A Randomized, Placebo-Controlled Study to Investigate the Efficacy and Safety of Circadin® To Alleviate Sleep Disturbances in Children with Neurodevelopment Disabilities.

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To compare the treatment effect of Circadin 2/5 mg to that of placebo on sleep maintenance (TST) as assessed by the Sleep and Nap Diary after 13 weeks of double-blind treatment.

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

Summary

ID

NL-OMON41494

Source
ToetsingOnline

Brief title
Not applicbale

Condition

- Sleep disturbances (incl subtypes)

Synonym
Sleep disorders; Sleep problems

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Children, Sleep Disturbances

Outcome measures

Primary outcome

The primary efficacy parameter is TST time as assessed by a Sleep and Nap Diary after the 13-week, double-blind treatment period.

Secondary outcome

* Sleep latency as assessed by a Sleep and Nap Diary after 13 weeks (Week 15) of double blind treatment
* Duration of wake after sleep onset from the Sleep and Nap Diary after 13 weeks (Week 15) of double blind treatment
* Number of awakenings from the Sleep and Nap Diary after 13 weeks (Week 15) of double blind treatment
* Longest sleep period from the Sleep and Nap Diary after 13 weeks (Week 15) of double blind treatment
* Social functioning at home, in school, and in community settings as assessed by the CGAS after 13 weeks (Week 15) of double blind treatment
* Behavior at home and in school as assessed by the SDQ after 13 weeks (Week 15) of double blind treatment
* Number of dropouts during the 13 week (Week 15) double blind treatment period

* Assessment of sleep parameters by actigraphy after 13 weeks (Week 15) of

double blind treatment

Study description

Background summary

Sleep disturbance is one of the most common complaints in children with autism spectrum disorder (ASD), mental retardation or other developmental delays. High prevalence for moderate sleep disturbances in these child populations are associated with significant sleep problems and subsequent distress for the families of these children, which in many cases, lead to the decision to institutionalize the children. Specifically, a frequent cause of families giving up their care is discontinuous sleep with frequent awakenings throughout the night. There is a growing body of evidence on abnormal melatonin secretion in children with neurodevelopmental disorders, which prompted the use of melatonin to treat sleep disorders in these populations. Several exploratory studies and case reports have led to strong consensus among researchers that exogenous melatonin is beneficial for treating chronic sleep disturbances of children who have neurodevelopmental and neuropsychiatric difficulties.

Study objective

To compare the treatment effect of Circadin 2/5 mg to that of placebo on sleep maintenance (TST) as assessed by the Sleep and Nap Diary after 13 weeks of double-blind treatment.

Study design

This is a randomized placebo controlled study in children diagnosed with autism spectrum disorders (ASDs) and neurodevelopmental disabilities caused by neurogenetic diseases. Children will have a documented history of these disorders, as confirmed or consistent with the International Classification of Diseases (ICD 10) or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Text Revision; DSM 5/4) criteria, having International Classification of Sleep Disorders (ICSD) criteria based sleep disturbances modified to take into account the uniqueness of insomnia in the pediatric population at screening. The children will undergo 4 weeks of basic sleep hygiene and behavioral intervention, which will serve as a wash out period from any hypnotics; a gradual withdrawal will take place during the first 2 weeks and a complete withdrawal of disallowed medications will take place during the last 2 weeks.
Children who are still found to be eligible for the study after the 4 week,

basic sleep hygiene and behavioral intervention wash out period, will continue in a 2 week single blind (SB) placebo run in period. In order to be eligible for the 2 week SB placebo run-in period, the patients will not have responded to sleep hygiene and behavioral intervention during the first 4 weeks and therefore will not need to continue this therapy during the study. Children with a documented history of sleep hygiene and behavioral intervention, who are still found eligible, will enter directly into the 2 week SB placebo run in period. After the 4 week sleep hygiene wash out and 2 week SB placebo run in periods, children who are still found eligible for study participation will be randomized in a 1:1 ratio to receive either Circadin® 2 mg or placebo for 3 weeks in a double blind treatment period. After 3 weeks of treatment, on the last day of Week 5 ±3 days (Visit 3), sleep variables will be assessed to determine if dose modification (an increase to 5 mg) is required. Children will then continue on 2 or 5 mg of Circadin® or placebo for an additional double blind period of 10 weeks. This double blind period will be followed by an open label period of 13 weeks. At the end of the 13 weekopen label period on the last day of Week 28 ±3 days (Visit 5), sleep variables will be assessed to determine if a potential additional dose modification (an increase to 5 mg or 10 mg) is necessary (If a dose increase is decided upon, the dose increase should be from 2 mg to 5 mg, or from 5 mg to 10 mg). Children will continue at 2, 5, or 10 mg Circadin® in an open label period for another 78 weeks of follow up, which will include continuous safety monitoring, and 2 efficacy assessment time points at Weeks 41 and 54. The study will end with a 2 week SB placebo run out period.
Each patient will participate in the study until the end of the second open label safety follow up period, and 2 week run out period. Study duration will be 112 weeks, including the 4 week wash out period with sleep hygiene and behavioral intervention.
Circadin and placebo are to be administered orally, 1 portion of minitablets daily, taken postprandial at 0.5 to 1hour before desired bedtime (bedtime should be age appropriate bedtime). The minitablets should be swallowed whole and should not be crushed or halved.
A minimum of 90 children are expected to complete the double-blind and first open-label period. A minimum of 50 children are expected to complete the second open-label safety follow-up period.

