CLINICAL STUDY PROTOCOL

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

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SIGNATURE PAGE

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This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

I have read and agree to abide by the requirements of this protocol.

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1 PROTOCOL SYNOPSIS

Compound:	**Melatonin**
Protocol Number and Title:	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**
Study Objectives:	**Primary Objective** 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. **Secondary Objectives** • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on sleep latency as derived from a Sleep and Nap Diary (Appendix 1) after 13 weeks of double-blind treatment • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on the duration of wake after sleep onset period as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on number of awakenings as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on the duration of the longest sleep period as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment • To assess the treatment effect of Circadin® 2/5 mg to that of placebo on children's social functioning at home, in school, and community settings as assessed by the Children Global Assessment Scale (CGAS; Appendix 3) after 13 weeks of double-blind treatment • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on children's behavior at home and in school as assessed by the Strength and Difficulties Questionnaire (SDQ; Appendix 4) after 13 weeks of double-blind treatment • To compare the number of dropouts between Circadin® 2/5 mg to that of placebo during the 13 weeks of double-blind treatment • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on sleep parameters as measured by actigraphy after 13 weeks of double-blind treatment • To compare the safety and tolerability of Circadin® treatment to that of placebo and evaluate the safety and tolerability throughout the study including the run-out (withdrawal) period by using the adverse event (AE)-eliciting method Treatment Emergent Signs and Symptoms questionnaire (TESS; Appendix 5) • To assess vital signs and physical examination in Circadin® and placebo groups **Exploratory Objectives** • To evaluate the effect of Circadin® 2/5 mg on all sleep variables derived from the Sleep and Nap Diary after 3 weeks of double blind treatment (Week 15), and after 13, 26, and 39 weeks of open label treatment (Weeks 28, 41, and 54) as compared to baseline (Week 2) • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on sleep disturbance as assessed by Composite Sleep Disturbance Index (CSDI; Appendix 6) score after 3 and 13 weeks of double blind treatment (Weeks 5 and 15), after 13, 26,

	39, and 91 weeks of open label treatment (Weeks 28, 41, 54, and 106, respectively), and at the end of study visit (Week 108) as compared to baseline (Week 2) • To assess the treatment effect of Circadin® 2/5 mg on children's social functioning at home, in school, and community settings as assessed by the CGAS (Appendix 3) after 13 weeks (Week 28) of Circadin® open label treatment as compared to baseline (Week 2) • To assess the treatment effect of Circadin® 2/5 mg on children's behavior at home and in school as assessed by the SDQ (Appendix 4) after 13 weeks (Week 28) of Circadin® open label treatment as compared to baseline (Week 2) • To assess the level of caregiver's daytime sleepiness (i.e., NOT the child's) during the study using the Epworth Sleepiness Scale (ESS; Appendix 7; at Weeks 0, 2, 5, 15, 28, 41, 54, 106 and 108) • To assess the level of caregiver's quality of sleep at night (i.e., NOT the child's) during the study using the Pittsburgh Sleep Quality Index (PSQI; Appendix 8) global score and components (at Weeks 0, 2, 5, 15, 28, 41, 54, 106 and 108) • To assess the level of caregiver's well-being (i.e., NOT the child's) during the study using the World Health Organization Well-Being Index (WHO-5; Appendix 9) well-being questionnaire (at Weeks 0, 2, 5, 15, 28, 41, 54, 106 and 108) • To compare the treatment effect of Circadin® 2/5 mg to that of placebo on children's body mass index (BMI) and Z-score after 3 and 13 weeks of double-blind treatment, and to evaluate the effect of Circadin® 2/5/10 mg compared to baseline, at the end of the open-label period and at the end of placebo run-out period • To assess the treatment effect of Circadin® 2/5/10 mg on children's pubertal status using the Tanner scale will be used in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI (baseline through Week 108) • In children diagnosed with epilepsy, to compare the effect of Circadin® 2/5 mg to that of placebo on the number and severity of epilepsy seizures during double-blind treatment and to assess the effect of Circadin® 2/5/10 mg during the open-label period using seizure diaries.
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 prohibited 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 child should 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. Children with a documented history of sleep hygiene and behavioral intervention who are

	taking a prohibited medication will not require additional training and will undergo a 2 week wash-out period before Visit 1 (e.g., Weeks -2 through 0 to wash out melatonin or any other prohibited medications). During these 2 weeks there is no need to complete the sleep and nap diary. 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 (i.e., an increase either to 5 mg for patients who are still on 2 mg or an increase to 10 mg for patients who are on 5 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.
Test Drugs/Study Medications:	**Test drug:** Circadin® 1 mg minitablets will be used in this study. These tablets are 3 mm in diameter and will allow flexibility of dosing for the required dose titrations from 2 mg to 5 mg or 10 mg. **Reference drug:** Placebo will be identical in appearance and formulation to active Circadin® minitablets, but will contain no active melatonin. Circadin® and placebo are to be administered orally, 1 portion of minitablets daily, taken postprandial at 0.5 to 1 hour before desired bedtime (bedtime should be age-appropriate bedtime). The minitablets should be swallowed whole and should not be crushed or halved.
Inclusion Criteria:	To be eligible for study entry, all patients must satisfy all of the following criteria at screening: 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 β-blockers. (Only morning administration of β-blockers is allowed since β-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 (for those who need it) 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:	Children who meet any of the following criteria will be excluded from participating in the study: 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 prohibited 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
Number of Patients:	Enough eligible male and female children of ages 2 to 17.5 years will be screened for the study to allow for 120 patients to then be randomized in a 1:1 ratio to receive Circadin® or placebo at Visit 2. 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.
Study Duration:	Each patient will participate in the study until the end of the second open-label safety follow-up period, and 2-week SB run-out period. Altogether, the study duration will be 112 weeks including 4-week wash-out period with sleep hygiene and behavioral intervention.
Study Endpoints:	**Primary Efficacy Endpoint** The primary efficacy endpoint is TST time as assessed by a Sleep and Nap Diary after the 13-week, double-blind treatment period. **Secondary Efficacy Endpoints**

- 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

Exploratory Efficacy Endpoints

- Sleep variables as assessed by the Sleep and Nap Diary at baseline (Week 2), after 3 weeks of double blind treatment (Week 5), and after 13, 26, and 39 weeks of open label treatment (Weeks 28, 41, and 54)
- Sleep disturbance as assessed by the CSDI score at baseline after 3 and 13 weeks of double-blind treatment (Weeks 5 and 15, respectively), after 13, 26, 39, and 91 weeks of open label treatment (Weeks 28, 41, 54, and 106, respectively), and at the end of study visit (Week 108)
- Social functioning at home, in school, and in community settings as assessed by the CGAS after 13 weeks (Week 28)of open-label treatment
- Behavior at home and in school as assessed by the SDQ after 13 weeks (Week 28) of open-label treatment
- Caregiver's daytime sleepiness (i.e., NOT the child's) during the study as assessed by the ESS (Weeks 0, 2, 5, 15, 28, 41, 54, 106 and 108)
- Caregiver's well-being (i.e., NOT the child's) during the study as assessed by the WHO-5 questionnaire (Weeks 0, 2, 5 15, 28, 41, 54, 106 and 108)
- Caregiver's quality of sleep at night (i.e., NOT the child's) during the study using the PSQI global score and components (at Weeks 0, 2, 5, 15, 28, 41, 54, 106 and 108)

Safety Endpoints

Safety Endpoints (Secondary)

- Assessment of AEs throughout the study and upon study withdrawal using the TESS
- Vital signs at each visit including the placebo run-out (withdrawal) period
- Physical examination at each visit including the placebo run-out (withdrawal) period

Safety Endpoints (Exploratory)

- BMI and Z-score assessed during the study
- Pubertal assessment using the Tanner scale during the study (The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8, the children's physical development will be determined using BMI.
- In children diagnosed with epilepsy, the number and severity of epilepsy seizures assessed during the study using seizures diaries completed by the parents at the time of the seizures

Sample Size Estimation:	To achieve 95% power at the 5% level for the primary objective (assuming a change of 0.72 hour in the Circadin® arm and 0.27 hour in the placebo arm and a standard deviation (SD) of 0.69 in the Circadin® arm and 0.45 in the placebo arm), 45 patients are required per combined group. Therefore, 90 patients in total are required to complete Visit 5. These estimations are based on previous studies conducted with Circadin®.
Statistical Methods:	**Primary Efficacy Analysis** Total sleep time will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using linear regression model (Analysis of Covariance [ANCOVA]) to test the null hypothesis so that these adjusted mean scores are equal. **Secondary Efficacy Analyses** Sleep latency will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. Duration of wake after sleep onset period will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. The number of awakenings will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. The longest sleep episode will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. The CGAS score will be summarized at baseline and after 13 weeks of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. The SDQ score will be summarized at baseline and after 13 weeks of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. The number of dropouts will be compared between the treatment groups and analyzed using a dichotomized data analysis (chi-square test). Sleep parameters, as measured by actigraphy, will be summarized at baseline and after

	13 weeks of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at each time point will be compared using an ANCOVA model to test the null hypothesis so that these mean scores are equal. For all primary and secondary analyses, a mixed-effect repeated-measures model (MMRM) will be fitted to assess any differences in treatment effects over time. The base models will contain the specified outcome measure after baseline as the dependent variable, with independent variables in the form of the baseline score, the study visit (categorical variable) and treatment allocation. A general covariance structure will be assumed. The global treatment effect estimates will be reported, with 95% confidence intervals (CIs) and p-values. Further analysis will include interaction between treatment and visit. Interaction p-values will be reported with treatment effect estimates at each visit with 95% CIs and p-values. **Exploratory Efficacy Analyses** All sleep variables will be assessed by a Sleep and Nap Diary, and will be summarized at baseline and after 3 weeks of double-blind treatment (actual and change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 3 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. Sleep disturbance will be assessed by CSDI score, and will be summarized at baseline, after 3 and 13 weeks of double-blind treatment (actual and change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum). For each treatment group, for this outcome, the mean score (actual and change from baseline) at each time point will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal. All sleep variables will be assessed by the CSDI and the Sleep and Nap Diary, and will be summarized at baseline and after 13, 26 and 39 weeks of Circadin® open-label treatment (Weeks 28, 41 and 54, actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). CSDI will be also summarized after 106 and 108 weeks of Circadin® open-label treatment. CGAS score will be summarized at baseline and after 13 weeks of Circadin® open-label treatment (Week 28; actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). The SDQ score will be summarized at baseline and after 13 weeks of Circadin® open-label treatment (Week 28; actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum). The ESS score for the parent and caregiver will be summarized at baseline and at the 5, 15, 28, 41, 54, 106 and 108 week time points (actual change from baseline) using descriptive statistics (n, mean, SD, median, minimum, and maximum). Note: The ESS is to assess the sleepiness of the parent/caregiver and NOT the child.) The WHO-5 score (parent's well-being assessment) will be summarized at baseline and at the 5, 15, 28, 41, 54, 106 and 108 week time points (actual change from baseline) using descriptive statistics (n, mean, SD, median, minimum, and maximum). Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.) The PSQI global score and components (parent's sleep variables) will be summarized at baseline and at the 5, 15, 28, 41, 54, 106 and 108 week time points (actual change from baseline) using descriptive statistics (n, mean, SD, median, minimum, and maximum). Note: The PSQI is to assess the quality of sleep of the parent/caregiver and NOT the child.) For all exploratory analyses for the double-blind period, a MMRM will be fitted to assess any differences in treatment effects over time. The base models will contain the specified outcome measure after baseline as the dependent variable, with independent variables in the form of the

	baseline score, the study visit (categorical variable) and treatment allocation. **Safety Analyses** **Secondary Safety Endpoints** Descriptive statistics will be provided for AEs, changes in physical examinations and vital signs measurements. The number of patients withdrawing during the treatment periods will be summarized by primary reason for withdrawal for each treatment group. **Exploratory Safety Endpoints** The changes in BMI and Z-score from baseline to the end of the study will be summarized using shift tables showing the number of children having values below, within and above Z-calculated normal at each treatment group separately. The BMI and Z-scores are designed to take into account the amount of weight gain that would be expected due to normal growth in children and adolescents. The BMI and Z-scores are categorized by age and gender standardized values (corresponding to a normal distribution with mean 0 and a SD of 1) of the actual weight measurements, based on the Growth Charts provided by the Centers for Disease Control. Tanner scores for pubertal assessment in children ≥8 years of age during the study will be analyzed using the web application (http://vps.stefvanbuuren.nl/puberty)[20]. This tool calculates SD scores of individual observations of Tanner scores and additionally plots those scores in stage line diagram[21]. Descriptive statistics will be provided for head and height measurements and changes in head and height measurements from baseline to Week 108 in children ≤5 years of age. Descriptive statistics will also be provided for the number and severity of epilepsy seizures in children diagnosed with epilepsy, using the Epilepsy Seizures Diaries that are completed by parents at the time of the seizures and entered in the eCRF at a later time point by the site.

2 TABLE OF CONTENTS

1 PROTOCOL SYNOPSIS 4
2 TABLE OF CONTENTS 12
DEFINITION OF TERMS 18
LIST OF ABBREVIATIONS 19
3 INTRODUCTION 20
4 OBJECTIVES OF THE STUDY 22
5 INVESTIGATIONAL PLAN 24
5.1 Overall study design 24
5.2 Efficacy Assessments 25
5.3 Safety Assessments 26
6 STUDY POPULATION AND SELECTION 31
6.1 Inclusion Criteria 31
6.2 Exclusion Criteria 32
6.3 Withdrawal of Patients from Treatment 32
6.4 Replacement of Patients 33
7 TREATMENTS ADMINISTERED 33
7.1 Prohibited Medications 34
7.2 Investigational Medicinal Product 34
7.3 Circadin® Administration 35
7.3.1 Dose Modification 35
7.3.2 Dose Reduction 36
7.4 Blinding 36
7.5 Dose Selection Rationale 37
7.6 Treatment Compliance 37
8 CONDUCT OF STUDY AND STUDY ASSESSMENTS 37
8.1 Screening Visit (Day 1 at -4 Weeks ±3 Days) 39
8.2 Pre-Visit 1 40
8.3 Visit 1 (Week 1 Day 1 ±3 Days) 40
8.4 Pre-Visit 2 Phone Call 41
8.5 Visit 2 (Randomization/Baseline Visit; Last Day of Week 2 ±3 Days) 41
8.6 Pre-Visit 3 42
8.7 Visit 3 (Possible Dose Modification; Last Day of Week 5 ±3 Days) 42
8.8 Pre-Vi sit 4 43
8.9 Visit 4 (Last Day of Week 15 ±3 Days) 43

