18 December 2014
EMA/85025/2015
Committee for Medicinal Products for Human Use (CHMP)

Circadin

(melatonin)

Procedure no.: EMA/H/C/695/P46/019

Marketing authorisation holder (MAH): RAD Neurim Pharmaceuticals EEC Ltd.

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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1. Introduction

On 8 September 2014, the MAH submitted a completed paediatric study for CHDR1219 (NEU child-PK), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the Measure 4 in agreed PIP (EMEA-000440-PIP02-11-M01; P/0117/02)

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that CHDR1219 (NEU child-PK) is part of a clinical development program. The variation application consisting of the full relevant data package (i.e containing several studies) is expected to be submitted by 02/18. A line listing of all the concerned studies is annexed below.

The studies should be listed by chronological date of completion.

Non clinical studies

Product Name: Circadin Active substance: Melatonin

Study title	Study number	Date of completion	Date of submission of final study report
Repeated dose (14 day) toxicity study by oral gavage with melatonin in juvenile rats	Measure 2 of the development program	29/11/2012	It is planned to submit it with measure 5 submission
Repeated dose toxicity and toxicokinetic study in juvenile rats with melatonin from weaning to sexual maturity.	Measure 3 of the development program	10/04/2013	It is planned to submit it with measure 5 submission

Clinical studies

Product Name: Circadin Active substance: Melatonin

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, pharmacokinetic cross over study of 2 mg and 10 mg prolonged release melatonin age-appropriate oral solid dosage form in chiidren with neurodevelopmental disorders with sleep disturbances from 2 years to less than 18 years.	Measure 4 of the development program	March 2014 (LPLV)	September 2014
Protocol Number: NEU_CH_7911 A Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Circadin® to Alleviate Sleep Disturbances in Children with Neurodevelopmental Disabilities – **first 28 week**	Measure 5 of the development program	February 2016 (LPLV) *(Currently agreed date is December 2014 – please see footnote below *)*	By August 2016 (within 6 months of study completion)
Protocol Number: NEU_CH_7911 A Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Circadin® to Alleviate Sleep Disturbances in Children with Neurodevelopmental Disabilities – **last OL 80 week**	Measure 6 of the development program	August 2017 (LPLV) *(Currently agreed date is May 2016 – please see footnote below *)*	February 2018 (within 6 months of study completion)

* As Neurim will not be able to meet the currently agreed timelines for measures 5 and 6, a request for modification of the PIP will be submitted to the PDCO in October 2014. This will include a request for changes to the relevant timelines, plus a request for Study 6 to be accepted as a FUM to a PUMA.

2.2. Information on the pharmaceutical formulation used in the study<ies>

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

CHDR1219 (NEU child-PK);

2.3.2. •Clinical study

CHDR1219 (NEU child-PK)

Description

Open label, Single Ascending Dose, Cross-over Study to Assess the Pharmacokinetics of Circadin® (Prolonged-Release Melatonin) Mini tablets in Children with Neurodevelopmental disorders and Sleep Disturbances

Methods

Objective(s)

- To establish the 24-hour baseline profile of endogenous saliva melatonin concentrations and urine 6-SMT excretion in children with neurodevelopmental disorders with sleep disturbances over the age of 2 and under the age of 18 years.

- To establish the concentration-time profile of saliva melatonin concentrations and 24 hour 6-SMT urine excretion after 2 and 10 mg Circadin® mini-tablets single dose administration in children with neurodevelopmental disorders with sleep disturbances over the age of 2 and under the age of 18 years.

- To evaluate the adverse event profile after a single dose of 2 or 10 mg Circadin® mini-tablets in children with neurodevelopmental disorders with sleep disturbances over the age of 2 and under the age of 18 years.

Study design

open-label, single ascending dose study of 2 and 10 mg Circadin® minitablets with a wash-out of ≥ 7 days.

Study population /Sample size

16 children (eight aged 2-10 years; eight aged 11-18 years) with autistic spectrum disorder (ASD), Smith-Magenis syndrome, Angelman syndrome or Tuberous Sclerosis Complex (Bourneville's disease) who suffer from sleep disturbances.

Treatments

Treatment arms will be (1) 2 mg Circadin (2 mini-tablets of 1 mg each), and (2) 10 mg Circadin (10 mini-tablets of 1 mg each).

Outcomes/endpoints

Endpoints of the study:

- 24-hour baseline profile of endogenous saliva melatonin concentrations and urine 6-SMT excretion (12 hours + 12 hours);

- Concentration-time profile of saliva melatonin concentrations and 24-hour 6-SMT urine excretion (12 hours + 12 hours) after intake of 2 or 10 mg Circadin® minitablets.

Statistical Methods

Planned sample size

The planned sample consists of 16 subjects (eight in the age group 2-10 years; eight in the age group 11-18 years).

