Clinical Study Report Synopsis (EU Analyses)

THE SOUNDER SLEEP STUDY

A DOUBLE-BLIND, PARALLEL GROUP, RANDOMISED, PLACEBO CONTROLLED STUDY OF EFFICACY AND SAFETY OF CIRCADIN® 2 MG IN THE TREATMENT OF INSOMNIA PATIENTS WITH LOW ENDOGENOUS MELATONIN

Version:	1.1
Study number:	NEU 112006
Investigational product:	Circadin® (prolonged-release melatonin)
Study indication:	Primary insomnia
Duration of study:	33 weeks
Study dates:	First patient enrolled: 24 October 2006 Last patient completed: 2 December 2008
Phase of development:	Therapeutic confirmatory (III)
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Name of Sponsor:	Neurim Pharmaceuticals (1991) Ltd 8 Hanechoshet Street Tel-Aviv 69710 Israel

Study centre(s)

This study was conducted on behalf of Neurim Pharmaceuticals (1991) by CPS Research, Glasgow in the United Kingdom. CPS Research worked with a network of 59 General Practitioners (GPs) in central Scotland in the conduct of this study.

Publications

None at the time of writing this report

Objectives

The Sounder Sleep Study was initially designed to satisfy FDA requirements to provide the agency with evidence that age characterized the target population better than melatonin production. The aim of the study was to examine the efficacy and safety of Circadin 2 mg tablets vs. placebo on sleep latency in adult insomniac out-patients, aged 18-80 years with low melatonin production capacity (defined as excretion of <8 µg of the melatonin metabolite 6-sulfatoxymelatonin [6-SMT] in urine per night) and in patients aged 65-80 years regardless melatonin production. Results are summarised in the Sounder Sleep Clinical Study Report Synopsis (8 June 2009).

In June 2007, whilst the study was ongoing, Circadin was approved in the European Union (EMEA) for short term use (3 weeks) in patients aged 55-80. To provide the EMEA with data supporting evidence for a change in posology, an amendment to the protocol was submitted in September 2008 that specified the long-term objectives and statistical analyses for the 55 years and older subpopulation. These are detailed below:

Primary objective: To evaluate the sustained long-term efficacy of Circadin 2 mg vs. placebo for up to 6 months of treatment as assessed by the rate of patients aged 55-80 in the Circadin (2 mg) and placebo treated groups with a score of 6 or less on the average global Pittsburgh Sleep Quality Index (PSQI) score at Visits 6 and 7 and improving at Visits 6 and 7 by 10% or more from baseline on the WHO-5 Index

Secondary objectives

To compare, in patients aged 55-80, between the treatment groups:

a) Sleep quality, as measured by the mean PSQI global score during Visits 6 and 7

b) Quality of life, as measured by the average WHO-5 Index at Visits 6 and 7

c) Subjective sleep latency, as measured by the average score on question 2 of the PSQI during Visits 6 and 7

d) Withdrawal effect after discontinuation, as measured by the Tyrer scale

Exploratory objectives: Short term

In the total population, low excretors and in different age bands:

Following three weeks treatment with Circadin 2 mg or placebo to compare the change from baseline of the efficacy variables measured by the PSQI, Sleep Diary, Clinical Global Impressions (CGI) Scale, WHO-5 and Leeds Sleep Evaluation Questionnaire (LSEQ) in the 2 treatment groups.

Exploratory objectives: Long-term

In patients over 55, in the total population and low excretors:

1. To assess, the sustained long-term efficacy of Circadin 2 mg vs. placebo for up to 6 months of treatment as assessed by changes from baseline in the remaining efficacy variables of the PSQI, CGI scale and Sleep Diary

2. To assess mean time to drop-out in the Circadin 2 mg group vs. placebo group

3. To assess safety parameters treated with Circadin 2 mg vs. placebo following 6 months of treatment

4. To assess rebound effects after discontinuation of Circadin vs. placebo following 6 months treatment

This synopsis focuses on the analyses carried out to address the requirements of the EMEA and thus concentrates on the efficacy analyses and safety data in patients aged 55-80 years only.