8.10 Pre-Visit 5 45
8.11 Visit 5 (Last Day of Week 28 ±3 Days) 45
8.12 Pre-Visit 6 46
8.13 Visit 6 (Last Day of Week 41 ±7 Days) 46
8.14 Pre-Visit 7 47
8.15 Visit 7 (Last Day of Week 54 ±7 Days) 47
8.16 Pre-Visit 8 47
8.17 Visit 8 (Last Day of Week 106 ±7 Days) 47
8.18 Pre-End of Study Visit 48
8.19 End of Study Visit (Last Day of Week 108 ±3 Days) 48
8.20 Unscheduled Visit(s) 49
10 CLINICAL PHARMACOLOGY ASSESSMENTS 51
10.1 Pharmacokinetic (PK) Assessments 51
10.2 Pharmacodynamic (PD) Assessments 51
10.3 Biomarker and Exploratory Assessments 51
11 SAFETY ASSESSMENTS 51
11.1 Adverse Events 51
11.1.1 Definition of an Adverse Event 51
11.1.2 Assessment of Severity 52
11.1.3 Assessment of Frequency 52
11.1.4 Assessment of Outcome 52
11.1.5 Assessment of Causality and Relatedness 53
11.1.6 Follow-up of Adverse Events 54
11.2 Serious Adverse Events 54
11.2.1 Definition of a Serious Adverse Event 54
11.2.2 Definition of an Unexpected Adverse Event 55
11.2.3 Reporting of Serious Adverse Events 55
11.3 Withdrawal Due to an Adverse Event 55
11.4 Monitoring of Patients with AEs 56
11.5 PHYSICAL EXAMINATION AND VITAL SIGNS 56
11.6 Treatment of Overdose of Study Medication 56
11.7 Pregnancy 57
11.8 Physical Examination and Vital Signs 57
11.9 Other Safety Assessments 57
12 DATA MANAGEMENT AND STATISTICAL ANALYSIS 57
12.1 Data Management 57
12.2 Statistical Analysis Plan 58
12.3 General Considerations 58

12.4 Randomization 58
12.5 Analysis Sets 58
12.6 Sample Size 59
12.7 Study Population 59
12.7.1 Patient Disposition 59
12.7.2 Demographic and Baseline Characteristics 59
12.8 Study Endpoints and statisitcal methods 59
12.8.1 Efficacy Endpoints 59
12.8.2 Safety Endpoints 62
12.8.3 Exploratory Endpoints 62
12.9 Study Termination Criteria 62
12.10 Data Safety Monitoring Board 63
12.11 Handling of Dropouts/Missing Data 63
12.12 Changes to the Planned Analysis 64
13 MONITORING PROCEDURES (QUALITY CONTROL AND QUALITY ASSURANCE) 64
13.1 Routine Monitoring 65
13.2 Inspections and Auditing Procedures 65
13.3 Protocol Amendments and Significant Protocol Deviations and Violations 66
13.3.1 Protocol Amendments 66
13.3.2 Protocol Deviations, Violations, and Exceptions 66
13.4 Information to Study Personnel 67
13.5 Record Keeping 67
14 STUDY MANAGEMENT AND MATERIALS 67
14.1 Electronic Case Report Forms 67
14.2 Data Collection 68
14.3 Source Documents Maintenance 68
14.4 Record Maintenance 69
14.5 Confidentiality 69
15 DRUG ACCOUNTABILITY 70
16 ETHICS AND INFORMED CONSENT 71
16.1 ETHICS 71
16.1.1 Regulatory and Ethical Approvals 71
16.1.2 Ethical Conduct of the Study 71
16.2 Patient Information and Informed Consent 71

17 FINANCING AND INSURANCE 71
18 REPORTING AND PUBLICATION 72
19 REFERENCES 73
20 APPENDICES 75

LIST OF APPENDICES

Appendix 1: Sleep and Nap Diary 75
Appendix 2: Sleep and Nap Diary Take-Home Instructions for Parents 78
Appendix 3: Children Global Assessment Scale and Rating Guidelines 84
Appendix 4: Strength and Difficulties Questionnaires 88
Appendix 5: Treatment Emergent Signs and Symptoms 103
Appendix 6: Composite Sleep Disturbance Index 107
Appendix 7: Epworth Sleepiness Scale 109
Appendix 8: Pittsburgh Sleep Quality Index 111
Appendix 9: WHO-5 Well-being Index 114
Appendix 10: Epilepsy Seizures Diary 116
Appendix 11: Prohibited Medication List 118

LIST OF IN-TEXT TABLES

Table 5-1: Study Treatment Schedule 27
Table 5-2: Schedule of Study Assessments 28
Table 8-1: Summary of Questionnaires 39

DEFINITION OF TERMS

Safety Analysis Set	All patients randomized to treatment who take at least 1 dose of study medication.
Full Analysis Set (FAS)	All patients in the Safety Analysis Set who satisfy all major entry criteria and who have efficacy data for the primary parameter recorded for baseline and at least 1 post-baseline period assessment
Per Protocol Set	All patients in the FAS for whom there were no serious violations of the protocol

LIST OF ABBREVIATIONS

AE	adverse events
ANCOVA	analysis of covariance
ASD	Autism Spectrum Disorder
BMI	Body mass index
CGAS	Children Global Assessment Scale
CSDI	Composite Sleep Disturbance Index
CSR	clinical study report
DSM-5/4	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (Text Revision)
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
ESS	Epworth Sleepiness Scale
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICD-10	International Classification of Diseases
ICF	informed consent form
ICH	International Conference on Harmonization
ICSD	International Classification of Sleep Disorders
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IR	immediate-release
IRB	Institutional Review Board
MMRM	mixed-effect repeated measures model
PI	Principal Investigator
PIP	Pediatric Investigational Plan
PR	prolonged-release
PSQI	Pittsburgh Sleep Quality Index
SAE	serious adverse event
SAP	statistical analysis plan
SB	single blind
SD	standard deviation
SDQ	Strength and Difficulties Questionnaire
SMS	Smith-Magenis syndrome
SSRI	selective serotonin reuptake inhibitor
TESS	Treatment-Emergent Signs and Symptoms Questionnaire
TST	total sleep time
WHO-5	World Health Organization Well-Being Index

3 INTRODUCTION

Sleep disturbance is 1 of the most common complaints in children with autism spectrum disorder (ASD), mental retardation or other developmental delays[1-3]. High prevalence for moderate sleep disturbances in these children populations is 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[4]. 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[5], 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. Although in none of these studies significant adverse events (AEs) as a result of melatonin use have been reported, the safe, appropriate dosing (including amounts and timing), have not been established for children. Moreover, in many cases, immediate-release (IR) melatonin preparations that are available as food supplements in the USA were used. These formulations did not improve total sleep time (TST) and sleep maintenance, which are the most disturbing parameters for families[6]. As melatonin has a very short half-life (40 minutes), prolonged-release (PR) formulations are sought to cover the night period, and should affect sleep maintenance.

Circadin® is a 2 mg PR melatonin formulation that mimics the physiological secretion profile of melatonin and can offer more sustained blood levels of melatonin overnight. Circadin® 2 mg is the first, fully developed melatonin pharmaceutical product and was approved for marketing in the European Union (EU) in 2007 for the treatment of primary insomnia in patients aged 55 years and older[7].

Several published studies performed in Canada[8-10] and France[8-14] have looked at the use of Circadin® to treat sleep wake cycle disturbances in children with neurodevelopmental disabilities. The efficacy and safety of Circadin® was evaluated in 42 children with chronic sleep–wake cycle disorders[10]. All 42 patients had severe neurodevelopmental difficulties. Initially, a randomized, double-blinded, cross-over design was used in 16 children, comparing the effectiveness of IR and PR Circadin®. In the remainder of the patients, the PR melatonin was studied on a clinical basis. The effectiveness of treatment was assessed by sleep charts and clinical follow-up. Emphasis was placed on the judgment of the parents, who had guidance from the physicians. The average final PR melatonin dose in the 42 patients was 5.7 mg (2 to 12 mg). The studies showed that the IR melatonin was most effective when there was only delayed sleep onset, but PR formulations were more useful for sleep maintenance.

Data from 44 children with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders who had participated in the placebo controlled, double-blind cross-over trial of PR-melatonin (not Circadin®) were reported in a prospective follow-up study[9]. The follow-up study involved a structured telephone interview of caregivers every 3 months for up to 3.8 years. Adverse reaction to melatonin therapy and development of tolerance were not evident. Better sleep was associated with reported improvement in health, behavior, and learning. At the end of the study, the

parental comments regarding the effectiveness of long-term melatonin therapy were highly positive. Parents whose children had sleep maintenance difficulties expressed a wish to have a commercially available PR-melatonin product which would promote sleep for 8 to 10 hours.

Treatment with Circadin® was reported in children who presented with Smith-Magenis syndrome (SMS), mental retardation, encephalopathy, autism, Angelman syndrome, Rett syndrome, Bourneville syndrome, blindness, and delayed-sleep-phase syndrome[12]. Patients aged 3 to 18 years were given Circadin® (4 to 6 mg/day) as a single evening dose over a treatment duration which ranged from 6 to 72 months. In the group of children for whom there were full reports by their parents (49 children) within 3 months, sleep latency with Circadin® decreased by 44.0% (p-value <0.001); sleep duration increased by 10.1% (p-value <0.001); and the number of midnight awakenings decreased by 75% (p-value <0.001) compared with baseline. Additionally, sleep quality improved by 75% compared with baseline (2.1±0.34 vs. 1.2±0.4, respectively, p-value <0.001). No serious adverse events (SAEs) or treatment related co-morbidities were reported. Other studies using PR-melatonin[15] (not Circadin®) indicated long-term effectiveness of PR-melatonin at a maximal dose of 4 mg in children 4 years or less and 6 mg over this age. In children aged 2.6 to 9.6 years with autism without other coexistent pathologies, PR-melatonin was evaluated openly. Treatment gains were maintained at 12 and 24-month follow-ups. It was concluded that PR melatonin may provide an effective and well-tolerated treatment for autistic children with chronic sleep disorders.

In order to establish the efficacy and safety of Circadin® in children with neurodevelopmental disorders and to determine the dose, this randomized, placebo-controlled study is planned to evaluate the efficacy of a double-blind, 13-week treatment period with Circadin® 2/5 mg in improving maintenance of sleep, sleep latency and additional parameters in children with neurodevelopmental disabilities. The efficacy and safety of Circadin® 2/5 mg will continue to be assessed during an open-label extension period of 13 weeks. Withdrawal effects will also be assessed during the 2-week single-blind (SB) placebo run-out period.

4 OBJECTIVES OF THE STUDY

Primary 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 (Appendix 1) after 13 weeks of double-blind treatment.

Secondary Objectives

- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on sleep latency as derived from a Sleep and Nap Diary (Appendix 1) after 13 weeks of double-blind treatment
- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on the duration of wake after sleep onset period as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment
- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on number of awakenings as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment
- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on the duration of the longest sleep period as derived from a Sleep and Nap Diary after 13 weeks of double-blind treatment
- To assess the treatment effect of Circadin® 2/5 mg to that of placebo on children's social functioning at home, in school, and community settings as assessed by the Children Global Assessment Scale (CGAS; Appendix 3) after 13 weeks of double-blind treatment
- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on children's behavior at home and in school as assessed by the Strength and Difficulties Questionnaire (SDQ; Appendix 4) after 13 weeks of double-blind treatment
- To compare the number of dropouts between Circadin® 2/5 mg to that of placebo during the 13 weeks of double-blind treatment
- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on sleep parameters as measured by actigraphy after 13 weeks of double-blind treatment
- To compare the safety and tolerability of Circadin® treatment to that of placebo and evaluate the safety and tolerability throughout the study including the run-out (withdrawal) period using AE eliciting method Treatment Emergent Signs and Symptoms questionnaire (TESS; Appendix 5)
- To assess vital signs and physical examinations in Circadin® and placebo groups

Exploratory Objectives

- To evaluate the effect of Circadin® 2/5 mg on all sleep variables derived from the Sleep and Nap Diary after 3 weeks of double-blind treatment (Week 15), and after 13, 26, and 39 weeks of open-label treatment (Weeks 28, 41, and 54) as compared to baseline (Week 2)

- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on sleep disturbance as assessed by Composite Sleep Disturbance Index (CSDI; Appendix 6) score after 3 and 13 weeks of double-blind treatment (Weeks 5 and 15), after 13, 26, 39, and 91 weeks of open-label treatment (Weeks 28, 41, 54, and 106, respectively), and at the end of study visit (Week 108) as compared to baseline (Week 2)
- To assess the treatment effect of Circadin® 2/5 mg on children's social functioning at home, in school, and community settings as assessed by the CGAS (Appendix 3) after 13 weeks (Week 28) of Circadin® open-label treatment as compared to baseline (Week 2)
- To assess the treatment effect of Circadin® 2/5 mg on children's behavior at home and in school as assessed by the SDQ (Appendix 4) after 13 weeks (Week 28) of Circadin® open-label treatment as compared to baseline (Week 2)
- To assess the level of caregiver's daytime sleepiness (i.e., NOT the child's sleepiness) during the study using the Epworth Sleepiness Scale (ESS; Appendix 7) at Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108
- To assess the level of caregiver's quality of sleep (i.e., NOT the child's quality of sleep) at night during the study using the Pittsburgh Sleep Quality Index (PSQI; Appendix 8) at Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108
- To assess the level of caregiver's well-being (i.e., NOT the child's well-being) during the study using the World Health Organization Well-Being Index (WHO-5) questionnaire (Appendix 9) at Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108
- To compare the treatment effect of Circadin® 2/5 mg to that of placebo on children's body mass index (BMI) and Z-score after 3 and 13 weeks of double-blind treatment, and to evaluate the effect of Circadin® 2/5/10 mg compared to baseline, at the end of the open-label period, and at the end of the placebo run-out period
- To assess the treatment effect of Circadin® 2/5/10 mg on pubertal status the Tanner scale will be used in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI (baseline through Week 108)
- In children diagnosed with epilepsy, to compare the effect of Circadin® 2/5 mg to that of placebo on the number and severity of epilepsy seizures during double-blind treatment and to assess the effect of Circadin® 2/5/10 mg during the open-label period using seizure diaries

5 INVESTIGATIONAL PLAN

5.1 OVERALL STUDY DESIGN

This is a randomized placebo-controlled study in children diagnosed with 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 prohibited 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 SB placebo run-in period. In order to be eligible for the 2-week SB placebo run-in period, the child should 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.

Children with a documented history of sleep hygiene and behavioral intervention who are taking prohibited medications will not require additional training and will undergo a 2-week wash-out period before Visit 1 (e.g., Weeks -2 through 0 to wash out melatonin or any other prohibited medications). During these 2 weeks there is no need to complete the sleep and nap diary.

After the 4-week sleep hygiene (for children who do not have a documented history of sleep hygiene and behavioral intervention) and 2-week SB placebo run-in period, 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-week open-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 (i.e., an increase either to 5 mg for patients who are still on 2 mg or an increase to 10 mg for patients who are on 5 mg) is necessary. 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 SB placebo 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 0.5 to 1 hour before desired bedtime (bedtime should be defined as age-appropriate bedtime). The minitablets should be swallowed whole and should not be crushed or halved.

The study population will include male and female children 2 to 17.5 years of age with confirmed history of ASDs or neurodevelopmental disabilities caused by neurogenetic diseases. At Visit 1, enough eligible male and female children, of ages 2 to 17.5 years, will be screened for the study to allow for 120 patients to then be randomized in a 1:1 ratio to receive Circadin® or placebo at Visit 2. 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.