Power calculation

This is an exploratory pharmacokinetic study in children with ASD or neurogenetic disorders. A formal power calculation has not been performed. However, based on previous experience, a sample size of 16 subjects should suffice for determination of PK parameters.

Statistical plan and methods to be employed

Results of questionnaires will be reported using descriptive statistics only. Adverse events will be listed as well as summarized by system organ class, dose level and treatment.

Pharmacometric analysis

Individual saliva melatonin profiles will be plotted and descriptive statistics per planned sampling time point and treatment will be provided, including mean, SD, minimum, maximum, and median.

Population pharmacokinetic modeling using NONlinear Mixed Effects Modeling (NONMEM) will be used to interpret the pharmacokinetic data. Effects of potential modulating factors like body weight or pubertal stage will be investigated. Individual PK parameters will be derived from the model, including (time to) peak concentration (Tmax, Cmax), area under the curve (AUC), clearance and elimination half-life (t1/2).

Selection of subjects to be included in the analysis

Before the data analysis, a data review will be done. This will allow identification of missing, unused, and spurious data. The data review will be an integral part of the report and includes the decisions on and documentation of the handling of the missing, unused, and spurious data. Data of all subjects participating in the study will be included in the analyses if the data can meaningfully contribute to the objectives of the study.

Reporting deviations from the original statistical plan

Deviations from the original statistical plan will be documented in the study report.

Results

Recruitment / Number analysed

A total of 16 subjects (12 male, 4 female) were enrolled in the study centre in the Netherlands. All subjects completed the study as planned.

The study was conducted from January 2013 to March 2014, with the first subject, first visit on 23 January 2013 and the first study drug administration on 7 February 2013. The last study drug administration was on 14 March 2013. The last follow up phone call was performed on 25 March 2014.

Baseline data

The demographic and key baseline characteristics of study subjects are summarised in Table 1. All subjects who were included in the study fulfilled the inclusion criteria and did not meet any of the exclusion criteria.

The study population was 75% male and 25% female. The mean age was 10.9 years (range 7 to 15 years), with a mean weight of 43.3 kg (range 26 to 67 kg). All subjects included in the study had autism spectrum disorder.

Table 1 Summary of subject population and disposition.

		Safety Population (n=16)		PK Population (n=14)		Sub-analysis Population (n=11)	
Demographic characteristics							
Sex (n and % of subjects)	Male	12	(75%)	10	(71%)	7	(64%)
	Female	4	(25%)	4	(29%)	4	(36%)
Age (years)	Mean (SD)	10.9	(2.4)	10.4	(2.2)	10.5	(2.3)
	Median (Range)	10.0	(7 to 15)	10.0	(7 to 15)	10.0	(7 to 15)
Baseline characteristics							
Weight	Mean (SD)	43.3	(13.1)	42.5	(13.4)	42.7	(13.9)
	Median (Range)	40.75	(26 to 67)	38.00	(26 to 67)	41.00	(26 to 67)
Pubertal stage (n and % of subjects)	Stage 1	8	(50%)	8	(57%)	6	(55%)
	Stage 2	3	(19%)	3	(21%)	3	(27%)
	Stage 3	1	(6%)	1	(7%)	1	(9%)
	Stage 4	1	(6%)	1	(7%)	0	-
	Stage 5	3	(19%)	1	(7%)	1	(9%)
Disease (n and % of subjects)	Autistic spectrum disorder	16	(100%)	14	(100%)	11	(100%)
	Angelman syndrome	0	-	0	-	0	-
	Smith-Magenis syndrome	0	-	0	-	0	-
	Tuberous sclerosis	0	-	0	-	0	-

Concomitant disease

All of the subjects had a recorded medical history. However, none of the anomalies reported affected their eligibility for the study.

Efficacy results

The endogenous levels of melatonin and its major metabolite 6-SMT in this patient group were generally low, with lower levels during the day compared to night hours. This confirms the low endogenous levels found in earlier studies in children with ASD.

The pharmacokinetic profile of the Circadin® mini tablets 2 mg was similar to the profile measured with the Circadin® 2 mg commercial tablet in adults demonstrating a prolonged release profile that mimics the endogenous profile of the hormone in healthy subjects.

Overall, this study demonstrated the safety, acceptability and prolonged-release profile of 2 mg and 10 mg Circadin® mini-tablets in school-aged children and adolescents with autistic spectrum disorder.

Measurements of treatment compliance

The investigator or his deputy supervised the drug administrations, which were specifically recorded in the CRF. The measurement of melatonin in saliva samples confirmed compliance.

Bioanalytical conduct

A total of 369 saliva samples were received frozen in good condition by ABL, the Netherlands; all were analyzed for melatonin. The final results are listed in Appendix 15.2. The analytical study report describes the accuracy, linearity, and precision of the analytical method employed. A total of 96 urine samples were received frozen in good condition by ABL, the Netherlands; all were analyzed for 6-SMT.

