



## Clinical trial results:

### A RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF CIRCADIN® TO ALLEVIATE SLEEP DISTURBANCES IN CHILDREN WITH NEURODEVELOPMENTAL DISABILITIES

#### Summary

EudraCT number	2013-001832-23
Trial protocol	Outside EU/EEA FI GB NL FR
Global end of trial date	28 February 2018

#### Results information

Result version number	v1 (current)
This version publication date	12 September 2018
First version publication date	12 September 2018

#### Trial information

##### Trial identification

Sponsor protocol code	NEU_CH_7911
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01906866
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Neurim Pharmaceuticals
Sponsor organisation address	Habarzel 27, Tel Aviv, Israel,
Public contact	VP Clinical and Regulatory Affairs, Neurim Pharmaceuticals (1991) Ltd., Talin@neurim.com
Scientific contact	VP Clinical and Regulatory Affairs, Neurim Pharmaceuticals (1991) Ltd., talin@neurim.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000440-PIP02-11
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	25 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2018
Global end of trial reached?	Yes
Global end of trial date	28 February 2018
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

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

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Regulatory reason
Long term follow-up duration	21 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Netherlands: 20
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United States: 200
Country: Number of subjects enrolled	Finland: 5
Worldwide total number of subjects	267
EEA total number of subjects	67

Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	174
Adolescents (12-17 years)	93

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment started on December 2013 first patient first visit was on January 2014 last patient last visit on February 28th 2018

### Pre-assignment

Screening details:

A screening visit was conducted 4 weeks prior to randomization. Children who did not have a documented history of sleep hygiene and behavioral intervention at screening underwent 4 weeks of basic sleep hygiene and behavioral intervention (Weeks -4 to 0). This period also served as a wash-out period from any hypnotics; a gradual withdrawal took place

### Period 1

Period 1 title	placebo run-in
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

### Arms

Arm title	placebo
Arm description: single blind	
Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

2 mini-tablets 0.5-1 hour before bedtime.

Number of subjects in period 1	placebo
Started	267
Completed	125
Not completed	142
non eligible	142

### Period 2

Period 2 title	double blind
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor
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## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Experimental
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Arm description:

Experimental product - 2 mg or 5 mg

Arm type	Experimental
Investigational medicinal product name	Melatonin prolonged release
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

2 mg for the first 3 weeks double blind period. After 3 weeks of double-blind treatment, on the last day of Week 5  $\pm$  3 days (Visit 3), sleep variables were assessed to determine if dose modification (an increase to 5 mg) was required. Children who did not improve by 60 minutes in TST, sleep latency or both at this time were eligible for dose increase. Children then continued on 2 or 5 mg of Circadin® or placebo for the remaining 10 weeks of double-blind treatment, with an efficacy assessment visit at Week 15 (Visit 4).

<b>Arm title</b>	placebo
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Arm description:

placebo

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

2 / 5 / 10 mini-tablets 0.5-1 hour before bedtime.

<b>Number of subjects in period 2</b>	Experimental	placebo
Started	60	65
Completed	51	44
Not completed	9	21
Consent withdrawn by subject	3	13
Physician decision	1	1
Adverse event, non-fatal	1	-
other	-	2
Lost to follow-up	2	5
Protocol deviation	2	-

**Period 3**

Period 3 title	open-label
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	experimental
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Arm description:

prolonged release melatonin 2, 5 or 10 mg

Arm type	Experimental
Investigational medicinal product name	prolonged release melatonin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

2 or 5 or 10 mg of prolonged release melatonin pediatric formulation; 0.5-1 hour before bed-time ;

Investigational medicinal product name	prolonged release melatonin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

2 or 5 or 10 mg of prolonged release melatonin pediatric formulation; 0.5-1 hour before bed-time ;

<b>Number of subjects in period 3</b>	experimental
Started	95
Completed	74
Not completed	21
consent withdrawn by parents	9
Consent withdrawn by subject	3
Physician decision	2
Adverse event, non-fatal	3
other	1
Lost to follow-up	1
Protocol deviation	2

**Period 4**

Period 4 title	single-blind run-out
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

**Arms**

<b>Arm title</b>	placebo
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Arm description:

placebo run-out

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Buccal use

Dosage and administration details:

two, five or ten mini-tablets buccal use 0.5-1 hour before bedtime for two weeks of the period

<b>Number of subjects in period 4</b>	placebo
Started	74
Completed	73
Not completed	1
Lost to follow-up	1