Study design

This was a Phase III study conducted using a randomised, double-blind, placebo controlled, parallel group design. The study comprised a 2-week placebo run-in period, a 3-week double-blind treatment period when patients received either Circadin 2 mg or placebo (1:1), a 26-week double-blind extension period when patients received either Circadin 2 mg or placebo (3:1) and a 2-week placebo run-out period. Randomisation was stratified by trial site, 6-SMT levels (low ≤8 µg /high >8 µg /night) and age group (<65/≥65). All patients entering the extension period on Circadin stayed on Circadin and all patients on placebo were randomised in a 1:1 ratio to receive either Circadin 2 mg or placebo for 26 weeks leading to a 3:1 ratio of Circadin to placebo. There were 8 clinic visits over the 33-week study (Visit 1, 0 weeks; Visit 2, 2 weeks; Visit 3, 5 weeks; Visit 4, 9 weeks; Visit 5, 15 weeks; Visit 6, 23 weeks; Visit 7, 31 weeks; Visit 8, 33 weeks).

Diagnosis and main inclusion criteria

Main inclusion criteria for entry into the run-in period: Male or female patients, aged 18-80 years suffering from primary insomnia according to DSM-IV criteria (based on a sleep history questionnaire) with a sleep latency of at least 20 minutes and who had not been using benzodiazepines and non-benzodiazepine hypnotics for the past 2 weeks or more, or psychotropic treatments for the past 3 months or more.

Main inclusion criteria for entry into the treatment period: Patients still eligible after the run-in, who were compliant with respect to treatment, had a negative hypnotic drugs screen and correctly completed assessments.

Number of patients - planned and analysed

Planned: A total of 930 patients recruited corresponding to 80% being in the age range 55-80, and 65% providing data for the primary endpoint at Visit 6 and/or 7 giving 360 patients in the Circadin treatment group and 120 patients in the placebo group.

Analysed: 55-80 safety population 630 patients (320 Circadin and 310 placebo); V2 randomised 55-80 population 632 patients (321 Circadin and 311 placebo); ITT 55-80 (EU) population 481 patients (Circadin 366, placebo 115, by Visit 3 randomisation)

Investigational product and comparator(s): dosage, mode of administration and batch numbers

All study medication was administered orally, 1 tablet daily, taken 1-2 hours before going to bed (preferably between 2100h and 2200h) and after food.

Investigational product: Prolonged-release tablet containing 2 mg melatonin (Circadin), batch number: 457-042

Comparator: Matched placebo tablet to Circadin, batch number: 032-3014

Duration of treatment

Total duration of treatment was 33 weeks.

Criteria for evaluation – efficacy

- Primary outcome variable: The responder rate in patients aged 55 to 80, where response is defined as a score of 6 or less on the average global PSQI score at Visits 6 and 7 and an improvement from baseline at Visits 6 and 7 by 10% or more on the WHO-5.
- Secondary outcome variables:
  - Changes from baseline in PSQI global, WHO-5 Index and PSQI question 2 scores to the average at Visits 6 and 7 in the 55-80 population

  - Change in Tyrer scores at start (Visit 7) and end of the run-out period (Visit 8) in the 55-80 population

- Exploratory outcome variables: Changes from baseline following 3 weeks and 26 weeks of treatment in PSQI global score, PSQI component and question 2 and 4 scores, sleep diary variables, CGI-improvement (CGI-I) scale, WHO-5 Index score, short-term (3 weeks) changes in LSEQ scores and time to discontinuation in the short and long-term periods.

Criteria for evaluation - safety

- Adverse events (AEs), changes in physical examination, ECG, laboratory tests (haematology, biochemistry, urinalysis, endocrine evaluations including cortisol syncathen tests) and rebound insomnia in the week after completing long-term treatment as assessed by sleep quality (sleep diary)

Statistical methods

The 55-80 safety population consisted of all randomised study participants aged ≥55 years at baseline who took at least 1 dose of study medication, regardless of their subsequent participation in the study. The ITT 55-80 (EU) population consisted of all members of the 55-80 safety population who met all major entry criteria and provided primary outcome at baseline and at least one of Visits 6 and 7. The efficacy analyses of the primary, secondary and exploratory variables were performed on patients from this dataset.