Pharmacokinetic results

Oral Contamination

A saliva sample was taken 2 minutes after administration to measure saliva contamination by melatonin. The sample taken after 2 minutes was not included in the PK analysis. Summary of saliva melatonin concentrations of the contamination sample are shown in Figure 1 and Table 2. Following administration of Circadin 2 mg and Circadin 10 mg, 3 and 8 samples were above the ULOQ, respectively. Following administration of Circadin 10 mg, 1 sample was below the LLOQ.

Figure 1 - Concentration of melatonin measured in saliva (contamination sample), PK population.

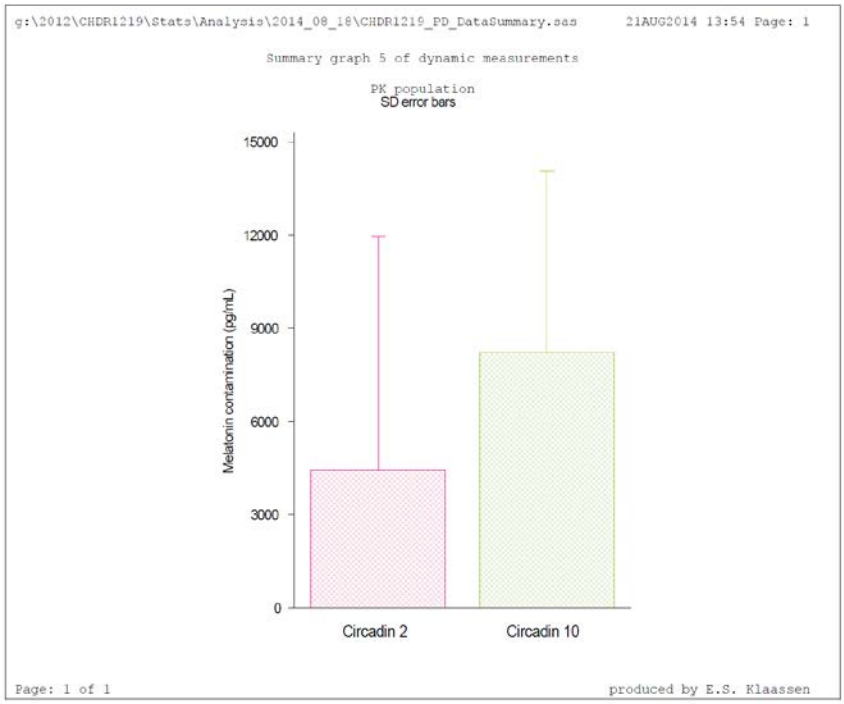

Table 2 Summary of melatonin contamination sample of melatonin measured in saliva, PK population.

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Summary 5 of dynamic measurements

PK population

Summary table: Melatonin contamination (pg/mL)

Treatment	N	Mean	SD	SEM	CV (%)	Median	Min	Max
Circadin 2	11	4441.545	7500.339	2261.437	168.9	1180.00	63.00	19700.00
Circadin 10	6	8219.167	5837.277	2383.058	71.0	9735.00	335.00	15400.00

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Endogenous melatonin and melatonin pharmacokinetics

Pharmacokinetic parameters of melatonin were calculated on the basis of the actual saliva-sampling time points. The summary figures are based on scheduled saliva-sampling time points.

For endogenous melatonin concentrations measured in the 24 hours prior to administration of Circadin mini-tablets, each individual had several observations above the LLOQ (2 pg/mL). For almost all subjects (14/16), melatonin levels were missing at time points between 23:00 PM and 7:00 AM, as samples were not taken because the subject was sleeping.

Lambda_z and its derived parameters (Term (t½), AUC_0_inf, PercAUCExtrap, CL_F,V_F) were excluded from analysis (Table 3) for the following subjects, as lambda could not be accurately estimated for these individuals.

Table 3 Excluded data based on Lambda_z

SubjectID	Treatment Code
6	Circadin 2
9	Circadin 2
9	Circadin 10
10	Circadin 2
10	Circadin 10
14	Circadin 2
14	Circadin 10

PK Population

Summaries of the PK parameters for the PK population of melatonin in saliva per treatment are presented in Table 4 (Circadin 2 mg), Table 5 (Circadin 10 mg). The plasma concentration-time profile of melatonin was characterized by rapid absorption and disposition (Table 4 and Table 5). The mean tmax was less than 2 hours for both 2 and 10 mg Circadin mini-tablets and concentrations remained elevated for several hours thereafter. Circadin exposure increased 5-fold with a 5-fold increase in dose saliva was dose-linear and apparent clearance in saliva was comparable between dose groups.