## Baseline characteristics

### Reporting groups

Reporting group title	placebo run-in
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Reporting group description: -

Reporting group values	placebo run-in	Total	
Number of subjects	267	267	
Age categorical			
Age 2 -18 years old			
Units: Subjects			
Children (2-11 years)	174	174	
Adolescents (12-17 years)	93	93	
Age continuous			
mean age			
Units: years			
arithmetic mean	8.6		
standard deviation	± 4.12	-	
Gender categorical			
Units: Subjects			
Female	71	71	
Male	196	196	

### Subject analysis sets

Subject analysis set title	FAS
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Subject analysis set type	Full analysis
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Subject analysis set description:

All patients in the Safety Analysis Set who satisfied all major entry criteria (Inclusion Criteria 1-5) and who had a valid mean TST result recorded for baseline and at least one post-baseline period assessment during the double blind phase.

Patients were classified according to randomized treatment. This analysis set was used for all efficacy analyses

Reporting group values	FAS		
Number of subjects	119		
Age categorical			
Age 2 -18 years old			
Units: Subjects			
Children (2-11 years)	78		
Adolescents (12-17 years)	41		
Age continuous			
mean age			
Units: years			
arithmetic mean	8.7		
standard deviation	± 4.15		
Gender categorical			
Units: Subjects			
Female	30		



Male	89		
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## End points

### End points reporting groups

Reporting group title	placebo
Reporting group description:	single blind
Reporting group title	Experimental
Reporting group description:	Experimental product - 2 mg or 5 mg
Reporting group title	placebo
Reporting group description:	placebo
Reporting group title	experimental
Reporting group description:	prolonged release melatonin 2, 5 or 10 mg
Reporting group title	placebo
Reporting group description:	placebo run-out
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	All patients in the Safety Analysis Set who satisfied all major entry criteria (Inclusion Criteria 1-5) and who had a valid mean TST result recorded for baseline and at least one post-baseline period assessment during the double blind phase. Patients were classified according to randomized treatment. This analysis set was used for all efficacy analyses

### Primary: total sleep time

End point title	total sleep time
End point description:	<ul style="list-style-type: none"><li>To compare the treatment effect of Circadin® 2/5 mg minitablets to that of placebo on total sleep time (TST) as assessed by the Sleep and Nap Diary after 13 weeks of double-blind treatment</li></ul>
End point type	Primary
End point timeframe:	13 weeks

End point values	Experimental	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: minutes				
arithmetic mean (standard error)	51.03 (± 10.46)	18.71 (± 10.82)		

<b>Attachments (see zip file)</b>	Total Sleep Time/Figure 2Change from baseline in mean total
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## Statistical analyses

<b>Statistical analysis title</b>	MMRM
Comparison groups	Experimental v placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

<b>Statistical analysis title</b>	MMRM
Statistical analysis description: mixed-effects model for repeated-measures	
Comparison groups	Experimental v placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	32.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.38
upper limit	62.26
Variability estimate	Standard error of the mean
Dispersion value	15.1

## Secondary: Sleep Latency

End point title	Sleep Latency
End point description: <ul style="list-style-type: none"><li>To compare the treatment effect of Circadin® 2/5 mg minitabets to that of placebo on sleep latency as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment</li></ul>	
End point type	Secondary
End point timeframe: 13 weeks	

End point values	Experimental	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	61		
Units: minutes				
arithmetic mean (standard error)	-37.77 ( $\pm$ 6.816)	-12.57 ( $\pm$ 7.005)		

<b>Attachments (see zip file)</b>	Sleep Latency/Figure 3Change from baseline in mean sleep
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## Statistical analyses

<b>Statistical analysis title</b>	MMRM
Statistical analysis description: mixed-effects model for repeated-measures	
Comparison groups	Experimental v placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-25.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.61
upper limit	-5.8
Variability estimate	Standard error of the mean
Dispersion value	9.787

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

104 weeks

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18
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### Reporting groups

Reporting group title	placebo DB
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Reporting group description:

adverse events during the double blind period on placebo 13 weeks

Reporting group title	prolonged release melatonin OL
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Reporting group description:

Prolonged release melatonin during the open label period 91 weeks

Reporting group title	prolonged release melatonin DB
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Reporting group description:

prolonged release melatonin double blind period 13 weeks

Serious adverse events	placebo DB	prolonged release melatonin OL	prolonged release melatonin DB
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 65 (1.54%)	6 / 95 (6.32%)	0 / 60 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 95 (1.05%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
AGGRESSION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 95 (1.05%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OPPOSITIONAL DEFIANT DISORDER			
subjects affected / exposed	0 / 65 (0.00%)	1 / 95 (1.05%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abnormal behaviour			
subjects affected / exposed	0 / 65 (0.00%)	1 / 95 (1.05%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	1 / 65 (1.54%)	0 / 95 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 65 (1.54%)	0 / 95 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EYE INFECTION			
subjects affected / exposed	0 / 65 (0.00%)	1 / 95 (1.05%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS MEDIA ACUTE			
subjects affected / exposed	0 / 65 (0.00%)	1 / 95 (1.05%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	placebo DB	prolonged release melatonin OL	prolonged release melatonin DB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 65 (76.92%)	80 / 95 (84.21%)	51 / 60 (85.00%)
Nervous system disorders			
SOMNOLENCE			
subjects affected / exposed	8 / 65 (12.31%)	24 / 95 (25.26%)	17 / 60 (28.33%)
occurrences (all)	8	31	18
HEADACHE			
subjects affected / exposed	4 / 65 (6.15%)	12 / 95 (12.63%)	8 / 60 (13.33%)
occurrences (all)	4	12	8

DIZZINESS subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	6 / 95 (6.32%) 8	0 / 60 (0.00%) 0
General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all)  PYREXIA subjects affected / exposed occurrences (all)  HANGOVER subjects affected / exposed occurrences (all)	 12 / 65 (18.46%) 13  4 / 65 (6.15%) 4  3 / 65 (4.62%) 4	 25 / 95 (26.32%) 33  7 / 95 (7.37%) 8  7 / 95 (7.37%) 8	 15 / 60 (25.00%) 19  5 / 60 (8.33%) 5  3 / 60 (5.00%) 4
Gastrointestinal disorders VOMITING subjects affected / exposed occurrences (all)  DIARRHOEA subjects affected / exposed occurrences (all)  NAUSEA subjects affected / exposed occurrences (all)  CONSTIPATION subjects affected / exposed occurrences (all)	 10 / 65 (15.38%) 10  3 / 65 (4.62%) 4  1 / 65 (1.54%) 1  1 / 65 (1.54%) 1	 20 / 95 (21.05%) 33  3 / 95 (3.16%) 3  9 / 95 (9.47%) 11  8 / 95 (8.42%) 11	 8 / 60 (13.33%) 11  3 / 60 (5.00%) 3  4 / 60 (6.67%) 4  3 / 60 (5.00%) 4
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)  DYSPNOEA subjects affected / exposed occurrences (all)  ASTHMA subjects affected / exposed occurrences (all)	 5 / 65 (7.69%) 5  4 / 65 (6.15%) 4  1 / 65 (1.54%) 1	 16 / 95 (16.84%) 27  10 / 95 (10.53%) 10  6 / 95 (6.32%) 8	 7 / 60 (11.67%) 7  6 / 60 (10.00%) 6  1 / 60 (1.67%) 1

RHINORRHOEA subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	5 / 95 (5.26%) 5	2 / 60 (3.33%) 2
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 3	10 / 95 (10.53%) 10	3 / 60 (5.00%) 3
Psychiatric disorders MOOD SWINGS subjects affected / exposed occurrences (all)	11 / 65 (16.92%) 12	17 / 95 (17.89%) 24	10 / 60 (16.67%) 10
AGITATION subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 8	8 / 95 (8.42%) 10	11 / 60 (18.33%) 12
ANXIETY subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	6 / 95 (6.32%) 8	0 / 60 (0.00%) 0
AGGRESSION subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	5 / 95 (5.26%) 5	0 / 60 (0.00%) 0
Infections and infestations UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 8	14 / 95 (14.74%) 24	9 / 60 (15.00%) 9
INFLUENZA subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	8 / 95 (8.42%) 8	0 / 60 (0.00%) 0
OTITIS MEDIA subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	7 / 95 (7.37%) 8	0 / 60 (0.00%) 0
GASTROENTERITIS subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	6 / 95 (6.32%) 8	0 / 60 (0.00%) 0
NASOPHARYNGITIS subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0	6 / 95 (6.32%) 8	0 / 60 (0.00%) 0



SINUSITIS			
subjects affected / exposed	0 / 65 (0.00%)	5 / 95 (5.26%)	0 / 60 (0.00%)
occurrences (all)	0	5	0

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29096777>

<http://www.ncbi.nlm.nih.gov/pubmed/30132686>