Primary analysis: The primary analysis was a χ^2-test for association, with continuity correction, of the percentage of patients that have a mean score of 6 or less on the global PSQI at Visits 6 and 7 and a 10% improvement from baseline on the mean WHO-5 score at Visits 6 and 7 in each treatment group of the ITT population aged 55-80 years. A logistic regression model was then applied, with the primary outcome as the response variable, adjusting for randomisation stratification variables and including an indicator variable for being in the Circadin group to estimate the odds ratio for achieving the primary outcome between the Circadin and placebo groups with a 95% CI.

Secondary analyses: PSQI global, PSQI question 2 and WHO-5 Index mean scores at Visits 6 and 7 were compared between treatment groups, adjusting for scores at Visit 2 and randomisation stratification variables, using a linear regression model. The percentage of patients reporting new symptoms on the Tyrer questionnaire during the run-out period were compared between treatment groups using a logistic regression model with adjustment for baseline stratification variables.

Exploratory analyses: Secondary (PSQI global score, PSQI question 2 and WHO-5 Index) and exploratory short-term efficacy variables were compared between treatment groups using a linear regression model with terms for treatment (Circadin vs. placebo), the baseline value for the outcome and age group (≥65 or <65). For each long-term outcome variable, a mixed-effects model for repeated measures (MMRM) was fitted which included terms for treatment, visit (as a categorical variable), the baseline values of the outcome measure, age group and baseline 6-SMT (≤8 or >8 µg/night). This model was used to estimate the global treatment effect, with a 95% CI and p-value.

Post-hoc analyses using data at Visit 5, repeating exploratory long-term analyses with the V-2 randomised 55-80 population and determining the proportion of responders with clinically relevant changes in PSQI global, PSQI question 2 and CGI-I were also performed.

Safety variables were mainly summarised descriptively for the safety population aged 55-80 years.

Patient disposition and baseline characteristics

In this study, 791 patients aged 18-80 years were randomised to receive Circadin (395 patients) or placebo (396 patients) for 3 weeks from the 930 patients who entered the run-in period. A total of 632 (Circadin 321, placebo 311) of the patients randomised to the 3-week treatment period were aged 55 to 80 years; 572 of these patients continued in the study and entered the extension period, with 278 patients previously treated with placebo re-randomised to Circadin (139) or placebo (139). Overall, 433 patients aged 55-80 received Circadin in the extension period. The main reason for discontinuation in the 3-week and 26-week study periods was the patient

not willing to continue. A total of 458 patients aged 55-80 (Circadin 346, placebo 112) completed the extension period and 454 completed the run-out period (Circadin 346, placebo 112).

The 481 patients in the ITT 55-80 (EU) population (137, 28.5% males; 344, 71.5% females) had a mean age of 65.8 years (range 55 to 80 years) and were predominantly white (478, 99%). Sleep latency as assessed by PSQI question 2 was a mean 75.8 minutes (SD 59.8) and the mean baseline PSQI global score was 10.2 (SD 2.8) indicating poor sleep quality. The mean WHO-5 Index score was 16.4 (SD 3.8) and CGI-S score was a mean 4.3 (SD 0.8) indicating that the patients were moderately ill. These characteristics appeared to be representative of the EU target patient population of 55 to 80 year-olds with primary insomnia and the treatment groups were generally comparable.

Efficacy results

In the primary analysis, the proportion of 55 to 80 year-old patients achieving a response (mean PSQI ≤6 and mean WHO-5 ≥110% of baseline) after up to 6 months of treatment was higher in the Circadin than placebo groups but not significantly (24.6% vs. 20.0%, χ^2-test p=0.311).

The results of the secondary analyses for PSQI global, PSQI question 2 and WHO-5 Index scores are summarised in Table S1. There was no evidence of an adverse withdrawal effect after 6 months of treatment with Circadin, with similar proportions of patients in both groups reporting new symptoms on the Tyrer questionnaire after the 2-week, placebo run-out period (28.3% vs. 27.5%, p=0.881).