5.2 EFFICACY ASSESSMENTS

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- 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 period 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

Exploratory Efficacy Endpoints

- Sleep variables as assessed by the Sleep and Nap Diary at baseline (Week 2), after 3 weeks of double-blind treatment (Week 5), and after 13, 26, and 39 weeks of open-label treatment (Weeks 28, 41, and 54)
- Sleep disturbance as assessed by the CSDI score at baseline after 3 and 13 weeks of double-blind treatment (Weeks 5 and 15, respectively), after 13, 26, 39, and 91 weeks of open-label treatment (Weeks 28, 41, 54, and 106, respectively), and at the end of study visit (Week 108)
- Social functioning at home, in school, and in community settings as assessed by the CGAS after 13 weeks (Week 28)of open-label treatment
- Behavior at home and in school as assessed by the SDQ after 13 weeks (Week 28) of open-label treatment
- Caregiver's daytime sleepiness (i.e., NOT the child's sleepiness) during the study as assessed by the ESS (Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108)
- Caregiver's well-being (i.e., NOT the child's well-being) during the study as assessed by the WHO-5 questionnaire (Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108)
- Caregiver's quality of sleep (i.e., NOT the child's quality of sleep) at night during the study as assessed by the PSQI questionnaire (Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108)

5.3 SAFETY ASSESSMENTS

Safety Endpoints (Secondary)

- Assessment of AEs throughout the study after Visit 1 and upon study withdrawal using the TESS
- Vital signs at each visit including the placebo run-out (withdrawal) period
- Physical examination at each visit including the placebo run-out (withdrawal) period

Safety Endpoints (Exploratory)

- BMI and Z-score assessed during the study
- Pubertal assessment using the Tanner scale during the study (The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8, the children's physical development will be determined using BMI.
- In children diagnosed with epilepsy, the number and severity of epilepsy seizures assessed during the study using Epilepsy Seizures Diaries.

Table 5-1: Study Treatment Schedule

Period	Wash-out Sleep Hygiene	Run-in, Single-blind		Double-blind				Open-Label								Run-out, Single-Blind	
Treat-ment	No drug inter-vention[1]	Placebo		Circadin® 2 mg or PBO		Circadin® 2 mg, 5 mg, or PBO		Circadin® 2 mg or 5 mg		Circadin® 2 mg, 5 mg, or 10 mg						Placebo	
Week	-4 to 0	1	2	3	5	6	15	16	28	29	41	42	54	55	106	107	108
Visit[3]	SCRN first day of Week -4, ±3 days	Visit 1 first day of Week 1, ±3 days	Visit 2 last day of Week 2, ±3 days random-ization/ baseline visit		Visit 3[2] last day of Week 5, ±3 days dose modi-fication		Visit 4 last day of Week 1 5, ±3 days		Visit 5[2] last day of Week 28, ±3 days dose modi-fication		Visit 6 last day of Week 4 1, ±7 days		Visit 7 last day of Week 54, ±7 days		Visit 8 last day of Week 10 6, ±7 days		End of Study last day of Week 108, ±3 days

SCRN = Screening; PBO = placebo

* The visit should be carried out within ±3 days.

** The visit should be carried out within ±7 days.

1. First 2 weeks are a gradual withdrawal and the last 2 weeks are a complete withdrawal of prohibited medications.
2. Data analysis (assessment of sleep variables) will be performed at the end of Week 5 (Visit 3) and Week 28 (Visit 5) to determine if a dose modification (i.e., an increase to 5 mg or 5/10 mg Circadin®, respectively) is required.
3. All visits, except screening and Visit 1 will occur on the last day of the week in which they occur, as indicated above.

Table 5-2: Schedule of Study Assessments

	Wash-out Sleep Hygiene		Run-in, Single-blind	Double-blind		Open-label				Run-out, Single-Blind
	Screening –4 Weeks*	Visit 1/ Week 0*	Visit 2 /Randomization/ Baseline Visit* Week 2	Visit 3/ Week 5*	Visit 4/ Week 15*	Visit 5/ Week 28[1]*	Visit 6/ Week 41**	Visit 7/ Week 54**	Visit 8/ Week 106**	End of Study Visit/ Week 108*
Screening procedures										
Explanation of Study	X									
Informed consent	X									
Eligibility	X	X	X							
Medical history	X	X								
Demographic data	X									
Sleep problem verification	X	X	X							
Inclusion/ Exclusion	X									
Sleep hygiene training booklet	X									
Randomization			X							
Dose Modification				X		X				
Safety Assessments										
Compliance verification			X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X
Body weight and height for BMI and Z-score	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X
Pregnancy test[2]	X		X		X					X

	Wash-out Sleep Hygiene		Run-in, Single-blind	Double-blind		Open-label				Run-out, Single-Blind
	Screening –4 Weeks*	Visit 1/ Week 0*	Visit 2 /Randomization/ Baseline Visit* Week 2	Visit 3/ Week 5*	Visit 4/ Week 15*	Visit 5/ Week 28[1]*	Visit 6/ Week 41**	Visit 7/ Week 54**	Visit 8/ Week 106**	End of Study Visit/ Week 108*
Pubertal Assessment (Tanner) and Physical Development [3]			X		X	X			X	X
Epilepsy Diary[4]	X	X	X	X	X	X	X	X	X	X
TESS[5]		X	X	X	X	X	X	X	X	X
Efficacy Assessments										
Sleep and Nap Diary[6]	X	X	X	X	X	X	X	X		
CSDI[7]		X	X	X	X	X	X	X	X	X
Actigraphy[8]		X	X[8]	X	X[8]					
CGAS[5]		X	X	X	X	X				
SDQ[7]		X	X	X	X	X				
ESS[7]		X	X	X	X	X	X	X	X	X
PSQI[7]		X	X	X	X	X	X	X	X	X
WHO-5[7]		X	X	X	X	X	X	X	X	X
IMP Dispensing		X	X	X	X	X	X	X[9]	X	

Footnotes for Table 5-2:

* The visit should be carried out within ±3 days.

** The visit should be carried out within ±7 days.

1. End of Phase I of the study

2. For female patients of childbearing potential, urine dipstick pregnancy tests will be administered.

3. The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI.

4. For patients with epilepsy and a history of seizures, the Epilepsy Seizures Diary is to be dispensed to the parent at each visit and completed only on the days that the patients has a seizure, which should include the date, time, duration and type of the seizure (Appendix 10). The Epilepsy Seizures Diary is to be completed only by the patient's parent/caregiver after each seizure and to be entered into the electronic case report form (eCRF) by the site at each study visit.

5. The TESS (Appendix 5) and CGAS (Appendix 9) must be administered and completed by the Investigator with the parent/caregiver's input at the study visit indicated.

6. Sleep and Nap Diary is to be completed 14 nights before each scheduled visit (Appendix 1 and Appendix 2). The parent will complete the questionnaire either directly into the eCRF or on the printed version. If the printed version is used, at a later time point, the site coordinator will enter the questionnaire data into the eCRF. At the screening visit, the Sleep and Nap Diary is dispensed. The study coordinator/Investigator must provide guidance to the parents on how to complete the diary by reviewing the diary question by question and explaining the importance of completing all required data entry every morning, preferably within 2 to 3 hours after the patient wakes up. It is critical that the study coordinator/Investigator provide a thorough review and explanation of the diary to the parents to ensure that the data retrieved is high quality and reliable. A follow-up phone call to remind patients to begin filling out Sleep and Nap Diaries will be made every week before Visits 1 and 2, as well as every week during the study period up to Visit 7. Between Visits 7 and Visit 8, the phone call will be made once a month.

7. CSDI (Appendix 6), SDQ (Appendix 8), ESS (Appendix 7), WHO-5 (Appendix 9), and PSQI (Appendix 8) are to be completed by the site coordinators/Investigators with the parents/caregiver, by posing the questions in the questionnaires and filling in the responses given by the parents/caregiver. Note: The ESS, WHO-5, and PSQI are to assess sleepiness, quality of sleep, and well-being of the parent/caregiver's and NOT the child.

8. Actigraphy (Actiwatches) is dispensed to patients at Visit 1 so that they can be worn for 14 days prior to Visit 2. The device is to be delivered to the patient's home no earlier than 3 weeks before Visit 4 to ensure the actigraphy maintains adequate battery strength. Actiwatches are to be worn 14 nights before Visit 2 and Visit 4 and collected at Visit 2 and Visit 4. The actigraphy should be worn by the patient from drug-intake at night until lights on in the morning.

9. The study site can choose to not dispense all investigational medicinal product (IMP) up to Visit 8 at once. The site can send new IMP to patients in quarterly intervals (i.e., in periods of 3 month intervals).

6 STUDY POPULATION AND SELECTION

The study population for this study will include patients with confirmed history of ASDs (pervasive developmental disorders) according to DSM-5/4 criteria or ICD-10 or neurodevelopmental disabilities caused by neurogenetic diseases (SMS, Angelman syndrome, Bourneville's disease [tuberous sclerosis]). Enough patients will be screened for the study to allow for 120 patients to be randomized in a 1:1 ratio to receive Circadin® or placebo at Visit 2. Patients will be screened for the study after their legal guardians provide written, informed consent on their behalf (refer to Section 16.2 for further details). In order to be randomized to treatment, patients must meet all inclusion criteria listed in Section 6.1 and none of the exclusion criteria listed in Section 6.2.

6.1 INCLUSION CRITERIA

To be eligible for study entry, all patients must satisfy all of the following criteria at screening:

- Must be children 2 to 17.5 years of age at Visit 2 who comply with taking the study drug.
- Must have written informed consent provided by a legal guardian and assent (if needed).
- 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 (SMS, 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.
- 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.)
- May be on a stable dose of non-excluded medication for 3 months, including anti-epileptics, anti-depressants (selective serotonin reuptake inhibitors [SSRIs]), stimulants, all mood changing drugs and β-blockers. (Only morning administration of β-blockers is allowed since β-blockers at night have the potential to reduce endogenous melatonin levels and might cause disturbed sleep).
- 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 (for those who need it) and 2 weeks of placebo run-in, patients will be eligible to continue the study if they comply with the following:

- Continue to fulfil sleep problem criteria (see Inclusion Criterion 4) based on the completed Sleep and Nap Diary entered into the electronic case report form (eCRF)

- 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

6.2 EXCLUSION CRITERIA

Children who meet any of the following criteria will be excluded from participating in the study:

- Have had treatment with any form of melatonin within 2 weeks prior to Visit 1
- Have a known allergy to melatonin or lactose
- Have a known moderate to severe sleep apnea
- Have an untreated medical/ineffectively treated/psychological condition that may be the etiology of sleep disturbances
- Did not respond to previous Circadin® therapy based on past medical history records in the last 2 years
- Are taking or have been taking prohibited medication within 2 weeks prior to Visit 1 (Section 7.1)
- 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.)
- Pregnant females
- 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).
- Children with known renal or hepatic insufficiency

6.3 WITHDRAWAL OF PATIENTS FROM TREATMENT

Children must be withdrawn from the clinical study if any of the following reasons occur:

- The parents or the patient withdraw their consent.
- The Investigator considers, for safety reasons, it is in the best interests of the patient that the patient be withdrawn from the study.
- A protocol violation or inter-current illnesses occurs, which, in the clinical judgment of the Investigator or after discussion with the Sponsor, may invalidate the study by interfering with the investigational medicinal product (IMP).
- It is discovered that the patient has entered the study in violation of the protocol.
- A significant protocol violation occurs during the study (e.g., a patient violates a major Inclusion/Exclusion criteria; Section 13.3.2).

- The randomization code is broken for that patient by any 1 of the staff at the clinical study site.
- The patient has taken any prohibited medication listed in Section 7.1 (Appendix 11).
- The patient is lost to follow-up.

The date and reason for withdrawal should be noted in the Withdrawal Form in the eCRF. A parent who withdraws consent will be asked by the Investigator to give a reason, but is not obligated to do so. A patient who withdraws from the clinical study should, if possible, be seen for a Withdrawal Visit scheduled as soon as possible and the end of study procedures should be carried out, as shown in Section 8.19, after the patient has withdrawn from the clinical study. No new information will be collected from the patient except information collected in relation to the scheduled Follow-up Visit or needed for the follow-up of AEs or SAEs.

If a patient is withdrawn from the study, no replacement will be considered.

6.4 REPLACEMENT OF PATIENTS

Patients who have been screened but have not been previously randomized to this study may be rescreened for participation if they are eligible.

7 TREATMENTS ADMINISTERED

Children found eligible who do not have documented sleep hygiene training in their history will start a 4-week sleep hygiene and behavioral intervention, which will serve as a wash-out period from any hypnotics with gradual withdrawal during the first 2 weeks and complete withdrawal during the last 2 weeks. Patients will then enter a 2-week SB placebo run-in period. Enough eligible children will be screened for the study to allow for 120 patients to be randomized in a 1:1 ratio to receive Circadin® or placebo at the end of the 2-week SB placebo run-in period, whether they are children who underwent the sleep hygiene and behavioral intervention or not.

Children with a documented history of sleep hygiene and behavioral intervention who are taking prohibited medications will not require additional training and will undergo a 2 week wash-out period before Visit 1 (e.g., Weeks 2 through 0 to wash out melatonin or any other prohibited medications). During these 2 weeks there is no need to complete the sleep and nap diary.

Children with 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 2-week placebo run-in period, patients who are still found eligible will be randomized in a 1:1 ratio to receive either Circadin® 2 mg or matching placebo for 3 weeks. At the end of the 3-week double-blind period, a decision on dose modification (i.e., an increase to 5 mg) will be made based on predefined criteria (Section 7.3.1). The double-blind period will continue for another 10 weeks (total 13 weeks) after which Circadin® 2 or 5 mg will be given open-label for another 13 weeks of follow-up to evaluate maintenance of efficacy and safety. At this time point (Week 28), data gathered from both the double-blind and open-label periods will be analyzed. The study will continue with a second opportunity for dose modification according to the same criteria as before (an increase either to 5 mg for patients who are still on 2 mg or to 10 mg for patients who are on 5 mg) after which open-label

treatment will continue for an additional 78 weeks of follow-up to evaluate maintenance of efficacy and safety. At the end of the Circadin® open-label period, patients will undergo a 2-week SB placebo run-out period to assess withdrawal effects. 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.

7.1 PROHIBITED MEDICATIONS

The following medications are not permitted for use for the duration of the study and within 2 weeks prior to Visit 1. If use of these medications is unavoidable for clinical reasons, then the patient will need to be withdrawn from the study:

- Melatonin or melatonin agonists (other than the study treatment)
- Excessive consumption of alcohol

The full list of prohibited medications is given in Appendix 11. This is a living list that will not cause any protocol amendment if needs to be amended.

7.2 INVESTIGATIONAL MEDICINAL PRODUCT

Circadin®

Generic name:	Melatonin
Trade name:	Circadin®
Chemical name:	N-Acetyl-5-Methoxytryptamine
Formulation:	Amino-methacrylate co-polymer
	Calcium hydrogen phosphate
	Lactose
	Silicon dioxide
	Talcum
	Magnesium stearate

The PR of melatonin is achieved primarily by the methacrylate polymer EUDRAGIT. The calcium hydrogen phosphate serves as a filling and binding agent and lactose as a diluent and bulking agent. Talc and magnesium stearate serve as lubricants. Circadin® 1 mg minitablets will be used in this study. These tablets are 3 mm in diameter and will allow flexibility of dosing for the required dose titrations from 2 mg to 5 mg or 10 mg.