Table 4 Summary PK parameters of Circadin 2 mg, PK population

Parameter	mean	sd	median	min	max
Cmax (pg/ml)	965	1170	403	174	3690
tmax (hr)	1.57	0.762	1.02	0.967	3.03
Term (hr)	5.74	3.31	4.55	3.36	14.8
AUC_0_inf (pg*hr/ml)	2420	1100	2280	1050	4310

Table 5 Summary PK parameters of Circadin 10 mg, PK population

Parameter	mean	sd	median	min	max
Cmax (pg/ml)	3970	2830	3280	533	11000
tmax (hr)	1.37	0.640	1.00	0.967	3.03
Term (hr)	4.44	1.69	3.86	2.72	8.32
AUC_0_inf (pg*hr/ml)	13300	7680	10600	3450	27000

Endogenous 6-SMT levels and 6-SMT pharmacokinetics

Total 6-SMT amounts are provided in Figure 5 for the safety population and Figure 6 for the PK population.

Figure 5 Total 6-SMT measured in urine during baseline, safety population.

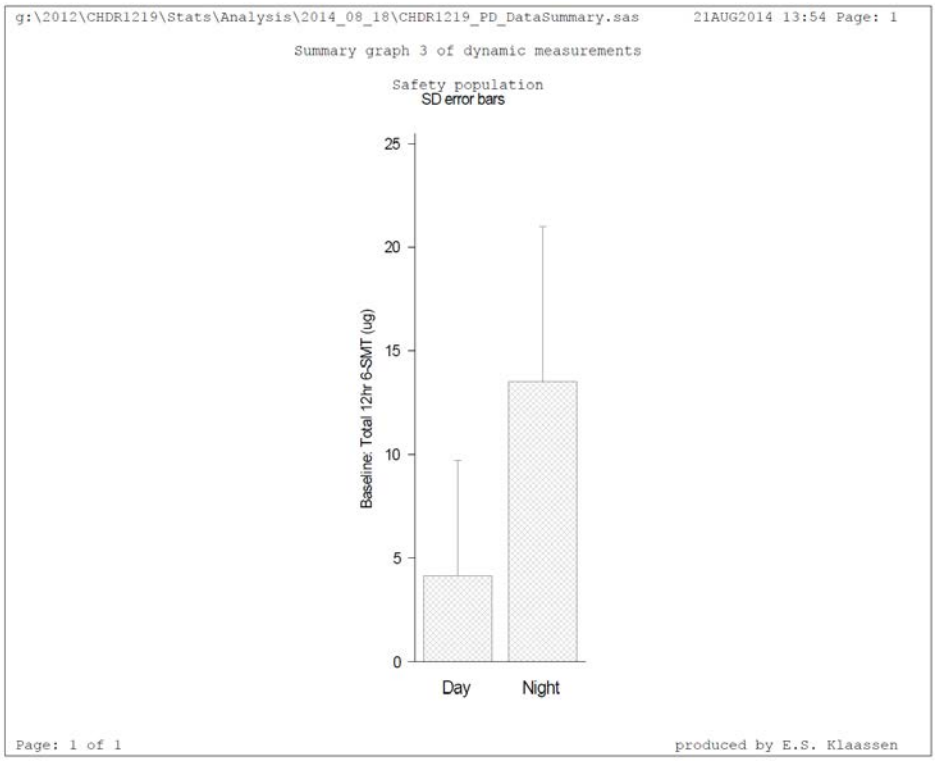
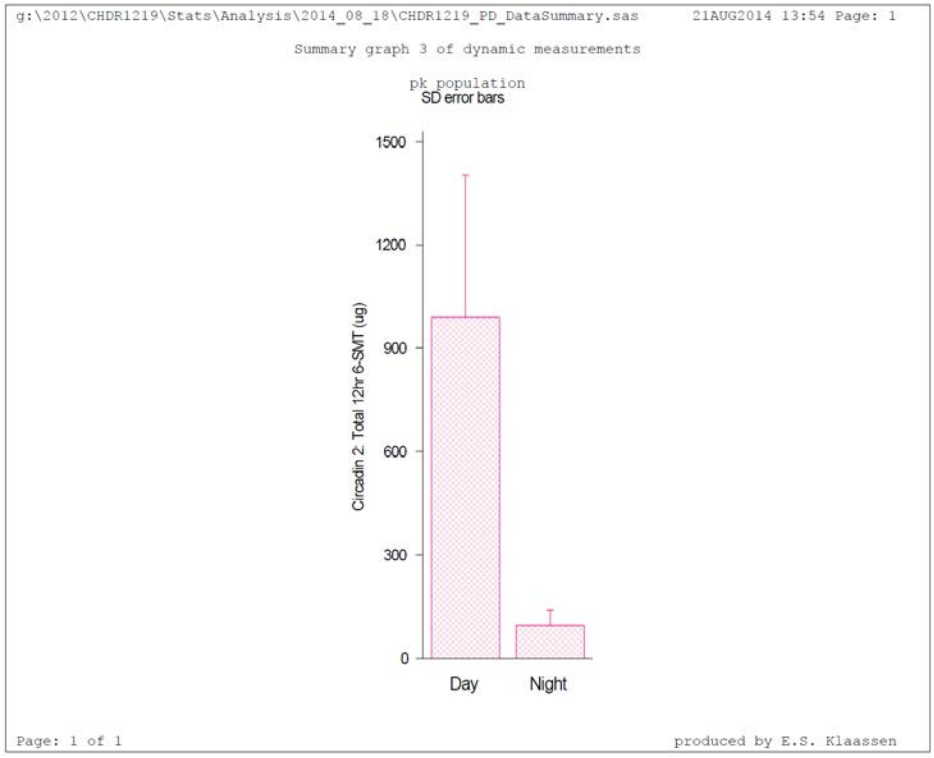


