American Academy of Sleep Medicine

• Improvement in sleep quality in both NT1 and NT2 subjects as obtained from

the Sleep and Symptom Daily Diary, VAS for sleep quality, and the VAS for a

more refreshing sleep

• Fewer SP and HH experiences as measured by Sleep and Symptom Daily Diary

Study description

Background summary

Narcolepsy is a chronic, life-disrupting neurologically-based sleep disorder characterized by 5 major symptoms, EDS, cataplexy, hypnagogic hallucinations (HH), sleep paralysis (SP), and disturbed nocturnal sleep (DNS). Narcolepsy is associated with increased morbidity, increased mortality, and reduced quality of life. In addition, there are significant social and economic impacts for subjects with narcolepsy, their families, and the healthcare system.
As part of a recent meeting for the narcolepsy community initiated by the Food and Drug Administration (FDA), the FDA inquired *Assuming there is no complete cure for your condition, what specific things would you look for in an ideal therapy for your condition?* In an interim report circulated from the patient advocacy community, Unite Narcolepsy, summarizing the results from a patient survey with 1350 responses in preparation for the FDA meeting, the first statement responding to the FDA*s question was an excerpt from a patient response stating *A drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require 1 dose taken at bedtime resulting in 8 hours of restorative sleep*.
Flamel Technologies has developed a drug delivery technology designed to extend and/or delay the absorption of a drug in order to control its pharmacokinetic (PK) profile. Based on this proprietary controlled-release delivery technology, Micropump®, Flamel Technologies has developed a new formulation of sodium oxybate which is more convenient for the subject in that it is dosed only once (ie, at bedtime). The once nightly dosing is an improvement beyond the current approved dosing regimen for Xyrem that requires narcolepsy subjects to wake up in the middle of the night to take a second dose. It is proposed that the FT218 once nightly dosing regimen represents an improved therapeutic option for subjects.

Study objective

Primary Objective

The primary objective of the study is:
• To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating EDS in both NT1 and NT2 subjects as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT) and by the Clinical Global Impression (CGI) rating of sleepiness
• To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating cataplexy in NT1 subjects as measured by the number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary

Secondary Objective
The secondary objective of the study is:
• To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating DNS in both NT1 and NT2 subjects as determined by PSG measures of sleep fragmentation defined as shifts to Wake or N1 from any sleep change

Tertiary Objectives
The tertiary objectives of the study are to compare the efficacy of 6.0, 7.5, and 9.0 g doses of FT218 to placebo for improving:
• EDS in both NT1 and NT2 narcolepsy as measured by patient report via the Epworth Sleepiness Scale (ESS)
• Number of arousals in both NT1 and NT2 obtained from a PSG as defined by the American Academy of Sleep Medicine (sleep quality in both NT1 and NT2 obtained from the Sleep and Symptom Daily Diary; visual analog scale (VAS) for sleep quality in the sleep diary; VAS for the refreshing nature of sleep)
• Hypnagogic hallucinations and SP symptoms in NT1 subjects as measured by the Sleep and Symptom Daily Diary

Safety Objective
The safety objective of the study is:
• To evaluate the relative safety of FT218 compared to placebo.

Study design

This is a double-blind, randomized, placebo controlled, 2 arm multicenter clinical study to assess the efficacy and safety of a once nightly formulation of sodium oxybate (FT218) for the treatment of EDS and cataplexy in subjects with narcolepsy. Randomization methods stratify study subjects according to narcolepsy type (ie, NT1/NT2) and in a 1:1 fashion to 1 of the 2 treatment arms (FT218 and placebo). A total of 132 study subjects will be randomized to each of the treatment arms where a minimum of 107 study subjects (> 80%) will have both EDS and cataplexy (ie, NT1) in each treatment arm. The study is divided into 4 sequential study periods. The study design incorporates scheduled dose titration to stabilized dose administration of FT218.
Two populations of narcoleptic subjects will be studied in a single parallel group design: 1) narcolepsy with both EDS and cataplexy (NT1), and 2) narcolepsy with EDS but with no cataplexy (NT2).