Study drug (IMP) will be stored in the medical center's local pharmacy or in the Investigator's office securely, separate from other drugs (IMP Handling Guidelines). Study drug should not be exposed to direct sunlight or other sources of heat, and is to be kept at room temperature (<25°C).

Placebo

Placebo will be identical in appearance and formulation to active Circadin® minitablets, but will contain no active melatonin.

7.3 CIRCADIN® ADMINISTRATION

The dose will be titrated from 2 mg (2 minitablets) to 5 mg (5 minitablets – Visit 3) to 10 mg (10 minitablets – Visit 5), as instructed in Section 7.3.2.

Circadin® and placebo are to be administered orally, 1 portion of minitablets daily, taken postprandial at 0.5 to 1 hour before desired bedtime (bedtime should be age-appropriate bedtime). The minitablets should be swallowed whole and should not be crushed or halved. Both Circadin® and placebo minitablets can be administered in foods such as orange juice, semi-skimmed milk, strawberry yogurt, and strawberry jam, to allow dosing of multiple minitablets to the children studied. Melatonin was found to be compatible and stable for up to 6 hours in these specific common foods and liquids[16].

7.3.1 Dose Modification

At the end of 3 weeks of double-blind treatment (Visit 3) and 13 weeks of open-label treatment (Visit 5), the Investigator will review the Sleep and Nap Diaries and the eCRF recommendation for dose increase and then make an assessment of treatment effect. If the Investigator decides that a dose increase is necessary, the following criteria must be met before the increase can take place:

- The patient has an absence of SAEs related to study drug.
- The patient has an absence of daytime fatigue related to study drug.
- The parents demonstrated 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 completed the diary pages with all mandatory questions (i.e., those marked with an asterisk [*], Appendix 1).
- The patient has received at least 5 of 7 doses in the current week based on Diary-reported data.

  AND

- The patient had ≤6 hours of continuous sleep AND/OR ≥0.5 hours of sleep latency from light off in ≥3 out of 5 nights (i.e., in 3 nights or more a week, as a minimum of 5 diaries must be completed each week) in each of the 2 weeks prior to Visit 3 or Visit 5. This will be derived from the Sleep and Nap Diary and calculated by the eCRF.

  OR

- The patient had ≤6 hours of continuous sleep AND/OR ≥0.5 hours of sleep latency from light off only in ≤2 out of 5 nights (i.e., in 2 nights or less a week, as a minimum of 5 diaries must be completed each week) in each of the 2 weeks prior to Visit 3 or Visit 5, AND did NOT improve from Visit 2 by at least 1 hour as measured by either shortening of sleep latency or increase in sleep duration or both. Change in sleep duration and sleep latency will be measured

by subtracting the Visit 2 mean duration and sleep latency values from the mean duration and the mean sleep latency values from all available nights 2 weeks prior to Visit 3 or Visit 5. Values will be derived from the Sleep and Nap Diary and calculated by the eCRF. The eCRF will advise whether a dose increase is recommended or not.

If any of the above criteria are not met, or if there is any doubt regarding a criterion, the current dose should be maintained.

Allowed dose increases include 2 mg to 5 mg at Visit 3, and/or 2 mg to 5 mg or 5 mg to 10 mg at Visit 5.

7.3.2 Dose Reduction

At any time, a patient's dose maybe reduced to 2 mg or 5 mg for reasons such as AEs that are considered related to the study drug, and/or specifically for the following reasons:

- An unacceptable increase in daytime fatigue
- An unacceptable behavioral change
- If the patient ceases to respond to study drug (sleep improved and then deteriorated on higher dose)

If a dose reduction is thought to be required following a scheduled telephone call, the Investigator should consult with the Principal Investigator (PI) or the Medical Monitor prior to a dose modification. If a dose reduction is agreed upon, an unscheduled visit should be arranged. Dose modifications should be documented in the eCRF.

If a dose is reduced for any reason, the Investigator may, at their discretion, restart the previous dosage at Visit 3 or Visit 5.

7.4 BLINDING

The initial 2-week SB placebo run-in period of this study is designed as a SB period with the patients blinded as to what study drug they will receive. All patients will receive placebo during the run-in period. The run-in period will be followed by 13 weeks of double-blind treatment, where the Investigator and the patient will be blinded to treatment allocation. Patients will be randomized using a 1:1 ratio to receive either Circadin® 2 mg (2 minitablets each containing 1 mg of Circadin®) or placebo (2 minitablets containing 1 mg of placebo). The placebo will have the same appearance as Circadin®. After 3 weeks of study, if dose modification is deemed necessary, patients will receive increased doses in the same manner (5 minitablets containing 1 mg of Circadin® or placebo). The randomization scheme will be designed to ensure that patients requiring dose modification will continue receiving the same treatment (Circadin® or placebo).

Except in an emergency, the blind should not be broken until all completed eCRFs are received by Data Management and the database is locked.

All sites will receive unblinding envelopes to facilitate emergency unblinding if needed.

7.5 DOSE SELECTION RATIONALE

Several studies have tested the effect of melatonin on sleep efficiency and quality in children with autistic spectrum disorders, delayed sleep phase syndrome and other neurodevelopmental disabilities[17]. Children in these studies received melatonin dosages in the range of 2 to10 mg, with a 5 mg dose given in 2, randomized placebo-controlled studies[18, 19]. Another study investigated the effect of Circadin® in doses of 4 to 6 mg in children with various neurodevelopmental disorders[12]. Results of these studies indicated that the proposed Circadin® dosage regimen provided optimal effects with respect to efficacy, and there were no safety concerns for the dose proposed for use in this study. A PR preparation, taken postprandial 0.5 to 1 hours before bedtime, will supply and sustain sufficient melatonin in the circulation during the whole sleep cycle.

7.6 TREATMENT COMPLIANCE

Treatment compliance will be calculated at each study visit by counting returned minitablets and using the following formula, except for Visit 8, where treatment compliance will be determined according to the parents reporting on the amount of tablets the child has taken since Visit 7:

$$\text{Compliance (\%)} = \frac{\text{Number of tablets dispensed} - \text{Number of tablets returned*} - \text{Number of tablets lost}}{\text{Number of minitablets per day x Number of days since last visit}} \times 100$$

* In case patients/parents forgot to bring in the unused IMP, the number of tablets returned is to be replaced by the number of tablets remaining in the IP pack, as reported by the patient.

Any divergence from the accepted level of compliance (70% to 130% of expected consumption) is to be investigated by the Investigator and could lead to withdrawal of the patient from the study.

Treatment compliance will be recorded in the patient's eCRF by the Investigator.

8 CONDUCT OF STUDY AND STUDY ASSESSMENTS

This study will be conducted as outlined in the following sections and in accordance with the treatment schedule (Table 5-1) and the schedule of study assessments (Table 5-2). The first study visit will occur at Week -4 and the final study visit will occur at the last day of Week 108. Sleep will be measured by (1) Sleep and Nap Diaries 14 nights before each scheduled visit from Visit 1 (Week 0) up to and including Visit 7 (54 weeks) and (2) actigraphy 14 nights before Visits 2 and 4. Phone calls to remind patients to begin filling out Sleep and Nap Diaries will be made every week before Visits 1 and 2, as well as every week during the study period up to Visit 7. Between Visits 7 and 8, a phone call will be made once a month.

This is a randomized placebo-controlled study in children diagnosed with ASDs and neurodevelopmental disabilities caused by neurogenetic diseases. Patients will start 4 weeks of basic sleep hygiene and behavioral intervention (wash-out period) followed by a 2-week SB placebo run-in period, and will then be randomized in a 1:1 ratio to receive either Circadin® 2 mg or matching

placebo for 13 weeks with a dose modification after the first 3 weeks. Patients who have been screened but have not been previously randomized can be rescreened they are eligible. This double-blind period will be followed by an open-label period of 13 weeks. Data will be gathered at the end of the 13-week open-label period (Week 28), and analyzed; however, children will continue in the study for another 78 weeks of follow-up. The study will end with a 2-week SB placebo run-out period. All together 10 visits are planned, including screening visit and end of study visit, and additional unscheduled visits may be necessary (Section 8.20).

At each visit, study questionnaires and diaries will be dispensed and completed according to the schedule in Table 5-2, and as described in the sections below. Questionnaires and diaries are to be completed as follows:

- The Sleep and Nap Diary is to be completed only by the patient's parent/caregiver during the 14 nights before each scheduled visit, every morning 2 to 3 hours after the child awakens (Appendix 1 and Appendix 2). The diary can be completed either directly in the eCRF or by using a paper version. If the diary is completed on paper, the site coordinator will enter the questionnaire data into the eCRF during the visit. The diaries prior to Visit 1 and Visit 2 must be entered in to the system at the respective visit in order to allow eligibility assessment to occur at Visit 1 and Visit 2. Prior to Visit 1, diaries are required only for children who had undergone the 4-week sleep hygiene and behavioral intervention training period, to check whether they responded to the therapy. Diaries prior to Visit 1 are not required for children with a documented history of sleep hygiene and behavioral intervention, as Visit 1 eligibility for these children is measured based on the parent's report of their child's sleep over the previous 3 months, which is reported at screening. If the child doesn't need the sleep hygiene but needs the 2-week wash-out period prior to Visit 1, the parent doesn't need to complete the sleep diary either.
- For patients with epilepsy and a history of seizures, the Epilepsy Seizures Diary is to be dispensed to the parents/caregivers at each visit and to be completed by the patient's parent/caregiver only on the days that the patients has a seizure. It should include the date, time, duration and type of the seizure (Appendix 10). The Epilepsy Seizures Diary is to be completed only by the patient's parent/caregiver after each seizure.
- The questionnaires CSDI, SDQ, ESS, WHO-5, and PSQI are to be completed by the site coordinators/Investigators with the parents/caregiver, by posing the questions in the questionnaires and filling in the responses given by the parents/caregiver. Note: The ESS, WHO-5, and PSQI are to assess sleepiness, quality of sleep, and well-being of the parent/caregiver and NOT the child.
- The TESS (Appendix 5) and CGAS (Appendix 3) must be administered and completed by the Investigator with the parent/caregiver's input.

The following table (Table 8-1) identifies to whom the questionnaire relates and who is responsible for completing the questionnaire.

Table 8-1: Summary of Questionnaires

Questionnaire	Information relates to:	Completed by:
Sleep and Nap Diary	Child	Parent/caregiver
Epilepsy Seizures Diary	Child	Parent/caregiver
CSDI	Child	Site coordinators/Investigator with parent/caregiver's input
SDQ	Child	Site coordinators/Investigator with parent/caregiver's input
ESS	Parent	Site coordinators/Investigator with parent/caregiver's input
WHO-5	Parent	Site coordinators/Investigator with parent/caregiver's input
PSQI	Parent	Site coordinators/Investigator with parent/caregiver's input
CGAS	Child	Investigator with parent/caregiver's input
TESS	Child	Investigator with parent/caregiver's input

8.1 SCREENING VISIT (DAY 1 AT -4 WEEKS ±3 DAYS)

These items may be carried out by the Investigator or a qualified designee:

- Explain the conduct of the study.
- Provide the informed consent form (ICF) and information sheet to patients and legal guardians to read and sign.
- Eligibility screening done by Investigator or a qualified designee:
- Record detailed medical history.
- Record of demographic data.
- Verify sleep problem based on completed diaries.
- Perform physical examination and measure vital signs.
- Measure body weight and height for the BMI and Z-score calculations.
- Review inclusion/exclusion criteria.
- Administer urine dipstick pregnancy tests to females of child-bearing potential.
- Explain sleep hygiene training and dispense training booklet.
- Explain and dispense the Sleep and Nap Diary (to be completed during the 14 nights before Visit 1; Appendix 1). The study coordinator/Investigator must provide guidance to the parents on how to complete the diary by reviewing the diary question by question and explaining the importance of completing all required data entry every morning, preferably within 2 to 3 hours after the patient woke up. It is critical that the study coordinator/Investigator provide a thorough review and explanation of the diary to the parents to ensure that the data retrieved is high quality and reliable. Please also refer to Appendix 2 (Sleep and Nap Diary Guidelines, Presentation and Take-Home Instructions for Parents).

- Explain and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- The visit should be carried out within ±3 days.

During the screening period, if a parent does not complete the diary appropriately due to a misunderstanding, then with the Investigator's approval, a patient can be re-screened.

8.2 PRE-VISIT 1

A follow-up phone call to remind patients to begin filling out Sleep and Nap Diaries will be made every week before Visits 1 and 2, as well as every week during the study period up to Visit 7. The site is to make a phone call at 2 weeks ahead of Visit 1 to remind patients to begin filling out Sleep and Nap Diaries. If sleep hygiene was not required (i.e., the patient entered the study with history of documented sleep hygiene at Visit 1), no call will be needed, as Visit 1 will be the first visit and serve as the screening visit.

8.3 VISIT 1 (WEEK 1 DAY 1 ±3 DAYS)

- Confirm eligibility.
- Verify sleep problem based on completed diaries.
- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record medical history.
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input. At Visit 1 TESS information is used to assess patient medical history. All symptoms that are at score of 1 of more should be recorded in the medical history as they will serve as the baseline for future AEs throughout the entire study.
- Fill out CGAS (Appendix 3; to be completed by the Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out SDQ (Appendix 4; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).

- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10); to be completed by the parent/caregiver after each seizure).
- Collect and dispense Sleep and Nap Diary (Appendix 1) to be completed by the parent/caregiver during the 14 nights before Visit 2). If the Sleep and Nap Diaries were completed on a paper version, then the diary data is to be entered into the eCRF.
- Explain and dispense of study drug (IMP Handling Guidelines).
- Explain the actigraphy procedure and dispense actigraphy (Actiwatches) and the take-home instructions. The actiwatches should be worn by the patient from drug-intake at night until lights on in the morning). Actigraphy (Actiwatches) are to be worn for 14 days prior Visit 2.
- The visit should be carried out within ±3 days.

8.4 PRE-VISIT 2 PHONE CALL

A phone call will be made every week before Visits 1 and 2 to remind patients to begin filling out Sleep and Nap Diaries and to have the patient wear the actigraphy (Actiwatch).

8.5 VISIT 2 (RANDOMIZATION/BASELINE VISIT; LAST DAY OF WEEK 2 ±3 DAYS)

- Confirm eligibility; if a patient does not meet the eligibility criteria for randomization, as listed in Section 6.1, the patient will be withdrawn from study and end of study procedures will be carried out, as listed in Section 8.19. Any end of study assessments performed should be entered on the visit at which the patient is deemed ineligible and the eCRF Study Completion/Withdrawal page should be completed, as described in Section 6.3.
- Verify compliance.
- Verify sleep problem based on completed diaries.
- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record AEs.
- Administer pregnancy test to females of child-bearing potential.
- Assess pubertal status using the Tanner scale. (The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI.)
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input).

- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out CGAS (Appendix 9; to be completed by the Investigator with the parent/caregiver's input).
- Fill out SDQ (Appendix 4; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Sleep and Nap Diary (Appendix 1; to be completed by the parent/caregiver during the 14 nights before Visit 3). If the Sleep and Nap Diaries were completed on a paper version, then the diary data is to be entered into the eCRF.
- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- Explain and dispense study drug (IMP Handling Guidelines).
- Collect actigraphy (Actiwatches).
- Perform randomization.
- The visit should be carried out within ±3 days.