Figure 6 Total 6-SMT measured in urine following Circadin 2 mg, PK population.



For the safety population, the mean amount of total 6-SMT recovered from urine during the baseline period was 4.2 ug following the 0-12 hour collection period, during the daytime and 13.5 ug following the 12-24 hour collection period, during the night. For the PK population, following administration with Circadin 2 mg the mean amount of total 6-SMT recovered from urine was 989.5 ug following the 0-12 hour collection period and 95.3 ug following the 12-24 hour collection period.

Following dosing with Circardin 10 mg, many of the 6-SMT values were above the upper limit of quantification (ULOQ) during the collection period 0-12 hours follow dosing (further dilution of the samples was not validated). This reflects the expected extensive metabolism of melatonin and excretion of 6-SMT in the first 12 hours following dose administration.

Conclusions on pharmacokinetic results

Baseline melatonin concentrations were characteristic, being low in the morning and increased over 12 hours towards the evening yet showed overall low endogenous levels. These results were confirmed by baseline 6-SMT measured with lower amounts recovered during the day-time collection period compared with the night-time collection period. In the safety population, the mean 6-SMT levels during the day were 4.2 ug/12 daytime hours and 13.5 ug /12 night-time hours showing normal pattern of higher levels during the night compared to daytime but very low absolute endogenous levels.

Following Circadin administration, melatonin concentrations peaked within 2 hours after administration and remained elevated for several hours thereafter. The pharmacokinetic profile achieved in the saliva is similar to the profile achieved with Circadin tablets in adults and the elderly, i.e., the desired prolonged release profile is demonstrated in ASD children after 2 and 10 mg minitablet administration.

Circadin exposure derived from area under the curve (AUC) data was dose-linear and apparent clearance was approximately 1,000 L/hr and comparable between dose groups. Median apparent terminal half-life was comparable between 2 and 10 mg dose groups. The apparent volume of

distribution in saliva appeared to be smaller (with comparable clearance) with increasing dose. However, data regarding dose effects on this parameter should be interpreted with caution as the Area Under the Moment Curve (AUMC) was established only on a limited number of subjects.

Pharmacodynamic results

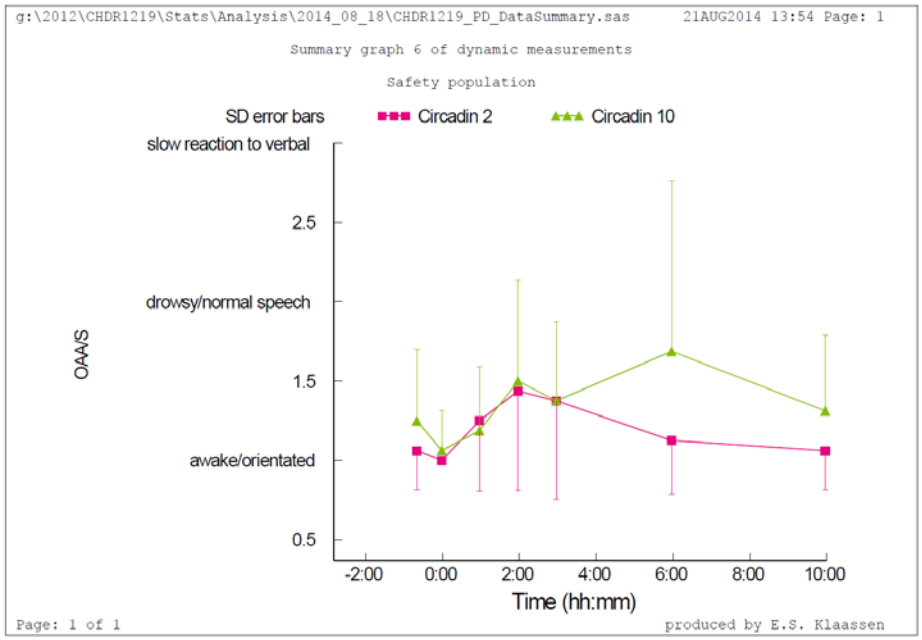
A summary of the pharmacodynamic results are given in this section. Full results are given in following sections, and any issues potentially affecting these results are discussed within the appropriate section.