The study treatment period from screening to follow-up will last approximately 17 weeks. There is a 3 week screening period, followed by a central assessment of PSG and next day MWT screening results (may take up to 2 days). If the subject is eligible, then randomization occurs. After randomization, dosing must start within 6 days (the window from randomization to dosing is to allow delivery of study drug to the site, total time from PSG and MWT to dosing will be no more than 7 days). For subjects randomized to the active arm of the study the maximum duration of treatment with FT218 will be 13 weeks incorporating up-titration over a period of 8 weeks with 5 weeks on stable dosing at 9.0 g/night. For subjects randomized to placebo, there is no exposure to the study treatment.
A follow-up visit will occur at least 1 week after the last dose of FT218 or placebo (ie, Period 4, Visit 9, Week 15, Day 1 [+4/ 0 (ie, a minimum of 7 days after the last onstudy dose)]). Additional follow up for safety surveillance and management will be done for unresolved adverse events (AEs) as determined by the study investigator.

Intervention

FT218 or placebo dosing will follow a 4 period up-titration as follows: FT218 4.5 g or placebo daily for 1 week, FT218 6.0 g or placebo daily for 2 weeks, FT218 7.5 g or placebo daily for 5 weeks, and FT218 9.0 g or placebo daily for 5 weeks. Study drug will be taken orally at bedtime.

Study burden and risks

Based on early studies of FT218, it is possible to predict some of the discomforts and risks. The data suggest that the potential risks of FT218 are likely to be manageable and will be monitored like Xyrem.

Contacts

Public
Flamel Ireland Limited (trading under the business name Avadel Ireland)

Blanchardstown Corporate Park lock 10 Unit 1
Ballycoolin Dublin 15
IE
Scientific
Flamel Ireland Limited (trading under the business name Avadel Ireland)

Blanchardstown Corporate Park lock 10 Unit 1
Ballycoolin Dublin 15
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male or female subjects 18 years of age or older;2. Willing and able to give written informed consent for study participation.
3. Documented evidence of a diagnosis of NT1 or NT2 as, in part, determined by an overnight PSG and next-day MSLT with 2 or more SOREMPs with mean sleep latency in the pathological range ie, < 8 minutes or meeting the NT1 or the NT2 as defined by the International Classification of Sleep Disorders -3 criteria.;4. Current continuing presence of EDS as defined by subject report for the last 3 months and an ESS > 10;5. For NT1 only, current continuing presence of cataplexy as defined by subject report for the last 3 months;6. Subjects may use concomitant stimulants, but must comply with the following:;a. They must be on a stable dose of stimulants for at least 3 weeks prior to starting the screening process for this study; AND;b. They must use the same stimulant regimen throughout the entire study period, including during screening and post treatment periods;c. They must discontinue all anti cataplexy drugs;7. Female subjects who:;a. Are postmenopausal for at least 1 year before the screening visit;b. Are surgically sterile, OR;c. If of childbearing potential agree to practice at least one highly effective method of contraception, from the time of the signing of informed consent through the last dose of study drug and for 30 days
after dosing stops (1 ovulatory cycle), or complete abstinence during the study if in line with the preferred and usual lifestyle of the subject.;8. Willing and able to comply with all study mandated requirements and procedures for the duration of the clinical study;9. Willing to adhere to all study restrictions including: ;a. Willingness to comply with the requirement to remain in bed for a minimum of 6 hours after taking the study drug;b. Adherence to concomitant drug washout requirements, as applicable, for the duration of the clinical study. ;c. Willing to refrain from operating a car or heavy machinery if determined necessary by the investigator or willingness to refrain from operating a car or heavy machinery for at least 6 hours after taking the nightly dose of FT218;d. Willing to abstain from alcohol for the duration of the clinical study;e. If a smoker, willing to abstain from smoking at night from approximately 9 pm to 7 am for the duration of the clinical study;10. Evidence of adequate support for the duration of the study, including transportation to and from the study site if

needed;To be eligible for inclusion, subjects must satisfy all of the following criteria at the Visit 3 dosing visit:;1. Written informed consent obtained during the screening assessment visit;2. Still eligible as per requirements in Protocol Section 8.3.2;3. Compliance with drug washout requirements;4. Compliance in completing the study screening/baseline Sleep and Symptom Daily Diary. Compliance is defined as completing the diary at least 4 times in each of the screening weeks.;5. Confirmation of EDS as defined by all of the following;a. Baseline ESS score > 10 points; AND;b. Baseline MWT mean sleep latency < 11 minutes following baseline PSG and as confirmed by the central scoring laboratory.;6. For NT1 only, current continuing presence of cataplexy as defined by an average of 8 reported cataplexy attacks per week in the screening/baseline Sleep and Symptom Daily Diary;7. Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine test within 7 days prior to treatment.