Table S1 **Summary statistics for the secondary analyses (PSQI global, PSQI question 2 and WHO-5) with mean change (Visit 6 /7 – baseline) and treatment effect estimate, ITT 55-80 (EU population)**

	Circadin (n=366)	**Placebo (n=115)**	**Treatment Effect Difference (Circadin - Placebo)**	
	Mean change (SD)	**Mean change (SD)**	**Estimate (95% CI)**	**p-value**
PSQI global score	-3.3 (3.0)	-2.7 (3.0)	-0.5 (-1.1, 0.1)	p=0.073
WHO-5 Index	1.7 (3.4)	1.1 (3.8)	0.5 (-0.1, 1.1)	p=0.116
PSQI question 2 (min)	-31.6 (45.5)	-18.2 (63.2)	-15.3 (-22.7, -7.8)	p<0.001

After 3 weeks of double-blind treatment, there were significant improvements in the quality of sleep (PSQI global score) and sleep latency (PSQI question 2, PSQI component 2 and LSEQ getting to sleep scores) in the Circadin group compared with placebo in the ITT 55-80 (EU) population. Using the larger V2-randomised 55-80 population, after 3 weeks of treatment, quality of sleep (PSQI global score), quality of life (WHO-5 Index), sleep latency as assessed by the sleep diary, PSQI question 2, PSQI component 2 and LSEQ getting to sleep scores, and sleep onset (sleep diary) were all significantly better in the Circadin group than with placebo.

Over 6 months of double-blind treatment, an MMRM analysis demonstrated significant global treatment improvements in quality of sleep (PSQI global score), sleep latency (PSQI question 2, PSQI component 2 and sleep diary), sleep onset (sleep diary) and overall clinical status (CGI-I) in the Circadin group compared with placebo in the ITT 55 80 (EU) population (Table S2). The median time to discontinuation from the extension period was 105 days in both treatment groups.

MMRM analyses in the V2-randomised 55-80 population demonstrated significant global treatment improvements with Circadin over the 6-month period in sleep latency, sleep quality, daytime functioning, overall clinical status and quality of life compared with placebo (Table S2).

Table S2 **Variables for the 26 week extension period showing statistically significant effect (p<0.05) with estimated global treatment effect differences (MMRM) in the ITT 55-80 and V2-randomised 55-80 populations**

Population / Variable		Global Treatment Effect difference Circadin – placebo [a]	
		Estimate (95% CI)	p-value
ITT 55-80			
Sleep quality	PSQI global score	-0.50 (-0.86, -0.14)	p=0.007
Sleep latency	PSQI component 2	-0.18 (-0.29, -0.07)	p=0.002
	PSQI question 2 (min)	-7.6 (-12.4, -2.8)	p=0.002
	Sleep diary (min)	-7.7 (-12.4, -3.1)	p=0.001
Sleep onset	Sleep diary (bedtime, h)	-0.13 (-0.22, -0.04)	p=0.006
Overall clinical status	CGI-I	-0.15 (-0.28, -0.01)	p=0.031
V2-randomised 55-80			
Sleep quality	PSQI global score	-0.51 (-0.85, -0.18)	p=0.003
	PSQI component 1	-0.08 (-0.16, -0.01)	p=0.037
Sleep latency	PSQI component 2	-0.15(-0.25, -0.05)	p=0.004
	PSQI question 2 (min)	-7.5 (-12.1, -2.9)	p=0.001
	Sleep diary (min)	-7.9 (-12.2, -3.6)	p<0.001
Sleep Onset	Sleep diary (bedtime, h)	-0.14 (-0.22, -0.05)	p=0.002
Daytime functioning	PSQI component 7	-0.09 (-0.15, -0.02)	p=0.013
Overall clinical status	CGI-I	-0.15 (-0.27, -0.02)	p=0.019
Quality of life	WHO-5 Index	0.53 (0.15, 0.91)	p=0.007

[a] Global treatment effect is estimated using a mixed-effect model for repeated measures (MMRM) and takes into account the treatment effect difference over the 26-weeks of the long-term period (at Visits 3, 4, 5, 6 and 7)

There was evidence of increased WHO-5 Index scores over the extension period for Circadin patients compared with placebo when the secondary analyses in both the ITT 55-80 (EU) population (p=0.043) and V2 randomised 55-80 population (p=0.042) were repeated excluding patients who switched treatments at Visit 3.