Intervention

Children who are still found eligible for the study after the 4-week, basic sleep hygiene and behavioral intervention will continue in a 2-week, single-blind, placebo run-in period. Children with a documented history of sleep hygiene and behavioral intervention, who are still found eligible, will enter directly into a 2-week, single-blind, placebo run-in period. After these 2 periods, children who are still found eligible for study participation will be randomized in a 1:1 ratio to receive either Circadin 2 mg or placebo for 3 weeks. After 3 weeks of treatment, sleep variables will be assessed to determine if dose modification (an increase to 5 mg) is required. Children will

then continue on the selected dose of Circadin (2 or 5 mg) or placebo for an additional double-blind period of 10 weeks. This double-blind period will be followed by an open-label period of 13 weeks. Children will continue in the study for another 78 weeks of follow-up with continuous safety monitoring and another 2 efficacy assessment time points (at Weeks 41 and 54). At the beginning of the additional 78 week open-label period (Visit 5), a second titration opportunity will be introduced (an increase to 10 mg). The study will end with a 2-week single-blind placebo run-out period.
Each patient will participate in the study until the end of the second open-label safety follow-up period, and 2 weeks run-out.

Study burden and risks

The study is designed to investigate if Circadin helps children with autistic spectrum disorders and neurodevelopmental disabilities caused by neurogenetic diseases to better fall asleep and to maintain sleep during the night. The study consists of:
* 4 weeks sleep hygiene and behavioural intervention (which means taking no medication - will only be performed if not done previously)
* 2 weeks single blind (only the participant will not know what they are taking) placebo 'wash out' to eliminate certain previous treatments (hypnotics) which are not allowed during the trial
* 13 weeks double blind (neither the participants or the study team know which medication is being taken) during which patients will receive either Circadin or placebo (ratio 1:1); the placebo control is needed to objectively demonstrate the effects of Circadin. This phase will be double blinded to avoid any bias.
* 91 weeks of treatment with Circadin (no placebo control anymore)
* 2 weeks single blind placebo run out (to wash out Circadin)

During the study there will be 10 visits during which the following procedures will be performed:
* Check-ups similar to those done for regular medical care including vital signs and check for concomitant medications.
* Assessment of puberty status; For female participants, information about birth control, including a pregnancy test (at certain visits only)
* Providing and checking diaries and actiwatches (diaries have to be completed daily at home; Actiwatches have to be worn on the wrist at night to measure activity during the night)
* Inmterview with the parents/guardians for completion of questionnaires (7) by the inverstigator.
* Providing study medication (the start dose for Circadin is 2 mg and can be increased to up to 10 mg if needed); the medication has to be taken once daily before bed time.
No blood samples will be taken for this study.

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

1.1. Must be children 2 to 17.5 years of age at Visit 2 who comply with taking the study drug
2. Must have written informed consent provided by a legal guardian and assent (if needed)
3. Must have a documented history of ASD according to or consistent with the ICD 10 or DSM 5/4 criteria, or neurodevelopmental disabilities caused by neurogenetic diseases (i.e., Smith Magenis syndrome, Angelman syndrome, Bourneville*s disease [tuberous sclerosis]) as confirmed by case note review showing that diagnosis was reached through assessment by a community pediatrician or pediatric neurologist or other health care professionals experienced in the diagnosis who took into account early developmental history and school records.
4. Must have current sleep problems including: a minimum of 3 months of impaired sleep defined as <=<6 hours of continuous sleep and/or ><=0.5 hour sleep latency from light off

in 3 out of 5 nights based on parent reports and patient medical history. (The maintenance and latency problems do not necessarily have to be in the same 3 nights of the week.)
5. May be on a stable dose of non excluded medication for 3 months, including anti epileptics, anti depressants (selective serotonin reuptake inhibitor [SSRIs]), stimulants, all mood changing drugs and * blockers. (Only morning administration of * blockers is allowed since * blockers at night have the potential to reduce endogenous melatonin levels and might cause disturbed sleep)
6. The sleep disturbance is not due to the direct physiological effects of any concomitant medications such as SSRIs, stimulants, etc.
After completing 4 weeks of sleep hygiene training and 2 weeks of placebo run in, patients will be eligible to continue the study if they comply with the following:
* Continue to fulfill sleep problem criteria (see Inclusion Criterion 4) based on the completed Sleep and Nap Diary entered into the electronic case report form
* Parents demonstrate compliance in Sleep and Nap Diary completion (5 out of 7 nights). Compliance means that in at least 5 out of 7 nights per week (total of 2 weeks before each scheduled visit) the parents complete the diary pages with all mandatory questions (mandatory questions are marked with an asterisk [*] in Appendix 1).
* Continue to fulfil all other eligibility criteria

Exclusion criteria

1. Have had treatment with any form of melatonin within 2 weeks prior to Visit 1
2. Have a known allergy to melatonin or lactose
3. Have a known moderate to severe sleep apnea
4. Have an untreated medical/ineffectively treated/psychological condition that may be the etiology of sleep disturbances
5. Did not respond to previous Circadin® therapy based on past medical history records in the last 2 years
6. Are taking or have been taking disallowed medication within 2 weeks prior to Visit 1 (Section 7.1)
7. Are females of child bearing potential that are not using contraceptives and/or breastfeeding and that are sexually active (Abstinence is an acceptable method of contraception.)
8. Pregnant females
9. Are currently participating in a clinical trial or have participated in a clinical trial involving medicinal product within the last 3 months prior to the study (this does not include patients who participated in the Phase I PK study who can be already included in the study)
10. Children with known renal or hepatic insufficiency

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):	16-02-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	30-01-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	24-03-2014
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	16-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-08-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-01-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-05-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2013-001832-23-NL
ClinicalTrials.gov	NCT01906866
CCMO	NL46261.101.14