Observer's Assessment of Alertness/Sedation Scale

A summary of responses to the Observer's Assessment of Alertness/Sedation Scale (OAA/S) are presented in Figure 7.

Following morning administration of Circadin (2 mg or 10 mg), most subjects were assessed by Observer's Assessment of Alertness/Sedation Scale to have a mild increase in sedation, with most scores indicating 'drowsy/normal speech' or 'slow reaction to verbal'. Only one subject (subject 9) reported a transitory score 'reacts to soft touch'.

Figure 7 Response-time profile of Observer's Assessment of Alertness/Sedation Scale, safety population.



Conclusions on pharmacodynamic results

Following morning administration of Circadin, most subjects were assessed by Observer's Assessment of Alertness/Sedation Scale to have a mild increase in sedation following Circadin (2 mg or 10 mg) administration, with most scores indicating 'drowsy/normal speech' or 'slow reaction to verbal'. Only one subject (subject 9) reported a transitory score 'reacts to soft touch'. Sedation after the 2 mg Circadin dose peaked at 2 hours which is around Tmax time of the PK profile demonstrating PK/PD correlation.

Safety results

The extent of exposure of each participant and the overall exposure was not described.

Adverse events

All AE are summarised in Table 6.

Table 6 Number (%) of subjects who had at least 1 adverse event, grouped by system organ class and preferred term, safety population

Summary of number of subjects with possibly/probably related adverse events
by treatment, SOC and preferred term

System Organ Class/ Preferred Term	Circadin 2 (N=16) Events N	Circadin 2 (N=16) Subjects N (%)	Circadin 10 (N=16) Events N	Circadin 10 (N=16) Subjects N (%)
ANY EVENTS	13	11 (68.8)	17	9 (56.3)
GASTROINTESTINAL DISORDERS	-	-	1	1 (6.3)
Nausea	-	-	1	1 (6.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	6	6 (37.5)	9	8 (50.0)
Fatigue	6	6 (37.5)	9	8 (50.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1	1 (6.3)	-	-
Sensation of heaviness	1	1 (6.3)	-	-
NERVOUS SYSTEM DISORDERS	6	5 (31.3)	7	7 (43.8)
Headache	1	1 (6.3)	3	3 (18.8)
Somnolence	3	3 (18.8)	2	2 (12.5)
Sudden onset of sleep	2	1 (6.3)	2	2 (12.5)

Adverse events with a possible or probable relationship with administration of 2 and 10 mg Circadin included fatigue (in 7 out of 16 subjects after 2 mg; 8 out of 16 after 10 mg), sensation of heaviness (1 out of 16 after 2 mg), somnolence (3 out of 16 after 2 mg; 2 out of 16 after 10 mg), falling asleep (2 out of 16 after both 2 and 10 mg), headache (1 out of 16 after 2 mg; 3 out of 16 after 10 mg), and nausea (1 out of 16 after 10 mg). All adverse events were transient and mild. Nausea, fatigue and headache were more frequently reported following Circadin 10 mg compared with Circadin 2 mg.

Deaths

No deaths occurred during the study.

Serious adverse events other than deaths

No subjects had a serious adverse event other than death during the study.

Discontinuations due to adverse events

No subjects were discontinued from study treatment due to an adverse event.

Other significant adverse events

No subjects had any 'other significant adverse event'.

Other observations

Follow-up questionnaire

A summary of responses to the follow-up questionnaire by children is presented in Table 7 and Table 8; responses by parents/legal guardians are given in Table 9.

Table 7 Number (%) of respondents (children) per closed question, safety population

Question	N (%) of respondents per question	
	All (n=16)	
	N	(%)
I found participating....		
Not nice at all	0	(0.00)
Not so nice	2	(12.50)
Rather nice	9	(56.25)
Very nice	5	(31.25)
The duration of the study days was...		
Far too long	0	(0.00)
Long	4	(25.00)
Not too long or short	11	(68.75)
Short	1	(6.25)
Far too short	0	(0.00)
I thought the sampling of saliva was...		
Very bothersome	0	(0.00)
A bit bothersome	4	(25.00)
Not too bothersome	3	(18.75)
Not bothersome at all	9	(56.25)
I thought the collection of urine was...		
Very bothersome	0	(0.00)
A bit bothersome	2	(12.50)
Not too bothersome	5	(31.25)
Not bothersome at all	9	(56.25)
Would you participate again?		
Yes	11	(68.75)
No	1	(6.25)
I'm not sure	4	(25.00)

