A single dose, randomized, four-way cross-over, bioavailability and food interaction study of PedPRM (Pediatric Prolonged Release Melatonin, Neurim Pharmaceuticals Ltd) and Circadin® tablets in healthy male and female volunteers.

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Primary Objective- To demonstrate dose proportionality between 1 mg and 5 mg of PedPRM (Neurim Pharmaceuticals Ltd.) following a single oral dose in healthy male and female volunteers (treatment A and C), under fed conditions.Secondary Objectives-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sleep disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON44644

Source
ToetsingOnline

Brief title
PedPRM bioavailability and food interaction study.

Condition

- Sleep disorders and disturbances

Synonym
Insomnia, sleeping disorder

Research involving
Human

Sponsors and support

Primary sponsor: Neurim Pharmaceuticals Ltd
Source(s) of monetary or material Support: Neurim Pharmaceuticals Ltd.

Intervention

Keyword: Bioavailability, Food interaction, Healthy volunteers, Melatonin

Outcome measures

Primary outcome

Safety and tolerability endpoints

* Adverse events which will be summarized by treatment, and will be categorized in subsets of all treatment-emergent AEs, and of all treatment-related AEs.

* Clinical laboratory and vital signs which will be summarized by treatment and change from baseline.

Pharmacokinetic Endpoints

A 24-hour individual baseline profile of plasma and saliva melatonin concentrations will be measured. PK parameters of PedPRM or Circadin® will be calculated after endogenous level subtraction.

Primary endpoints are the following pharmacokinetic (PK) parameters:

* AUC0-* PedPRM.

* Cmax PedPRM.

Secondary outcome

Secondary PK endpoints include:

* AUC0-* Circadin® and Cmax Circadin®.

* Other pharmacokinetic parameters derived from serum samples

including AUC0-t, tmax, kel, t1/2, clearance (CL/F), and Vd/F.

* Pharmacokinetic parameters derived from saliva samples (e.g. AUC0-

*, AUC0-t, Cmax and tmax).

Study description

Background summary

Circadin®, prolonged-release melatonin (2 mg), is a melatonin receptor agonist and is registered for treatment of primary insomnia in many countries globally. Children with neurodevelopmental disorders have difficulties swallowing normal tablets like Circadin®. Moreover, crushing the Circadin® tablets would make them act as an immediate release formulation, losing their prolonged release profile which results in sleep maintenance effects. Neurim Pharmaceuticals Ltd. developed an age appropriate formulation (PedPRM, 1 and 5 mg minitablets) that would be suitable for children that have difficulties in swallowing, that would maintain the prolonged release profile and would allow titration of the dose, if required.

Study objective

Primary Objective
- To demonstrate dose proportionality between 1 mg and 5 mg of PedPRM (Neurim Pharmaceuticals Ltd.) following a single oral dose in healthy male and female volunteers (treatment A and C), under fed conditions.

Secondary Objectives
- To assess the correlation between saliva and plasma concentrations following a single dose of 1 mg PedPRM (treatment A).
- To investigate a potential food effect on the bioavailability following a single dose of 5 mg PedPRM (treatment C and D).
- To assess pharmacokinetic comparability between Circadin® and PedPRM treatment (treatment A, B and C).

Study design

This is a single dose, randomized, four-way cross-over, bioavailability and food interaction study of PedPRM (Neurim Pharmaceuticals Ltd.) and Circadin®

tablets in healthy male and female volunteers. Subjects who meet the entry criteria will be randomly assigned to one of the following four treatment sequences:

Sequence 1 A B C D
Sequence 2 C A D B
Sequence 3 B D A C
Sequence 4 D C B A

Treatment A: A single dose of 1 mg PedPRM, administered to the subjects in a fed condition.
Treatment B: A single dose of 2 mg Circadin®, administered to the subjects in a fed condition.
Treatment C: A single dose of 5 mg PedPRM, administered to the subjects in a fed condition.
Treatment D: A single dose of 5 mg PedPRM, administered to the subjects in a fasted condition.

Prior to the start of the first treatment period, baseline melatonin plasma levels will be measured for each subject during a period of 24 hours. After each dose administration, safety and pharmacokinetic data will be collected and reviewed up to approximately 24 hours post-dose.