8.6 PRE-VISIT 3

Phone calls should be made weekly. In addition, on the phone call 2 weeks prior to Visit 3, parents are to be reminded to begin filling out the Sleep and Nap Diary.

8.7 VISIT 3 (POSSIBLE DOSE MODIFICATION; LAST DAY OF WEEK 5 ±3 DAYS)

- Perform potential dose modification.
- Verify compliance.
- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.

- Record AEs.
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out CGAS (Appendix 9; to be completed by the Investigator with the parent/caregiver's input).
- Fill out SDQ (Appendix 4; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Sleep and Nap Diary (Appendix 1; to be completed by the parent/caregiver during the 14 nights before Visit 4). If the Sleep and Nap Diaries were completed on a paper version, then the diary data is to be entered into the eCRF.
- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- Explain the actigraphy procedure and provide take-home instructions for actigraphy (Actiwatches) to be worn for 14 days prior Visit 4. The device is not provided at Visit 3, but is to be mailed or given to the patient at least 17 days, and no earlier than 3 weeks, before Visit 4 to ensure the actigraphy maintains adequate battery strength.
- Explain and dispense study drug (IMP Handling Guidelines).
- The visit should be carried out within ±3 days.

8.8 PRE-VISIT 4

Phone calls should be made weekly. The site should confirm with parents that the actigraphy device was received. On the phone call 2 weeks prior to Visit 4, parents are to be reminded to begin filling out the Sleep and Nap Diary and to have patients wear the actigraphy (Actiwatch).

8.9 VISIT 4 (LAST DAY OF WEEK 15 ±3 DAYS)

- Verify compliance.

- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record AEs.
- Administer pregnancy test to females of child bearing potential.
- Assess pubertal status using the Tanner scale (The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI.)
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out CGAS (Appendix 9; to be completed by the Investigator with the parent/caregiver's input).
- Fill out SDQ (Appendix 4; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- Collect and dispense Sleep and Nap Diary (Appendix 1; to be completed by the parent/caregiver during the 14 nights before Visit 5). If the Sleep and Nap Diaries were completed on a paper version, then the diary data is to be entered into the eCRF.
- Explain and dispense study drug (IMP Handling Guidelines).
- Collect actigraphy (Actiwatches).
- The visit should be carried out within ±3 days.

8.10 PRE-VISIT 5

Phone calls should be made weekly. In addition, on the phone call 2 weeks prior to Visit 5, parents are to be reminded to begin filling out the Sleep and Nap Diary.

8.11 VISIT 5 (LAST DAY OF WEEK 28 ±3 DAYS)

- Perform potential dose modification
- Verify compliance.
- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record AEs.
- Assess pubertal status using the Tanner scale (The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI.)
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out CGAS (Appendix 9; to be completed by the Investigator with the parent/caregiver's input)
- Fill out SDQ (Appendix 4; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Sleep and Nap Diary (Appendix 1; to be completed by the parent/caregiver during the 14 nights before Visit 6). If the Sleep and Nap Diaries were completed on a paper version, then the diary data is to be entered into the eCRF.

- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- Explain and dispense study medication (IMP Handling Guidelines).
- The visit should be carried out within ±3 days.

8.12 PRE-VISIT 6

Phone calls should be made weekly. In addition, on the phone call 2 weeks prior to Visit 6, parents are to be reminded to begin filling out the Sleep and Nap Diary and to have patients wear the actigraphy (Actiwatch).

8.13 VISIT 6 (LAST DAY OF WEEK 41 ±7 DAYS)

- Verify compliance.
- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record AEs.
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Sleep and Nap Diary (Appendix 1; to be completed by the parent/caregiver during the 14 nights before Visit 7). If the Sleep and Nap Diaries were completed on a paper version, then the diary data is to be entered into the eCRF.
- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- Explain and dispense study drug (IMP Handling Guidelines).
- The visit should be carried out within ±7 days.

8.14 PRE-VISIT 7

Phone calls should be made weekly. In addition, on the phone call 2 weeks prior to Visit 7, parents are to be reminded to begin filling out the Sleep and Nap Diary.

8.15 VISIT 7 (LAST DAY OF WEEK 54 ±7 DAYS)

- Verify compliance.
- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record AEs.
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/ Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- Collect the Sleep and Nap Diary (Appendix 1; to be completed by the parent/caregiver during the 14 nights before Visit 8). If the Sleep and Nap Diaries were completed on a paper version, then the diary data is to be entered into the eCRF.
- Explain and dispense study drug (IMP Handling Guidelines).
- The visit should be carried out within ±7 days.

8.16 PRE-VISIT 8

Make follow-up phone call once a month until Visit 8.

8.17 VISIT 8 (LAST DAY OF WEEK 106 ±7 DAYS)

- Verify compliance.

- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record AEs.
- Assess pubertal status using the Tanner scale (The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI.)
- Fill out TESS (Appendix 5; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/ Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect and dispense Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10; to be completed by the parent/caregiver after each seizure).
- Explain and dispense study medication (placebo run-out) (IMP Handling Guidelines).
- The visit should be carried out within ±7 days.

8.18 PRE-END OF STUDY VISIT

Make follow-up phone call 1 week before the end of study visit to ensure that patients are taking study treatment and to schedule an end of study visit.

8.19 END OF STUDY VISIT (LAST DAY OF WEEK 108 ±3 DAYS)

- Verify compliance.
- Measure vital signs.
- Perform physical examination.
- Measure body weight and height for the BMI and Z-score calculations.
- Record AEs.

- Assess pubertal status using the Tanner scale (The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI.)
- Administer pregnancy test to females of child bearing potential.
- Fill out TESS (Appendix 5; to be completed by the Investigator with the parent/caregiver's input).
- Fill out CSDI (Appendix 6; to be completed by the site coordinators/Investigator with the parent/caregiver's input).
- Fill out ESS (Appendix 7; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the parent/caregiver and NOT the child.).
- Fill out WHO-5 questionnaire (Appendix 9; to be completed by the site coordinators/ Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the parent/caregiver and NOT the child.).
- Fill out PSQI questionnaire (Appendix 8; to be completed by the site coordinators/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the parent/caregiver and NOT the child.).
- Collect Epilepsy Seizures Diaries for patients diagnosed with epilepsy (Appendix 10 to be completed by the parent/caregiver after each seizure).
- The visit should be carried out within ±3 days.

8.20 UNSCHEDULED VISIT(S)

At any point during the study, the Investigator could call the patient in for an unscheduled visit if the Investigator was concerned about safety issues; the unscheduled visit page in the eCRF should be completed if such a visit takes place.

9 EFFICACY ASSESSMENTS

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- 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 period 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 weeks (Week 15) of double-blind treatment period.
- Assessment of sleep parameters by actigraphy after 13 weeks (Week 15) of double-blind treatment

Exploratory Efficacy Endpoints

- Sleep variables as assessed by the Sleep and Nap Diary at baseline (Week 2), after 3 weeks of double-blind treatment (Week 5), and after 13, 26, and 39 weeks of open-label treatment (Weeks 28, 41, and 54)
- Sleep disturbance as assessed by the CSDI score at baseline after 3 and 13 weeks of double-blind treatment (Weeks 5 and 15, respectively), after 13, 26, 39, and 91 weeks of open-label treatment (Weeks 28, 41, 54, and 106, respectively), and at the end of study visit (Week 108)
- Social functioning at home, in school, and in community settings as assessed by the CGAS after 13 weeks (Week 28) of open-label treatment
- Behavior at home and in school as assessed by the SDQ after 13 weeks (Week 28) of open-label treatment
- Caregiver's daytime sleepiness (i.e., NOT the child's) during the study as assessed by the ESS (Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108)

- Caregiver's well-being (i.e., NOT the child's) during the study as assessed by the WHO-5 questionnaire (Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108)
- Caregiver's quality of sleep at night (i.e., NOT the child's) during the study as assessed by the PSQI questionnaire (Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108)

10 CLINICAL PHARMACOLOGY ASSESSMENTS

10.1 PHARMACOKINETIC (PK) ASSESSMENTS

Not applicable.

10.2 PHARMACODYNAMIC (PD) ASSESSMENTS

Not applicable.

10.3 BIOMARKER AND EXPLORATORY ASSESSMENTS

Not applicable.

11 SAFETY ASSESSMENTS

11.1 ADVERSE EVENTS

It is the responsibility of the Investigator to document all AEs that occur during the study. Adverse events should be elicited using the TESS (Appendix 5).

11.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient who is administered a pharmaceutical product during participation in an investigational study, which may or may not have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding or physical examination), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes whether associated with the study drug and whether or not considered drug related. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, which do not represent a clinically significant exacerbation or worsening, need not be considered AEs.

Patient entry into the study is defined as the time at which informed consent is obtained (this must be before any protocol-specific diagnostic procedures or interventions). All AEs on this study subsequent to Visit 1 must be reported regardless of whether or not they are considered related to study drug. Any

AEs experienced subsequent to signing of the informed consent/assent will be recorded as a medical history item.

At Visit 1, the TESS questionnaire (Appendix 5) is completed and the information is used to assess medical history. All symptoms that are score of 1 or more should be recorded in the medical history as it will serve us throughout the study as a baseline to see if a symptom was worsen or not. At Visit 2 and all subsequent visits thereafter, the TESS questionnaire is used to report all treatment-emergent signs and symptoms that may have occurred since Visit 1. As instructed in Appendix 5, a given sign and symptom is to be reported as a corresponding AE if a score of 1 or above is selected, and if the sign or symptom is a new symptom or if there is an increase in severity of an existing symptom from the first visit (i.e., Visit 1). If a specific symptom has the same score or lower from Visit 1 AEs should not be reported.

Adverse events are also to be reported on the appropriate page of the patient's eCRF.

11.1.2 Assessment of Severity

Each AE will be assigned a category as follows:

Mild: Not sufficiently intense to result in discontinuation of the study drug. Symptomatic treatment may have been given.

Moderate: Sufficiently intense to result in discontinuation of the study drug. Symptomatic treatment may have been given.

Severe: More intense than moderate; moreover the AE interferes significantly with ability to do work or usual activity.

A change in the severity of an AE will require it to be recorded as a separate event.

11.1.3 Assessment of Frequency

Frequency should be assessed using the following categories:

- Unique
- Intermittent
- Continued

11.1.4 Assessment of Outcome

Outcome should be assessed using the following categories:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal

- Unknown

11.1.5 Assessment of Causality and Relatedness

Every effort should be made by the Investigator to explain each AE and assess its relationship, if any, to study drug. Even if the Investigator feels there is no relationship to the study drug, all adverse experiences MUST be recorded in the eCRF. The Investigator is requested to assess the relationship of any clinical adverse experiences to treatment using the following definitions:

Causality should be assessed using the following categories:

- Not related: those AEs which are clearly and incontrovertibly due to extraneous causes (concurrent drugs, environment etc.) and do not meet the criteria for drug relationship listed under Unlikely, Possible, Probable or Related.
- Unlikely to be related: an adverse experience may be considered unlikely if it includes at least the first 2 features:
    - It does not follow a reasonable temporal sequence from administration of the drug
    - It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
    - It does not follow a known pattern to the suspected drug
    - It does not reappear or worsen when the drug is re-administered
- Possibly related: an adverse experience may be considered possible if it includes at least the first 2 features:
    - It follows a reasonable temporal sequence from administration of the drug
    - It could readily have been produced by the patient's clinical state, environment or toxic factors, or other modes of therapy administered to the patient
    - It follows a known response pattern to the suspected drug
- Probably related: an adverse experience may be considered probable if it includes at least the first 3 features:
    - It follows a reasonable temporal sequence from administration of the drug.
    - It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient
    - It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.).
    - It follows a known pattern of response to the suspected drug.

- Definitely related: An adverse experience may be considered related if it includes all of the following features:
    - It follows a reasonable temporal sequence from administration of the drug.
    - It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
    - It disappears or decreased on cessation or reduction in dose. There are exceptions when an AE does not disappear upon discontinuation of the drug. For example: bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.
    - It follows a known pattern of response to the suspected drug.
    - It reappears or worsens if the drug is re-administered.

11.1.6 Follow-up of Adverse Events

All Investigators should follow-up with patients who experience AEs until the event is resolved or until, in the opinion of the Investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

11.2 SERIOUS ADVERSE EVENTS

11.2.1 Definition of a Serious Adverse Event

An SAE is defined as any event which is:

- Fatal
- Life threatening:
    - An AE is life threatening if the patient is at immediate risk of death from the event as it occurs (i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Disabling or incapacitating :
    - An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient’s ability to carry out normal life functions.
- Results in hospitalization or prolongs a hospital stay:
    - Complications occurring during hospitalization are considered AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not considered an AE. The details of such hospitalizations must be recorded on the medical history/physical examination page of the eCRF.

In addition, medical and scientific judgment is required to decide if prompt notification is required in other situations (i.e., any event which the Investigator regards as serious that does not strictly meet the

criteria above but may jeopardize the patient or required intervention to prevent 1 of the outcomes listed above, or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the study drug.

11.2.2 Definition of an Unexpected Adverse Event

An unexpected AE, is defined as 1 that has not been reported as expected in this protocol or the Investigator's Brochure, either from previous clinical studies or the pre-clinical studies.

11.2.3 Reporting of Serious Adverse Events

Any SAE must be reported by the Investigator if it occurs during the study or within 30 days of receiving study drug, whether or not the SAE is related to the study drug. A SAE report consists of the SAE form, the AE form and the concomitant medication form. A copy of these forms must be faxed by the Investigator for the attention of the study Safety Officer within 24 hours following knowledge of the SAE.

The Investigator should not wait to receive additional information to fully document the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records and autopsy reports should be obtained.

Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of study medication and linked by the Investigator to this study should be reported to the study monitor immediately.

Serious adverse events should be reported to:

Tali Nir, DVM
Vice President Clinical and Regulatory Affairs
Neurim Pharmaceuticals Ltd.
Tel: +972-3-7684902
Fax: +972-3-6494568
talin@neurim.com
www.neurim.com

Please also send a copy to PharSafer:
drugsafety@pharsafer.com

11.3 WITHDRAWAL DUE TO AN ADVERSE EVENT

Any patient who experiences an AE may be withdrawn from the study drug at any time at the discretion of the Investigator. If a patient is withdrawn wholly or in part because of an AE, both the AEs page and termination page of the eCRF will be completed at that time. As described in Section 6.3, a patient who withdraws from the clinical study is required to be seen for a Withdrawal Visit scheduled as soon as possible after the patient has withdrawn, and end-of-study procedures are to

be carried out as shown in Section 8.19. The patient will be monitored until the event has resolved or stabilized, until a determination of a cause unrelated to the study drug or study procedure is made, or until the patient is referred to the care of a local health care professional. The Investigator must inform the medical monitor as soon as possible of all patients who are being considered for withdrawal due to AEs. Additional reports must be provided when requested.

If a patient is withdrawn from the study drug for multiple reasons that include AEs, the termination page of the eCRF should indicate that the withdrawal was related to an AE.