Table 8 Number (%) of respondents (children) per open question, safety population

Question	N (%) of respondents per question	
	All (n=16)	
	N	(%)
What did you find most enjoyable?		
That I didn't need to go to school and that I could be on the computer the whole day.	1	(6.25)
The remuneration and the extra computer time	1	(6.25)
The remuneration	2	(12.50)
Don't know	1	(6.25)
Exciting new experiences	1	(6.25)
Playing computer games with others. Location CHDR.	1	(6.25)
Could do my own thing, do nothing.	1	(6.25)
Location of Ronald McDonald House	2	(12.50)
Location of Ronald McDonald House. Remuneration.	1	(6.25)
Location -> Ronald McDonald house study personnel	1	(6.25)
I could do fun things the whole day	1	(6.25)
Not applicable.	1	(6.25)
Reward	1	(6.25)
Tickets as reward	1	(6.25)
What did you find least enjoyable?		
- (no answer)	2	(12.50)
Filling 2 tubes, prefer 1	1	(6.25)
Limited food (Amount was too little). Duration of days (going later to bed than used to)	1	(6.25)
That I had to spit so much	1	(6.25)
Diet restrictions	1	(6.25)
Don't know	1	(6.25)
Food was disappointing (dinner)	1	(6.25)
Location (CHDR), nothing to do	1	(6.25)
Location	1	(6.25)
Could not go outside	1	(6.25)
Not applicable	1	(6.25)
Periods of tiredness combined with saliva sampling	1	(6.25)
Stopping with medication (melatonin) in accordance to visits	1	(6.25)
Many saliva samples on dosing days. And very short intervals	1	(6.25)
Don't know, no annoying things	1	(6.25)

Table 9 Number (%) of respondents (caregivers) per question, safety population

Question	N (%) of respondents per question All (n=16)	
	N	**(%)**
I found my child's participation....		
Not nice at all	0	(0.00)
Not so nice	1	(6.25)
Rather nice	10	(62.50)
Very nice	5	(31.25)
The duration of the study days was...		
Far too long	0	(0.00)
Long	1	(6.25)
Not too long or short	15	(93.75)
Short	0	(0.00)
Far too short	0	(0.00)
I thought the sampling of saliva was...for my child		
Very bothersome	0	(0.00)
A bit bothersome	2	(12.50)
Not too bothersome	2	(12.50)
Not bothersome at all	12	(75.00)
I thought the collection of urine was...for my child		
Very bothersome	0	(0.00)
A bit bothersome	1	(6.25)
Not too bothersome	5	(31.25)
Not bothersome at all	10	(62.50)
I would/would not consent again for participation of my child in similar research		
Yes	14	(87.50)
No	1	(6.25)
I'm not sure	1	(6.25)

Overall, participants and caregivers were positive about burden and duration of the study. Nearly all of subjects (68.75%) and their caregivers (87.5%) stated they would consider (consent for) participation again. Most children found saliva sampling not bothersome. The 4 subjects who indicated that saliva sampling was somewhat bothersome were 10, 11, 13 and 15 year old. The child who would not participate again, found participation rather nice, but found study day duration long and the urine sampling a bit bothersome. The parent who would not consent for participation in similar research found the child's participation very nice, but thought saliva and urine sampling were a bit bothersome, as did the child. The child itself found participating not so nice and didn't know if it would participate again.

Conclusions on safety results

All subjects were able to swallow the tablets, none of the subjects chewed, spat out, chocked on or refused to take the tablets.

In general, both treatments were well tolerated. Just over half of the 16 subjects reported at least one AE of mild intensity during the study following either Circadin 2 mg (N=11, 68.8%) or Circadin 10 mg (N=9, 56.3%) administration. No moderate or severe AEs and no deaths or other SAEs occurred.

The most frequently reported treatment-emergent AEs were headache, fatigue, somnolence, sudden onset of sleep, sensation of heaviness and nausea. Most of these are to be expected based on the known effects of melatonin.

Overall, subjects and caregivers were positive about burden and duration of the study. Nearly all of subjects (68.75%) and their caregivers (87.5%) stated they would consider (consent for) participation again.

2.3.3. Discussion on clinical aspects

Endogenous Melatonin and Pharmacokinetics

Baseline melatonin concentrations were characteristic of daytime sampling, being low in the morning and increased over 12 hours towards the evening yet showed overall low endogenous levels. These results were confirmed by baseline 6-SMT measured with lower amounts recovered during the day-time collection period compared with the night-time collection period. In the safety population, the mean 6-SMT levels during the day were 4.2 ug/12 daytime hours and 13.5 ug /12 night-time hours showing normal pattern of higher levels during the night compared to daytime but very low absolute endogenous levels.