Exclusion criteria

Subjects will be excluded from the study if one or more of the following criteria are applicable: ;1. Any prior use of sodium oxybate;2. Current use of sodium valproate;3. Any use of the following prohibited medications for the duration of the
clinical study: (Section 8.4.8.1)
a. Anticonvulsants
b. Clonidine
c. SSRIs and serotonin and norepinephrine re-uptake inhibitors (SNRIs)
d. MAOIs
e. TCAs
f. Sedative Antihistamines
g. Antipsychotics
h. Tramadol
i. Benzodiazepines
j. Barbiturates
k. Alcohol and CNS depressants
l. Gamma hydroxybutyrate (GHB) dehydrogenase inhibitors
m. Topiramate
n. Opioids
o. Other experimental medications designed to treat narcolepsy, cataplexy or any other condition;4. Treatment with any investigational products within 3 months before study enrollment;5. Any drug known to affect sleep-wake function. Concomitant stimulant use is permitted. ;6. A diagnosis of sleep apnea or any other sleep disorder known to cause EDS as determined by PSG and sleep ;history, including any PSG results indicating an apnea-hypopnea index (AHI) >= 15;7. The presence of any unstable or clinically significant medical and psychiatric disorders (as determined by medical or psychiatric history, physical examination, and/or clinical laboratory test) which in the opinion of the investigator may either put the subject at risk by participation in the study, or may influence the results of the study;8. Subjects with a previous history or current ideation of suicide attempt;9. Subjects who have a history of drug or alcohol use that, in the opinion of the investigator would interfere with study subject safety and adherence to study requirements;10. Required

commercial or equivalent driving during the study period;11. An occupation that requires variable shift work or routine night shifts;12. Any travel across more than 3 time zones during the course of the study;13. Consuming more than 14 standard alcoholic drinks per week, on average, before participating in the clinical research study;14. Smoking during the night (approximately between 9 pm and 7 am) during the course of the study;15. Female subjects who are lactating or have a positive pregnancy test. Females of reproductive potential not willing or able to employ at least one highly effective method of contraception to prevent pregnancy for the duration of the study and for 30 days after dosing stops (1 ovulatory cycle) or complete abstinence during the study if in line with the preferred and usual lifestyle of the stubjects.;16. Any current malignancy and/or any history of malignancy within last 3 years;17. A history of seizure disorder, head trauma, or past invasive intracranial surgery;18. Subjects with severe chronic obstructive pulmonary disease. Subjects with mild to moderate chronic obstructive pulmonary disease and assessed as stable by the principal investigator (PI) are eligible;19. Principal investigator judgement on other underlying respiratory and/or other underlying condition or disorder that would potentiate risk of respiratory or CNS depression with concomitant use of sodium oxybate;20. Known hepatitis B surface antigen-positive status or known or suspected active hepatitis C infection;21. Known human immunodeficiency virus infection or acquired immunodeficiency syndrome related illness;22. Scheduled for procedures requiring general anesthesia during the study;23. Known contraindication/allergy/sensitivity/intolerance to the study drug, sodium oxybate, or the inactive ;ingredients of FT218 or placebo;24. Atrial fibrillation or an abnormal electrocardiogram (ECG) demonstrating clinically significant dysrhythmia(s);25. Recent myocardial infarction or coronary revascularization (less than 3 months);26. Uncontrolled hypertension;27. Known succinic semi-aldehyde dehydrogenase deficiency ;28. Moderately or severely altered blood chemistry as defined by any one of the following:;a. A Cockcroft-Gault calculated creatinine clearance < 60 mL/min; OR ;b. Liver function tests more than twice the upper limit of normal; OR;c. Serum bilirubin more than 1.5 times the upper limit of normal;29. Subjects with a medical diagnosis of major depression as defined by
the DSM-V Criteria for Major Depressive Disorder (MDD).

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):	16-08-2017
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sodium Oxybate for Extended Release Oral Suspension
Generic name:	Sodium Oxybate for Extended Release Oral Suspension

Ethics review

Approved WMO

Date:	12-07-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	09-11-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	10-01-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	13-03-2017
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-06-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-11-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	01-12-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	29-05-2018
Application type:	Amendment

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2016-000359-29-NL
CCMO	NL57991.058.16