11.4 MONITORING OF PATIENTS WITH AES

Each patient must be carefully monitored for AEs. Assessments must be made of the seriousness, intensity and relationship to the administration of the study treatment. After the initial AE/SAE report the Investigator is required to follow-up proactively each patient and provide further information to PRA Health Sciences on the patient's condition. During the study all AE/SAEs should be followed up to resolution unless the event is considered by the Investigator to be unlikely to resolve due to the patient's underlying condition, or the patient is lost to follow-up.

11.5 PHYSICAL EXAMINATION AND VITAL SIGNS

Vital signs and physical examination will be assessed at screening each visit including the placebo run-out (withdrawal) period. Physical examination findings at screening will be classified using standard categories as listed on the Medical History eCRFs. Any physical examination finding that is judged by the Investigator as a clinically significant change (worsening) compared to a baseline value (Visit 2) will be considered an AE, recorded on the adverse event eCRF, and monitored as described in Section 11.4.

A complete physical examination will include examination of body systems (including, but not limited to, general appearance, skin, neck, eyes, ears, nose, throat, breasts, lungs, heart, abdomen, back, lymph nodes, extremities, and nervous system).

The Tanner scale will be used to assess and stage physical development in children ≥8 years of age. For children ≤5 years of age, only height and head circumference will be used to stage children development. Between the age of 5 and 8 the children's physical development will be determined using the BMI.

11.6 TREATMENT OF OVERDOSE OF STUDY MEDICATION

There is no experience of overdosing with Circadin®. No specific treatment for overdosing is known. Administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions have been reported in the literature.

If overdose occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12 hours after ingestion. Treatment given to a patient in case of overdosing should be symptomatic and supportive.

Any overdose, with or without associated AEs, in a clinical study must be reported to PRA Health Sciences. All reports of overdoses must be filed in the Study Center File. Any AEs associated with the overdose should be reported on relevant AE/SAE sections in the eCRF.

11.7 PREGNANCY

Pregnancy will not be considered an AE or SAE. If pregnancy does occur during the study, a pregnancy notification form will be completed, and the patient will discontinue study medication and the Investigator will remove the patient from the study. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs (Section 11.2.3). Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to PRA Health Sciences.

11.8 PHYSICAL EXAMINATION AND VITAL SIGNS

Vital signs and physical examination will be assessed at each visit including the placebo run-out (withdrawal) period.

11.9 OTHER SAFETY ASSESSMENTS

BMI and Z-score calculations will be assessed at each visit including the placebo run-out (withdrawal) period.

In children diagnosed with epilepsy the number and severity of epilepsy seizures during the study will be completed by the parents throughout the study in Epilepsy Seizures Diaries.

12 DATA MANAGEMENT AND STATISTICAL ANALYSIS

12.1 DATA MANAGEMENT

An eCRF will be used for the current study and a data management plan will be prepared.

The site will be supplied with the following data collection tools: a web browser address for an Electronic Data Capture (EDC) system database that has been fully validated and conforms to 21 CFR Part 11 and the Guidance for Industry on Computerized Systems Used in Clinical Trials requirements. The EDC system database will be maintained by Datatrial.

Trained site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture forms as needed) into the EDC system. All information on the eCRFs must be traceable to these source documents. Data recorded directly on the eCRFs will be defined before study start. The eCRFs will be completed for all patients randomized to study treatment. The eCRFs for patients who are randomized but not treated will be completed with all data collected at the time of patient study discontinuation. Screen failures should also be entered into the eCRF. Clinical Research Associates will review the eCRFs entered by investigational staff for completeness and accuracy.

Automatic validation programs check for data discrepancies in the eCRFs resulting in electronic queries generated for resolution by the investigational site. Designated site staff is required to respond to queries and make any necessary changes to the data. After database lock, the Investigator will receive the patient data on a CD for archiving at the investigational site.

All treatment-emergent AEs (events occurring from the first dose of study medication through the last study evaluation) will be recorded in the EDC system. AEs will be coded using the MedDRA dictionary (version 16.1) and concomitant medications will be coded using a standard dictionary (e.g., WHODrug, dated March 2013).

The process of randomization and allocating randomized treatments using the eCRF is described in the eCRF completion guidelines and the IMP Handling Guidelines.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by written agreement between Neurim and the PRA Health Sciences project team.

12.2 STATISTICAL ANALYSIS PLAN

A Statistical Analysis Plan (SAP) will be written and finalized prior to any lock of the study database. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol. Additional analyses may be added. Tables, listing and figures shells will also be provided.

12.3 GENERAL CONSIDERATIONS

Results of primary, secondary and selected exploratory efficacy analyses will be summarized at the end of the first open-label period (Week 28; Visit 5), and will be submitted in the form of a clinical study report (CSR) to the regulatory authorities for evaluation of approval of the study drug for use in the investigated population. At the completion of the study (at the end of the second open-label safety follow-up period [Week 108]), another final CSR will be submitted to regulatory authorities. This report will include all the remaining results and analyses (this is in compliance with the final Pediatric Committee opinion on Neurim Pharmaceuticals (1991) Pediatric Investigational Plan [PIP] for the study drug, Circadin® (IMP), deferring the completion of the safety follow-up part of the study - EM EA-000440- PIP02 -11).

12.4 RANDOMIZATION

At Visit 1, enough eligible male and female children, of ages 2 to 17.5 years, will be screened for the study to allow for 120 patients to then be randomized in a 1:1 ratio to receive Circadin® or placebo at Visit 2. 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. The process of randomization and allocating randomized treatments using the eCRF is described in the eCRF completion guidelines and the IMP Handling Guidelines.

12.5 ANALYSIS SETS

Full Analysis Set

Efficacy analyses will be performed on the Full Analysis Set (FAS), and will include all patients in the Safety Analysis Set who satisfy all major entry criteria (Inclusion Criteria 1-5, Section 6.1) and who have efficacy data for the primary endpoint recorded for baseline and at least 1 post-baseline period assessment.

Per Protocol Set

The Per Protocol Set is a subset of the FAS, which excludes all patients for whom there were no serious violations of the protocol.

Safety Analysis Set

Safety analyses will be performed on the Safety Analysis Set, which includes all patients randomized to treatment who take at least 1 dose of study medication.

12.6 SAMPLE SIZE

Statistical analysis will be performed on the combined group of patients. To achieve 95% power at the 5% level for the primary objective (assuming a change of 0.72 hour in the Circadin® arm and 0.27 hour in the placebo arm and a standard deviation (SD) of 0.69 in the Circadin® arm and 0.45 in the placebo arm), 45 patients are required per combined group. Therefore, 90 patients in total are required to complete Visit 5. These estimations are based on previous studies conducted with Circadin®.

12.7 STUDY POPULATION

The set of enrolled patients (see Section 12.5) will be used for all study population summaries unless otherwise noted. Summaries will be presented for all patients.

12.7.1 Patient Disposition

A summary of patient disposition will include all patients enrolled. Data from patients who are enrolled, patients enrolled but not treated, patients in the FAS, patients who complete the study, and patients who withdraw from the study will be summarized using descriptive statistics. Data from patients who were enrolled but not treated will be listed, with the reason why the patient was not treated. Data from patients who were withdrawn from the study will also be summarized by reason for withdrawal using descriptive statistics. The denominator for calculating percentages will be the set of enrolled patients.

12.7.2 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics taken at screening, consisting of medical history, physical examination findings, vital signs, and BMI and Z-score will be summarized using descriptive statistics. For continuous variables, descriptive statistics (n, mean, SD, SE, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary.

12.8 STUDY ENDPOINTS AND STATISITCAL METHODS

12.8.1 Efficacy Endpoints

Primary

Total sleep time will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using linear regression model (Analysis of Covariance [ANCOVA]) to test the null hypothesis so that these adjusted mean scores are equal.

Secondary

Sleep latency will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal.

Duration of wake after sleep onset period will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal.

The number of awakenings will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal.

The longest sleep episode will be assessed by a Sleep and Nap Diary, and will be summarized after 13 weeks (mean of the last 14 days before visit) of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal.

The CGAS score will be summarized at baseline and after 13 weeks of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal.

The SDQ score will be summarized at baseline and after 13 weeks of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median,

minimum, and maximum). For each treatment group for this outcome, the mean score at 13 weeks will be compared, adjusting for baseline, using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal.

The number of dropouts will be compared between the treatment groups and analyzed using a dichotomized data analysis (chi-square test).

Sleep parameters, as measured by actigraphy, will be summarized at baseline and after 13 weeks of double-blind treatment (actual change from baseline) for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For each treatment group for this outcome, the mean score at each time point will be compared using an ANCOVA model to test the null hypothesis so that these mean scores are equal.

For all primary and secondary analyses, a mixed-effect repeated-measures model (MMRM) will be fitted to assess any differences in treatment effects over time. The base models will contain the specified outcome measure after baseline as the dependent variable, with independent variables in the form of the baseline score, the study visit (categorical variable) and treatment allocation. A general covariance structure will be assumed. The global treatment effect estimates will be reported, with 95% CIs and p-values. Further analysis will include interaction between treatment and visit. Interaction p-values will be reported with treatment effect estimates at each visit with 95% CI and p-values.

Exploratory

Sleep variables and sleep disturbance will be assessed by the Sleep and Nap Diary and the CSDI, respectively, at baseline (Week 2) and after 3 and 13 weeks of double-blind treatment (Weeks 5 and 15, respectively) by presenting actual and change from baseline for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). For this outcome, the mean score at 3 weeks will be compared between treatment groups, adjusting for baseline, and by using an ANCOVA model to test the null hypothesis so that these adjusted mean scores are equal.

The CSDI and Sleep and Nap Diary variables will also be summarized after 13, 26, and 39 weeks of open-label treatment (Weeks 28, 41, and 54) by presenting actual values and change from baseline for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum). CSDI will be also summarized after 91 weeks of open-label treatment and at the end of study visit (Week 108) using descriptive statistics (n, mean, SD, median, minimum, and maximum).

The CGAS and SDQ scores will be summarized at baseline (Week 2), after 3 and 13 weeks of double-blind treatment (Weeks 5 and 15, respectively), and after 13 weeks of open-label treatment (Week 28) by presenting actual values and change from baseline for each treatment group using descriptive statistics (n, mean, SD, median, minimum, and maximum).

The ESS, PSQI and WHO-5 scores (for the parent/caregiver) will be summarized at baseline (Week 2), after 3 and 13 weeks of double-blind treatment (Weeks 5 and 15, respectively), after 13, 26, 39, and 91 weeks of open-label treatment (Weeks 28, 41, 54, and 106, respectively), and at the end of study visit

(Week 108) by presenting actual values and change from baseline using descriptive statistics (n, mean, SD, median, minimum, and maximum).

For all exploratory analyses for the double-blind period, a MMRM will be fitted to assess any differences in treatment effects over time. The base models will contain the specified outcome measure after baseline as the dependent variable, with independent variables in the form of the baseline score, the study visit (categorical variable) and treatment allocation.

12.8.2 Safety Endpoints

Descriptive statistics will be provided for AEs, changes in physical examinations and vital signs measurements. The number of patients withdrawing during the treatment periods will be summarized by primary reason for withdrawal for each treatment group.

12.8.3 Exploratory Endpoints

The changes in BMI and Z-score from baseline to the end of the study will be summarized using shift tables showing the number of children below, within and above z calculated normal at each treatment group, separately. The-BMI and Z-scores are designed to take into account the amount of weight gain that would be expected due to normal growth in children and adolescents. The BMI and Z-scores are categorized by age and gender standardized values (corresponding to a normal distribution with mean 0 and a SD of 1) of the actual weight measurements, based on the Growth Charts provided by the Centers for Disease Control.

Tanner scores for pubertal assessment in children ≥8 years of age during the study will be analyzed using the web application (http://vps.stefvanbuuren.nl/puberty)[20]. This tool calculates SD scores of individual observations of Tanner scores and additionally plots those scores in stage line diagram[21].

Descriptive statistics will be provided for head and height measurements and changes in head and height measurements from baseline to Week 108 in children ≤5 years of age.

Descriptive statistics will also be provided for the number and severity of epilepsy seizures in children diagnosed with epilepsy, using the Epilepsy Seizures Diaries that are completed by parents at the time of the seizures and entered in the eCRF at a later time point by the site.

12.9 STUDY TERMINATION CRITERIA

Neurim Pharmaceuticals (1991) Ltd reserves the right to discontinue the study at any time. The reasons will be discussed with the Investigator and Data Safety Monitoring Board (DSMB). A study site may also be discontinued by Neurim Pharmaceuticals (1991) Ltd for significant deviations from the protocol or due to insurmountable difficulties experienced in running the study at that center.

The study may be terminated before the planned number of patients has been achieved for the following reasons:

- Safety and tolerability issues with study IMP which have come to light since study started.
- Slow patient recruitment
- Global recruitment target achieved

- Sponsors decision
- Investigator's decision
- Force Majeure

Specifically, the study may be terminated prematurely at any time that emergent data indicate that the potential benefit of participation is outweighed by observed risks. Additionally the Sponsor may terminate the study if information emerges which demonstrates that the study will not meet its primary objective or progress is unsatisfactory.

A written statement fully documenting the reasons for premature termination will be provided to the responsible Ethics Committees (ECs) and Regulatory Authorities within the timelines required by local regulations.

12.10 DATA SAFETY MONITORING BOARD

A DSMB will be involved in the management of this study. The DSMB will monitor safety data generated by the study at regular intervals for the duration of the study. Their role is to protect the interests of patients in the study and those to be entered, by review of accumulating safety and tolerability data generated in this study. The data provided to the DSMB will not be considered 'clean' until the database is locked. Data will be provided to the DSMB by an independent Biostatistician who is not assigned to the project.

Further details regarding the DSMB will be provided in the DSMB charter. The DSMB charter will define the primary responsibilities of the DSMB, guide its activities, its relationship with other trial components, its membership and the purpose and timing of its meetings. It will provide the procedures for ensuring confidentiality, formal communication and outline of the content of the reports that will be provided by the DSMB.

12.11 HANDLING OF DROPOUTS/MISSING DATA

Missing data will not be replaced for both primary and secondary criteria. The following will be applied concerning start and end dates:

- If the day is unknown and the month and the year are known, it will be replaced by 01 in case of a start date or by the last day of the month in case of an end date.
- If the day and the month are unknown, they will be replaced by 01/01 in case of a start date or 31/12 in case of an end date.
- If the day, the month and the year are unknown, the date will be considered as missing.

For start and end dates of AEs, there is an exception from the above mentioned rules:

- If the day is unknown and the month and the year are the same as the first treatment intake known, it will be replaced by the date of first treatment intake.
- If the day and the month are unknown and the year is the same as the first treatment intake known, it will be replaced by the date of first treatment intake.

At least 3 documented attempts must be made to contact any patient lost to follow-up at any 1 time point prior to the last scheduled contact (clinic visit or telephone contact). One of these documented attempts must include a written communication sent to the patient's last known address via a courier or mail (with acknowledgement of receipt request) asking that they return any unused IMP and return to the clinic/site for final safety evaluations.