In the PK population, the plasma concentration-time profile of melatonin was characterized by rapid absorption and disposition, with a mean Cmax of 965 pg/mL, mean tmax of 1.57 hours, mean AUC0-∞ of 2370 pg h/mL, and t½ of 5.74 hours following Circadin 2 mg. Following oral administration of Circadin 10 mg a mean Cmax of 3970 pg/mL, mean tmax of 1.37 hours, mean AUC0-∞ of 13,300 pg.h/mL, and t½ of 4.44 hours was observed. In the sub-analysis population, representing a group of subjects who did not seem to have much saliva melatonin contamination from the mini-tablets, the plasma concentration-time profile of melatonin was also characterized by rapid absorption and disposition, with a mean Cmax of 410 pg/mL, mean tmax of 1.73 hours, mean AUC0-∞ of 2150 pg.h/mL, and t½ of 4.87 hours following Circadin 2 mg.

Determination of the melatonin metabolite, 6-SMT, in urine indicated extensive metabolism and excretion in the first 12 hours following dose administration.

Pharmacodynamics

Following morning administration of Circadin, most subjects assessed by Observer's Assessment of Alertness/Sedation Scale had a mild increase in sedation following Circadin (2 mg or 10 mg) administration with peak levels at 2 hours, around tmax time with the 2 mg dose.

Safety and tolerability

In this study of children with autism spectrum disorder (aged 7 -15 years), single morning doses of Circadin of 2 or 10 mg were well tolerated, with no severe, serious, or significant AEs. Most AEs are to be expected based on the mechanism of action of melatonin. The most frequently reported treatment-emergent AEs were headache, fatigue, somnolence, sudden onset of sleep, sensation of heaviness and

nausea. Nausea, fatigue and headache were more frequently reported following Circadin 10 mg compared with Circadin 2 mg.

3. CHMP's overall conclusion and recommendation

This study accomplishes Measure 4 of the agreed PIP for melatonin. It should be of note that morning administration of melatonin is not physiological. As such, both efficacy and safety data relate to a non-physiological administration. Notwithstanding, the PK / safety / saliva as an acceptable method of melatonin kinetics tool, were objectives fulfilled by the study. It has provided reasonable data in the studied population regarding administration of prolonged release melatonin tablets. Data on two other relevant aspects was also presented: pharmacodynamic insight from sleep related symptoms and the easiness of the study sampling, questionnaires, and overall methodology, both for the caregivers (parents) and children.

Regarding safety, most adverse events are within the expected effect of the product (somnolence), and previously known AEs, particularly fatigue, headache and GI events.

The extent of exposure as a group and individually has not been specifically presented on graph or table, although it was mentioned that this information would be presented. This aspect should be addressed by the time of submission of a consolidated application.

The CHMP concluded that these preliminary data did not impact the current B/R profile of Circadin.

Overall conclusion

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Circadin Active substance: Melatonin

Study title	Study number	Date of completion	Date of submission of final study report
Repeated dose (14 day) toxicity study by oral gavage with melatonin in juvenile rats	Measure 2 of the development program	29/11/2012	It is planned to submit it with measure 5 submission
Repeated dose toxicity and toxicokinetic study in juvenile rats with melatonin from weaning to sexual maturity.	Measure 3 of the development program	10/04/2013	It is planned to submit it with measure 5 submission

Clinical studies

Product Name: Circadin Active substance: Melatonin

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, pharmacokinetic cross over study of 2 mg and 10 mg prolonged release melatonin age-appropriate oral solid dosage form in chiidren with neurodevelopmental disorders with sleep disturbances from 2 years to less than 18 years.	Measure 4 of the development program	March 2014 (LPLV)	September 2014
Protocol Number: NEU_CH_7911 A Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Circadin® to Alleviate Sleep Disturbances in Children with Neurodevelopmental Disabilities – **first 28 week**	Measure 5 of the development program	February 2016 (LPLV) *(Currently agreed date is December 2014 – please see footnote below *)*	By August 2016 (within 6 months of study completion)
Protocol Number: NEU_CH_7911 A Randomized, Placebo-controlled Study to Investigate the Efficacy and Safety of Circadin® to Alleviate Sleep Disturbances in Children with Neurodevelopmental Disabilities – **last OL 80 week**	Measure 6 of the development program	August 2017 (LPLV) *(Currently agreed date is May 2016 – please see footnote below *)*	February 2018 (within 6 months of study completion)

* As Neurim will not be able to meet the currently agreed timelines for measures 5 and 6, a request for modification of the PIP will be submitted to the PDCO in October 2014. This will include a request for changes to the relevant timelines, plus a request for Study 6 to be accepted as a FUM to a PUMA.