Intervention

Investigational drug:
1 mg PedPRM (Neurim Pharmaceuticals Ltd., tablet), administered to the subjects in a fed state.
5 mg PedPRM (Neurim Pharmaceuticals Ltd., tablet), administered to the subjects in a fed and fasted state.

Comparative drug:
2 mg Circadin® (tablet), administered to the subjects in a fed state.

Study burden and risks

Adverse reactions related to the use of Circadin® that have been reported occasionally (0.1 * 1%) include nervosity, feeling restless, insomnia, having nightmares and dizziness. All adverse events are considered well-manageable particularly when the study is performed in a dedicated research unit. Moreover the safety of PedPRM in the clinical study is comparable to that of Circadin® in adults.

The subjects will be screened thoroughly prior to study enrolment. In addition, subjects will also be monitored closely during the conduct of the study to

minimize the risks.

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. Signed informed consent prior to any study-mandated procedure.
2. Healthy male or female subjects, 18 to 55 years of age, inclusive at screening.
3. Body mass index (BMI) between 18 and 30 kg/m2, inclusive at screening.
4. All women of child bearing potential must practice effective contraception during the study and be willing and able to continue contraception for at least 90 days after the final administration of study treatment. All males must practice effective contraception and abstain from sperm donation during the study and be willing and able to continue contraception and abstention from sperm donation for at least 90 days after the final administration of study treatment.

5. Has the ability to communicate well with the investigator in the Dutch language and willing to comply with the study restrictions.

Exclusion criteria

1. A history of gastrointestinal disorder likely to influence drug absorption
2. Evidence of renal, hepatic, cardiovascular or metabolic dysfunction or any active or chronic disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would pose an unacceptable risk to the subject in the opinion of the investigator (following a detailed medical history, physical examination, vital signs (systolic and diastolic blood pressure, pulse rate, body temperature) and12-lead electrocardiogram (ECG)). Minor deviations from the normal range may be accepted, if judged by the investigator to have no clinical relevance.
3. Clinically significant abnormalities, as judged by the investigator, in laboratory test results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant for healthy subjects.
4. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab), or human immunodeficiency virus antibody (HIV Ab) at screening.
5. Use of melatonin (Circadin®, food supplement, pharmacy preparation) within 4 weeks before first dose administration.
6. Use of any medications (prescription or over-the-counter [OTC]), within 14 days of dose administration, or less than 5 half-lives (whichever is longer). An exception is paracetamol (up to 2 g/day). Other exceptions will only be made if the rationale is clearly documented by the investigator.
7. Use of any vitamin, mineral, herbal, and dietary supplements within 7 days of dose administration, or less than 5 half-lives (whichever is longer). Exceptions will only be made if the rationale is clearly documented by the investigator
8. Current or previous clinically relevant neurological disorders or neurosurgery.
9. Current or previous clinically relevant history of psychiatric disorders or sleep-wake disorders.
10. Current or previous clinically relevant history of drug or alcohol abuse.
11. Current or previous clinically relevant history of chronic headache or migraine.
12. A history of drug or food allergies or other clinically significant allergies (e.g. asthma, hay fever, neurodermatitis).
13. A history of hypersensitivity and/or idiosyncrasy to any of the test compounds or excipients employed in this study.
14. Participation in an investigational drug or device study within 3 months prior to dose administration or more than 4 times a year.
15. Night-shift worker or subjects with a significantly shifted diurnal activity pattern.
16. Subjects who have traveled across 3 different time zones within 1 week prior to screening or baseline.
17. Following a diet, e.g. kosher, halal, vegetarian, vegan or medically prescribed diet.
18. Positive test for drugs of abuse or alcohol at screening or pre-dose.

19. Smoker of more than 5 cigarettes per day within one month prior to screening or who use tobacco products equivalent to more than 5 cigarettes per day.
20. Excessive consumption of xanthine-containing products (more than eight cups of coffee or equivalent per day).
21. Loss or donation of blood over 500 mL within three months prior to screening.
22. If a woman: pregnant, breast-feeding, or planning to become pregnant during the study.
23. Any known factor, condition, or disease that might interfere with treatment compliance, study conduct or interpretation of the results such as drug or alcohol dependence or psychiatric disease in the opinion of the investigator.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-11-2017
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Circadin®
Generic name:	Melatonin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-003815-20-NL
CCMO	NL63414.056.17