Sleep and Nap Diaries should not be amended by site personnel, with exception of the following situations:

- Dates presented with inconsistent formatting can be edited for consistency.
- Missing or incorrect dates in a sequence can be corrected (e.g., the dates Dec 2014 to Jan 2014 could be corrected to Dec 2014 to Jan 2015)
- Time entered using the 12-hour format can be revised to the 24-hour format.
- Hours can be converted to minutes and vice versa, as needed.
- If at any visit the site determines that parents were not compliant in completing the Sleep and Nap Diaries (i.e., mandatory questions in the diaries were not correctly completed for at least 5 out of 7 nights per week (total of 2 weeks before each scheduled visit), it will be at the discretion of the Investigator to determine whether the patient will be excluded from study as a result of lack of compliance (Section 6.1). At Visits 1 and 2, this criterion is required to be met for patients to be eligible to continue on study and is considered a major entry criterion. As well, at Visit 3 and Visit 5, if parents were not compliant in completing the Sleep and Nap Diaries the Investigator cannot increase a patient's dose if so desired by the Investigator (Section 7.3.1). If parents were not compliant in completing the Sleep and Nap Diaries at Visits 3 and 5, this is to be considered a significant violation (Section 13.3.2) and reported in the eCRF. If a patient visit is delayed the parents are required to continue with completing diaries until the next visit. Compliance will be judged on the diaries completed in the 2 weeks prior to the newly scheduled visit.

The study coordinator should follow-up with parents during the phone calls to ensure diaries are completed in a timely manner and to make all attempts to prevent missing data and/or inconsistent data entry, according to the instructions in the Sleep and Nap Diary Guidelines.

12.12 CHANGES TO THE PLANNED ANALYSIS

Not applicable.

13 MONITORING PROCEDURES (QUALITY CONTROL AND QUALITY ASSURANCE)

The Sponsor has ethical, legal, and scientific obligations to conduct this study in accordance with established research principles and ICH GCP guidelines, and according to applicable SOPs, the protocol, and other written instructions and regulatory guidelines. As such, in order to fulfil these obligations and to maintain current of study progress, the Sponsor's monitors or representatives will

visit the investigative sites during study conduct, in addition to maintaining telephone and written communication. On-site visits, telephone calls, and regular inspection of the eCRFs will be conducted in order to assess patient enrolment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The Investigator must provide the monitor with full access to all source and study documents.

13.1 ROUTINE MONITORING

The study monitors will contact each Investigator and visit the study center at regular intervals throughout the study. Sponsor assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) for all study patients considered for study entry for the purpose of verifying entries made in the eCRF, and assist with their activities, if requested. The site must complete the eCRFs in a timely manner and on an ongoing basis to allow regular review by the study monitor. The study monitor will indicate verification by electronically applying source document verification flags to the eCRF and will ensure that all required electronic signatures are implemented accordingly at the end of study. Adequate time and space for monitoring visits should be made available by the Investigator.

Whenever a patient name is revealed on a document that is to be collected for the Sponsor the name must be blacked out permanently by the site personnel, and annotated with the patient number as identification.

As part of the supervision of study progress, other Sponsor personnel may, on request, accompany the study monitor on visits to the study center. Each Investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

13.2 INSPECTIONS AND AUDITING PROCEDURES

This study will be subject to audit by the Sponsor or their representatives. The audits will be undertaken to check compliance with the requirements of Good Clinical Practice (GCP) and the ICH Guidelines and will include a minimum of:

- In-house study file audit
- Audit of computer database quality control
- Audit of clinical report quality control

The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to patient notes, study documentation and facilities, laboratories used for the study drug supply, presence of required documents, and the informed consent process and comparison of eCRFs with source documents. All medical records (progress notes) must be available for audit. The Investigator agrees to participate with audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs. He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

13.3 PROTOCOL AMENDMENTS AND SIGNIFICANT PROTOCOL DEVIATIONS AND VIOLATIONS

13.3.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the Independent Ethics Committee (IEC) or other regulatory authorities, except when necessary to eliminate immediate safety concerns to the patients or when the change involves only logistics or administration. The PI and the Sponsor will sign the protocol amendment.

13.3.2 Protocol Deviations, Violations, and Exceptions

A protocol deviation is nonadherence to protocol-specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e., nonadherence on the part of the patient, the Investigator, or the Sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines. Protocol violations will be identified and recorded, by study site personnel, on the eCRF.

In this study, significant protocol violations will be defined as those that affect the assessment of safety or efficacy. The significant protocol violations will be agreed prior to database lock and will be categorised as follows:

- Patient's overall treatment compliance for the study is less than 70% or greater than 130% throughout the study
- Patient fails to meet any inclusion criteria or meets any exclusion criteria
- Any issues related to Sleep and Nap Diary completion
- Patient takes a prohibited medication during the study
- Wrong IMP kit dispensed
- Patient has an insufficient wash-out of prohibited medications prior to beginning the 2-week SB placebo run-in period of the study
- Other, defined as any deviation that causes the Investigator to withdraw the patient from the study for the reason "protocol violation", "protocol deviation" or "protocol non-compliance" on the study completion/withdrawal page of the eCRF

As a matter of policy, the Sponsor will not grant exceptions to protocol-specific entry criteria to allow patients to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular patient, prior approval from the Sponsor and the responsible Institutional Review Board (IRB)/IEC, in accordance with the SOP, is required before the patient will be allowed to enter the study. If investigative site personnel learn that a patient who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the Sponsor. Such patients will be discontinued from the study, except in a rare instance following review and written approval by the Sponsor and the responsible IRB/IEC, according to the applicable SOP.

13.4 INFORMATION TO STUDY PERSONNEL

Each Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the practical performance of the study and during the course of the study (e.g., when new staff become involved). Each Investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the site authorization form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including each Investigator, and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the Investigator or the study monitor.

13.5 RECORD KEEPING

After completion of the study, all documents and data relating to the study will be kept by the Investigator in a secure study file. This file will be available for inspection by the Sponsor and/or their representatives. Essential documents must be retained for 2 years after the final marketing approval in an ICH region or at least 2 years have elapsed since the discontinuation of clinical development of the IMP. The Investigator must contact the Sponsor before destroying any trial-related documentation. In addition, all patients' medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution or medical practice.

14 STUDY MANAGEMENT AND MATERIALS

14.1 ELECTRONIC CASE REPORT FORMS

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

It is preferred that the Sleep and Nap diary be entered directly into the eCRF but dairies are permitted to be completed on a paper diary as well. If the diary is entered directly to the eCRF by the parent, then the eCRF serves as the source data. If the diary is completed on paper and later entered into the

eCRF by the site, then the paper version serves as the source data. No amendment can be made to the parent-reported data except in cases indicated in Section 12.11 (missing data).

The eCRF must be reviewed and electronically signed, and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

14.2 DATA COLLECTION

During each study visit, a physician participating in the study will maintain progress notes, in ink, in the patient's medical records to document all significant observations. At a minimum, these notes will contain:

The date of the visit and the corresponding day or visit in the study schedule (e.g., screening, Day 1, Day 28, etc.)

- General condition and status remarks by the patient, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the Investigator's assessment as to whether or not the reported AE is study drug-related
- Changes in concomitant medications or dosages
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the patient via telephone or other means that provides significant clinical information and record of any scheduled phone call will also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents will be promptly transcribed to the appropriate section of the eCRF.

Changes to information in the medical record (progress notes), eCRF, and other source documents will be initialled and dated on the day the change is made by the Investigator or designee. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change.

14.3 SOURCE DOCUMENTS MAINTENANCE

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs and recorded data from automated instruments.

Source documents from this study will be maintained by the Investigator and made available for inspection by authorized persons with the exception of the Sleep and Nap Diary. As described above,

if the Sleep and Nap Diary is entered directly to the eCRF by the parent, then the eCRF serves as the source data. If the diary is completed on paper and later entered in to the eCRF by the site, then the paper version serves as the source data.

The original signed informed consent for each patient shall be filed with records kept by the Investigator and a copy shall be given to the patient.

14.4 RECORD MAINTENANCE

All data derived from the study will remain the property of Neurim.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents including records of patients, source documents, eCRFs and study drug (IMP) inventory must be kept on file.

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, consent forms, and medical inventory records, must be retained by the PI for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Sponsor or their representative will notify the PI of these events.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational products. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the Investigator when these documents need no longer be retained.

The Investigator will not dispose of any records relevant to this study without written permission from the Sponsor, and will provide the Sponsor the opportunity to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives and regulatory authorities.

If an Investigator moves, withdraws from an investigation or retires the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

14.5 CONFIDENTIALITY

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential. For disclosure of any such information, an agreement will be obtained in writing.

The Investigator must ensure that each patient's anonymity is maintained. On eCRFs and other documents submitted to the Sponsor or the CRO, patients must not be identified by name. Instead,

patients will only be known by their initials and by the unique patient number allocated to them in order to ensure confidentiality on all study documentation. Patients will retain this unique number throughout the study. The Investigator will keep a separate log of these codes.

In order to comply with government regulatory guidelines and to ensure patient safety, it may be necessary for the Sponsor and its representative, the CRO personnel, the local research review board, or the US FDA to review patients' medical records as they relate to this study. Only the patient's unique number on the eCRFs will identify him/her, but their full names may be made known to a drug regulatory authority or other authorized government or health care officials, if necessary, and to personnel designated by the Sponsor.

Documents that are not for submission to the Sponsor or the CRO (e.g., consent forms) will be maintained by the Investigator in strict confidence, except to the extent necessary to allow monitoring by the Sponsor and the CRO, and auditing by regulatory authorities. No documents identifying patients by name will leave the investigative site and patient identity will remain confidential in all publications related to the study.

15 DRUG ACCOUNTABILITY

Investigators will be provided with sufficient amounts of the IMP to carry out this protocol for the agreed number of patients. The Investigator or designee will acknowledge receipt of the IMP documenting shipment content and condition. Accurate records of all IMP dispensed, used, returned and/or destroyed must be maintained. Sites are responsible for ordering sufficient amounts of IMP to manage their IMP stock.

The Investigator or his/her designee (as documented in by the Investigator in the applicable study delegation log) will dispense the IMP only to patients included in the study following the procedures set out in the protocol. Each patient will be given only the IMP carrying his/her treatment assignment. All dispensing will be documented on the eCRFs and/or other IMP record. The Investigator is responsible for assuring the retrieval of all study supplies from patients.

No IMP stock or returned inventory from a Neurim sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. If such a transfer is authorized by the Sponsor, all applicable local, state and national laws must be adhered to for transfer.

16 ETHICS AND INFORMED CONSENT

16.1 ETHICS

16.1.1 Regulatory and Ethical Approvals

The regulatory permission to perform the study will be obtained in accordance with applicable regulatory requirements. The EC or IRB will approve this protocol, the patient information sheet, the ICF and their updates. The regulatory and ethical approvals must be available before a patient is exposed to any study-related procedure, including screening tests to determine eligibility for the study.

16.1.2 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles stated in the current Declaration of Helsinki, as revised in Seoul in 2008 as well as ICH, GCP, European Commission Directive, and Code of Federal Regulations, including relevant Sponsor or Designee's Standard Operating Procedures.

16.2 PATIENT INFORMATION AND INFORMED CONSENT

It is the responsibility of the Investigator to obtain written informed consent from all study patients prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Written consent will be obtained from each patient's legal guardian/guardians after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspect of the study which is relevant to his/her decision to participate. The consent form will be signed and dated by the patient's legal guardian before the patient is exposed to any study-related procedure, including screening tests for eligibility. Each patient's legal guardian will authorise in writing that his/her custodian's source records may be reviewed by a monitor, an auditor or a regulatory inspector, in accordance with applicable regulatory requirements.

A written assent will be obtained from the patient provided the young patient has a sufficient understanding and intelligence to understand what is proposed.

A patient legal guardian/guardians or a young patient who has the sufficient understanding can withdraw consent/assent at any time during the study, without obligation or prejudice. This will not affect the future care and treatment of the patient.

Patient Information Sheets and Consent Forms, versions must be approved by an EC prior to consenting a patient.

17 FINANCING AND INSURANCE

The Investigator is required to disclose any financial arrangements during the study and for 1 year after, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in the IMP; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2 (b) (1998).

In consideration of participation in the study, the Sponsor pays the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator Agreement.

The Sponsor responsible for this study is:

Neurim Pharmaceuticals
27 Habarzel St.
Tel Aviv, 69710, Israel

The Sponsor will provide appropriate Insurance cover for this study.

18 REPORTING AND PUBLICATION

Neurim Pharmaceuticals Ltd. (1991) has the ownership of all data and results collected during this study. In consequence, Neurim Pharmaceutical Ltd. reserves the right to use the data from the present study, either in the form of eCRFs (or copies of these), or in the form of a CSR (with or without comments and with or without analysis) in order to submit them to the Health Authorities of any country. Furthermore, in the event that the clinical research leads to patentable results, the Investigator (or entity acting on his behalf following local requirements) shall refrain from filing patent(s) application which will be filed by Neurim Pharmaceuticals Ltd. or any other entity delegated by Neurim Pharmaceuticals Ltd.

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20 APPENDICES

Appendix 1: Sleep and Nap Diary

This is to be completed by the parent/caregiver daily at home, preferably 2-3 hours after the child wakes up.

Site:

Subject number:

NEU_CH_7911 - Sleep and Nap Diary

For all questions below please try to give the exact times and durations however if you do not remember the exact times please give your best estimation	
Date of diary (morning after medication administration)	
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Did the child take his/her medicine last night?	○ Yes ○ No ○ Unknown
If yes, when? (24 hr clock)	
Comments	
Sleep last night and feeling this morning:	
* What time did the child go to bed last night? (24 hr clock)	
* How long did it take the child to fall asleep (minutes)?	
* How many times did the child wake up in the night?	
* For each wake period please try to provide the exact times and duration awake	
Wake period number	
Wake time (24 hr clock)	
Waking duration in minutes	
Wake period number	
Wake time (24 hr clock)	

Site:

Subject number:

NEU_CH_7911 - Sleep and Nap Diary

Waking duration in minutes	
Wake period number	
Wake time (24 hr clock)	
Waking duration in minutes	
* How long did the child stay awake during the night (minutes)?	
* How many hours of actual sleep did the child get that night (hours:minutes)? (This may be different than the number of hours he/she spent in bed)	
* What time did the child wake up? (24 hr clock)	
What time did the child get out of bed? (24 hr clock)	
Can you describe the child's sleep quality last night as one of the following:	○ Very bad ○ Bad ○ Fair ○ Good ○ Very good ○ Unknown
Can you describe the child's feeling now as one of the following:	○ Very alert ○ Alert ○ Quite alert ○ Tired ○ Very tired ○ Unknown
Can you describe the child's feeling when he/she woke up for the day as one of the following:	○ Very refreshed ○ Refreshed ○ Somewhat refreshed ○ Fatigued ○ Very fatigued ○ Unknown
The child's daily naps yesterday:	
How many naps did the child have (naps are defined as any sleep	

Site:

Subject number:

NEU_CH_7911 - Sleep and Nap Diary

in periods outside his/her normal bedtime)?	
Please record the duration of each nap on a new row below	
Nap number	
Nap start time (24 hr clock)	
Nap duration in minutes	
Nap number	
Nap start time (24 hr clock)	
Nap duration in minutes	
Nap number	
Nap start time (24 hr clock)	
Nap duration in minutes	

Appendix 2: Sleep and Nap Diary Take-Home Instructions for Parents

The Diary has to be completed for 14 days prior to each visit in the first year of participation. The diary should be completed every morning preferably 2-3 hours after the child went out of bed.