At Visit 5 (after 13 weeks of double-blind treatment), a higher proportion of patients in the Circadin group (25.8%) achieved a treatment response (PSQI global score ≤6 and ≥10% improvement in WHO-5 Index relative to baseline) compared with placebo (15.7%) in the ITT 55-80 (EU) population (χ^2-test p=0.026, Odds ratio 1.83, 95% CI 1.05 to 3.20). Significant benefits of treatment with Circadin were demonstrated for sleep latency (as assessed by question 2 of the PSQI, p<0.001) and sleep quality (as assessed by PSQI global score, p=0.014) compared with placebo in the ITT 55 80 (EU) population.

An MMRM analysis of the primary variable in the ITT 55-80 (EU) population, which estimated the global treatment effect over the 6-month period showed that the proportion of responders, as measured by a combination of the PSQI global score and WHO-5 Index, was significantly higher in the Circadin group than placebo (p=0.040). Significant differences in responder rate between Circadin and placebo treatment groups were also observed after 3 and 13 weeks of double-blind treatment (Visit 3, p=0.044; Visit 5, p=0.006;Table S3).

Table S3 **Number (%) of patients achieving a treatment response (mean PSQI ≤6 and mean WHO-5 ≥110% of baseline) at Visit 3, 5 and 7, MMRM results, ITT 55-80 population**

Visit (weeks of double-blind treatment)	Circadin	Placebo	Treatment Effect difference Circadin – placebo	
	N/Total (%)	N/Total (%)	Odds ratio (95% CI)	p-value
Visit 3 (3 weeks)	41/246 (16.7%)	25/235 (10.6%)	1.63 (1.01, 2.62)	p=0.044
Visit 5 (13 weeks)	94/365 (25.8%)	18/115 (15.7%)	2.09 (1.23, 3.55)	p=0.006
Visit 7 (29 weeks)	103/342 (30.1%)	30/109 (27.5%)	1.24 (0.79, 1.95)	p=0.358
	Global Treatment Effect		1.40 (1.02, 1.93)	p=0.040

The differences between the treatment groups regarding the proportion of patients with clinically relevant changes in sleep latency (PSQI question 2), PSQI global score and CGI-I response (much or very much improved) in the ITT 55-80 population at Visit 3, 5, and Visits 6 and 7 are shown in Table S4.

Table S4 **Number (%) of patients with clinically relevant responses for PSQI question 2, PSQI global and CGI-I, at Visits 3, 5 and at Visits 6 and 7 (3, 13, and at 21and 29 weeks of double-blind treatment), ITT 55-80 (EU) population**

Responder at Visit	Circadin	Placebo	χ2-test p-value	Effect estimate Odds ratio (95% CI)
PSQI Q2 ≤30 min [a]				
Visit 3	52/178 (29.2%)	28/162 (17.3%)	χ^2 =6.7, p=0.010	1.98 (1.17, 3.34)
Visit 5	115/255 (45.1%)	27/84 (32.1%)	χ^2 =4.4, p=0.037	1.69 (1.00, 2.86)
Mean V6, V7	110/256 (43.0%)	25/84 (29.8%)	χ^2 =4.6, p=0.032	1.71 (1.00, 2.94)
PSQI-G ≤90% baseline				
Visit 3	152/246 (61.8%)	122/235 (51.9%)	χ^2 =4.8, p=0.029	1.49 (1.04, 2.15)
Visit 5	283/366 (77.5%)	79/115 (68.7%)	χ^2 =3.7, p=0.055	1.54 (0.97, 2.47)
Mean V6, V7	292/366 (79.8%)	77/115 (67.0%)	χ^2 =8.1, p=0.005	1.92 (1.20, 3.07)
CGI-I response				
Visit 3	60/246 (24.4%)	57/233 (24.5%)	χ^2 =0.0, p=0.985	1.01 (0.66, 1.53)
Visit 5	155/365 (42.5%)	38/114 (33.3%)	χ^2 =3.0, p=0.083	1.47 (0.94, 2.30)
Visits 6 and 7	127/340 (37.4%)	29/108 (26.9%)	χ^2 =4.0, p=0.046	1.60 (0.99, 2.60)

[a] ITT 55-80 (EU) population with baseline PSQI question 2 ≥30 minutes

Safety results

A total of 29 patients (aged 55 to 80 years) reported 40 serious adverse events (SAEs) during the study, including 1 death in a placebo-treated patient. The number (%) of patients experiencing an AE during the treatment and extension periods of the study are summarised in Table S4. One patient treated with Circadin experienced an SAE of palpitations during the long-term period, which was assessed as possibly drug-related and was reported as a suspected unexpected serious adverse reaction (SUSAR). Overall, a total of 45 patients discontinued treatment with study drug due to an AE. The AE rates and AE profiles of the 2 treatment groups were generally similar.

Table S4 **Number (%) of patients who had an adverse event in any category in the short and long-term periods, 55-80 safety population**

Category of AE	Short-term period (3 weeks)		Long-term period (26 weeks)	
	Circadin	Placebo	Circadin	Placebo
No of patients	320	310	433	139
Any adverse event (AE)	109 (34.1%)	124 (40.0%)	319 (73.7%)	112 (80.6%)
Any serious adverse event (SAE)	1 (0.3%)	3 (1.0%)	15 (3.5%)	8 (5.8%)
SAE leading to death	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)
Discontinuation due to AE	7 (2.2%)	7 (2.3%)	23 (5.3%)	8 (5.8%)
Drug-related AE [a]	17 (5.3%)	19 (6.1%)	56 (12.9%)	24 (17.3%)
Drug-related SAE [a]	0 (0%)	0 (0%)	1 (0.2%)	0 (0%)

[a] AE or SAE considered to be possibly, probably or definitely related to study drug

There was no evidence of rebound insomnia from the sleep quality data in the first week of the run-out period following the withdrawal of treatment in the safety 55-80 population. Changes in clinical laboratory results including endocrine function and cortisol were generally small and showed no treatment-related trends. In general, there were no apparent differences between treatment groups in vital signs, ECG, physical examination or any of the safety outcomes recorded.

Conclusions

- There was evidence of superior efficacy with Circadin in 55 to 80 year-old patients with primary insomnia, based on responder analysis, where responders were defined as mean PSQI ≤6 and mean WHO-5 ≥110% of baseline over the entire 26-week extension period. Circadin significantly increased the proportion of responders based on that definition at 3 and 13 weeks, but not at 21 and 29 weeks of double-blind treatment.
- Beneficial effects on sleep latency (as assessed by the PSQI question 2 and supported by other variables) and sleep quality (as assessed by the PSQI global score) were demonstrated in 55 to 80 year olds with primary insomnia following 3 and 26 weeks of treatment with Circadin 2 mg. There was evidence that the overall clinical status (as assessed by CGI-I) improved with long-term Circadin treatment, with some evidence also of improvement in patients' quality of life (as assessed by the WHO-5 Index).
- Efficacy was shown to be maintained and improved across multiple variables, and translated into clinically meaningful terms.
- The rate of responders increased after the initial 3 weeks of treatment with evidence of an optimal effect at 13 weeks and maintenance of the effect beyond this, indicating that some patients may need longer than 3 weeks to fully respond to the drug.
- Circadin 2 mg was well tolerated and demonstrated a good safety profile during both short and long-term treatment (up to 29 weeks) of patients with primary insomnia. The only new or unexpected finding was a suspected unexpected serious adverse reaction of palpitations. There was no evidence of any withdrawal or rebound insomnia effects after stopping long term treatment with Circadin.

Date of synopsis: 28 July 2009