- **What time did the child go to bed?**
  - This is the moment that bedtime routines are over (lights off). From this moment onwards, no further reading or parent interaction should happen and the child is expected to attempt to sleep. Use 24 hour clock (i.e. 21:35) to record times.
  - When all bedtime routines are over (lights off), the event marker button on the Actiwatch is to be pushed. Ensure the time entered in the diary for the child going to bed is the same as the one appearing on the Actiwatch screen.
    - If Actiwatch was not pushed, in error, at the correct moment, please use the actual time the child went to bed (the time bedtime routines were over) for the Diary
  - Do not change the initial time entered in the diary if the child has difficulties falling asleep i.e. calls you into the bedroom or leaves the bedroom to find you.
- **How long did it take your child to fall asleep?**
  - This is the duration in **minutes** from first attempt to fall asleep (bedtime routines are over, lights off) to final sleep.
- **Times and durations of wakes up during the night.**
  - Enter the accurate times and durations. Do not round times up or down. For times use 24 hours clock i.e. 01:35 – 02:45. Durations should be entered in **minutes**, i.e. 70 minutes.
  - In case you do not remember exact times and durations please give your best estimation.
- **How many hours of actual sleep did the child get that night?** –
  - Please use hours:minutes for example six and a half hours should be entered as 6:30
- **What time did the child wake up?**
  - This is the time your child finally woke up and did not fall asleep anymore (lights on). This may be different from the time the child got out of bed. Use 24 hour clock (i.e. 07:35) to record times.
  - The time of wake up (lights on) should be marked also by pushing the event marker button on the Actiwatch – use the time that appears on the Actiwatch for the diary.
  - Example responses to the questions of the Sleep Nap diary are provided in the table –on the next page.

Question	Response	Comment
What time did the child go to bed last night?	21:00 (9 o'clock in the evening)	24 hour clock
How long did it take the child to fall asleep (minutes)?	30 minutes	Minutes if sure do not round ↑↓
How many times did the child wake up in the night?	2	
Wake period number	1	
Wake time	02:30	24 hour - (two thirty in the morning)
Wake duration in minutes	25	Minutes if sure do not round ↑↓
Wake period number	2	
Wake time	04:50	24 hour - (four fifty in the morning)
Wake duration in minutes	40	Minutes if sure do not round ↑↓
What time did the child wake up?	06:30	24 hours

Electronic Sleep and Nap Diary Completion Guidelines

You will be given a unique username and password and the URL (web address) to allow access to the
Sleep and Nap Diary at the site. The diary will be displayed in your local language.

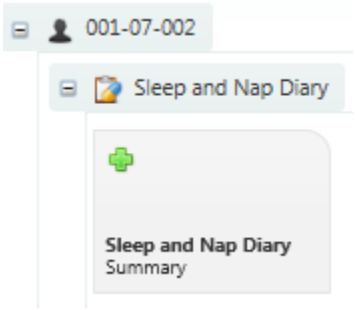
The login screen will ask you to enter your username and password. Please note these are case sensitive. Then select 'Login'.

When you first log into the system, you will be asked to change your password. Enter the current password you were given by the site and create a new password for your account that you will remember.

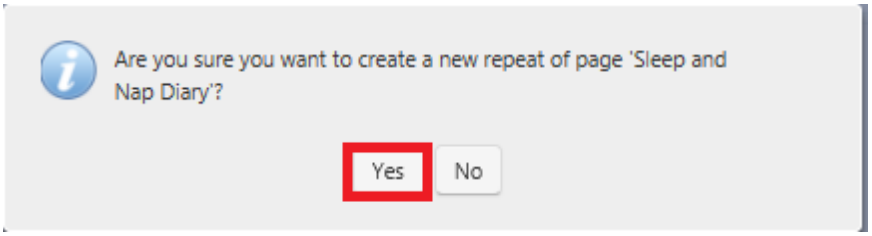
If you forget your password at any time, please contact your site and they will be able to reset this for you.

For security reasons, after 60 days you will be asked again to change your password. The "Change
Expired Password" screen will appear as it did the first time you logged into the system.

When you login, you will see your child's screening number and the Sleep and Nap Diaries that you enter beneath it.



To create a new Diary, click on the '+' sign and confirm that you would like to create a new repeat.



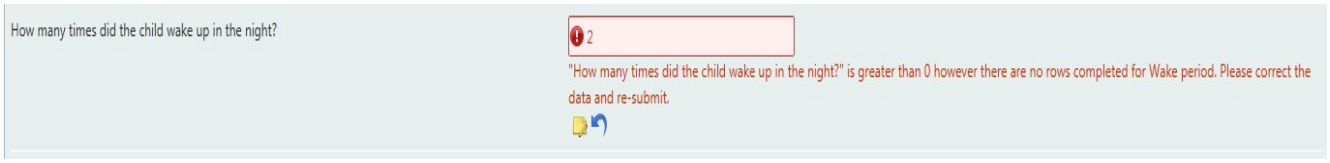
This will create repeat (1) of the page. You should create a new repeat for every day that you complete the Sleep and Nap Diary, for 14 days prior to each visit.

When you create a new repeat, this will open the page where you will enter the information required into the Sleep and Nap Diary.

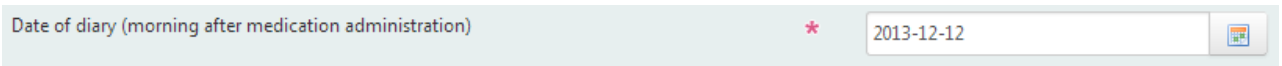
Each diary should be completed in the morning for the previous night's sleep.

Validation prompts are present on the page to ensure that the data is entered logically.

If the data entered is inconsistent you will be prompted to update the data, in some cases a comment can be entered to explain why the data entered is inconsistent. The prompt below requires data to be updated.



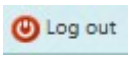
The page can only be saved when questions with a red star next to them have been answered.



When you have entered the data onto the page, select 'Submit' from the buttons at the bottom right of the screen. This will save the page and take you to a 'Browse' view of the page.

If you were unable to answer any of the questions with a red star, you can select 'Submit as incomplete'. Please note that incomplete diaries might affect suitability to continue in the study.

Once you have entered your Sleep and Nap Diary, you can logout using the logout button at the top right of the page.



Once you have completed entry, the pages will be locked to prevent further editing. If you have made an error and would like to amend any of your diary data after you have saved it, you should contact your site who can unlock the page for you to edit or amend the data on your behalf.

Actiwatch Guidelines for the Parents

General introduction

Actiwatch is a device that will monitor the activity level of your child. It enables your study doctor to determine sleep and activity patterns. It should be worn all night. It should be considered no more intrusive than a wristwatch. The Actiwatch should not be removed except as instructed below.

- Try to acclimate the child to wearing the watch by introducing plastic bracelets and toy watches
- The non-dominant wrist is preferred, the same wrist should always be used every night
- Place the Actiwatch on the subject's wrist and fasten it in such a way as to be slightly snug, but comfortable
- The Actiwatch should be worn for 14 nights before visit 2 and visit 4
- Remember: keep the Actiwatch in a safe place during the day
- Actiwatches are considered water resistant (not water proof). However, please try to avoid showering, bathing, washing the device
- Please stop using the Actiwatch and contact your study doctor in case:
  - skin reddening or inflammation appears
  - the device becomes damaged

What to do at night

- Place the Actiwatch 30 minutes before bedtime
- The Actiwatches display will change when it is put on the wrist.
- After bedtime routine (lights off), press the Marker Button on the Actiwatch - Immediately record this time on the sleep diary as time the child went to bed.
- Do not press the marker button again during the night. Even if the child requires additional assistance (calls you again, comes to your room etc.) there is no need to press the marker button again.
- Pressing the event Marker Button will not turn on/off the device but rather mark the time of going to sleep/ waking up in the morning.

What to do in the morning

- In the morning press the marker button as soon as the child awakens for the day (lights on). Record this time in the diary as time of wake up.
- Remove the Actiwatch 30 minutes after the child wakes up in the morning

Appendix 3: Children Global Assessment Scale and Rating Guidelines

This is to be completed by the Investigator with the parent/caregiver's input.

Site:

Subject number:

NEU_CH_7911 - Children Global Assessment Scale (CGAS)

Was the Children Global Assessment Scale performed?	○ Yes ○ No
Date of assessment	
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Enter the overall score based on the below scale:	
100 - 91: Doing very well 90 - 81: Doing well 80 - 71: Doing alright, some minor impairment 70 - 61: Some problems, in one area only 60 - 51: Some noticeable problems, in more than one area 50 - 41: Obvious problems, moderate impairment in most areas or severe in one area 40 - 31: Serious problems, major impairment in several areas and unable to function in one area 30 - 21: Severe problems, unable to function in almost all situations 20 - 11: Very severely impaired, so impaired that considerable supervision is required for safety 10 - 1: Extremely impaired, so impaired that constant supervision is required for safety	
Overall Score	

CGAS Rating Guide

The coding guidance notes and vignettes are provided to assist in the process of rating the clinical severity of all the young people who have been admitted to your service. The vignettes provided were originally developed for the 'Children and Young Persons In-patient Evaluation (CHYPIE) Study.

CODING THE CGAS

Code the CGAS on the basis of your patient's worst level of emotional and behavioural functioning in the past three months by selecting the lowest level which describes his/her functioning on a hypothetical continuum of health-illness. The scores can range from 1, which is the very worst, to 100, which is the very best. Use intermediary levels (e.g., 35, 58, 62).

Rate actual functioning regardless of treatment or prognosis.

Do not count functional physical impairments unless they are clearly related to emotional functioning, (i.e., functional handicap due to cerebra/palsy or blindness would not be coded, but difficulty as a consequence of soiling would be). (Note that the HoNOSCA coding differs here - cf area A6.)

It will be helpful to take into account how your patient functions in four major areas:

1. At home with family
2. At school
3. With friends
4. During leisure time

The overall score will represent an overall rating from these four areas.

Locating the score

1. Locate a decile based on the descriptions that follow.
2. Consider the appropriate decile in thirds and locate the functioning in the upper middle or lower third of the decile.
3. Choose a score within that third as the overall score.

CHILDREN'S GLOBAL ASSESSMENT SCALE

David Shaffer, M.D., Madelyn S. Gould, Ph.D., Hector Bird, M.D., Prudence Fisher, B.A Adaptation of the Adult Global Assessment Scale (Robert L. Spitzer, M.D., Nathan Gibbon, M.S.W., Jean Endicott, Ph.D.)

The examples of behaviour provided are only illustrative and are not required for a particular rating.

Specified time period: 1 month

100-91 DOING VERY WELL

Superior functioning in all areas (at home, at school and with peers), involved in a range of activities and his many interests (e.g., has hobbies or participates in extracurricular activities or belongs to an organised group such as Scouts, etc.). Likeable, confident, everyday worries never get out of hand. Doing well in school. No symptoms.

90-81 DOING WELL

Good functioning 'in all areas. Secure in family, school, and with peers. There may be transient difficulties and "everyday" worries that occasionally get out of hand (e.g., mild anxiety associated with an important exam, occasionally "blow-ups" with siblings, parents or peers).

80-71 DOING ALL RIGHT - minor impairment

No more than slight impairment in functioning at home, at school, or with peers. Some disturbance of behaviour or emotional distress may be present in response to life stresses (e.g., parental separations, deaths, birth of a sibling) but these are brief and interference with functioning is transient, such children are only minimally disturbing to others and are not considered deviant by those who know them.

70-61 SOME PROBLEMS - in one area only

Some difficulty in a single area, but generally functioning pretty well, (e.g., sporadic or isolated antisocial acts, such as occasionally playing hooky, petty theft; consistent minor difficulties with school work, mood changes of brief duration, fears and anxieties which do not lead to gross avoidance behaviour; self-doubts). Has some meaningful interpersonal relationships. Most people who do not know the child well would not consider him/her deviant but those who do know him/her well might express concern.

60-51 SOME NOTICEABLE PROBLEMS - in more than one area

Variable functioning with sporadic difficulties or symptoms in several but not all social areas. Disturbance would be apparent to those who encounter the child in a dysfunctional setting or time but not to those who see the child in other settings.

50-41 OBVIOUS PROBLEMS- moderate impairment in most areas or severe in one area.

Moderate degree of interference in functioning in most social areas or severe impairment functioning in one area, such as might result from, for example, suicidal preoccupations and ruminations, school refusal and other forms of anxiety, obsessive rituals, major conversion symptoms, frequent anxiety attacks, frequent episodes of aggressive or other antisocial behaviour with some preservation of meaningful social relationships.

40 1 SERIOUS PROBLEMS - major impairment in several areas and unable to function in one area

Major impairment in functioning in several areas and unable to function in one of these areas (i.e., disturbed at home, at school, with peers, or in the society at large [e.g., persistent aggression without clear instigation; markedly withdrawn and isolated behaviour due to either mood or though disturbance, suicidal attempts with clear lethal intent]). Such children are likely to require special schooling and/or hospitalisation or withdrawal from school (but this is not a sufficient criterion for inclusion in this category).

30-21 SEVERE PROBLEMS - unable to function in almost all situations.

Unable to function in almost all areas (e.g., stays at home, in ward or in bed all day without taking part in social activities) OR severe impairment in reality testing OR serious impairment in communication (e.g., sometimes incoherent or inappropriate).

20-11 VERY SEVERELY IMPAIRED - considerable supervision is required for safety.

Needs considerable supervision to prevent hurting others or self (e.g., frequently violent, repeated suicide attempts OR to maintain personal hygiene) OR gross impairment in all forms of communication (e.g., severe abnormalities in verbal and gestural communication, marked social aloofness, stupor, etc.).

10-1 EXTREMELY IMPAIRED - constant supervision is required for safety.

Needs constant supervision (24-hour care) due to severely aggressive or self-destructive behaviour or gross impairment in reality testing, communication, cognition, affect, or personal hygiene.

Appendix 4: Strength and Difficulties Questionnaires

This is to be completed by the site coordinator/Investigator with the parent/caregiver's input.

Age 2 – 4

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 2 – 4

Was the Strengths and Difficulties Questionnaire performed?	○ Yes ○ No
Age range	○ Age 2 - 4 years (use if 4 years)
Date of birth	
Gender	○ Male ○ Female
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Date of assessment	
Considerate of other people's feelings	○ Not true ○ Somewhat true ○ Certainly true
Restless, overactive, cannot stay still for long	○ Not true ○ Somewhat true ○ Certainly true
Often complains of headaches, stomach-aches or sickness	○ Not true ○ Somewhat true ○ Certainly true
Shares readily with other children, for example toys, treats, pencils	○ Not true ○ Somewhat true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 2 – 4

	○ Certainly true
Often loses temper	○ Not true ○ Somewhat true ○ Certainly true
Rather solitary, prefers to play alone	○ Not true ○ Somewhat true ○ Certainly true
Generally well behaved, usually does what adults request	○ Not true ○ Somewhat true ○ Certainly true
Many worries or often seems worried	○ Not true ○ Somewhat true ○ Certainly true
Helpful if someone is hurt, upset or feeling ill	○ Not true ○ Somewhat true ○ Certainly true
Constantly fidgeting or squirming	○ Not true ○ Somewhat true ○ Certainly true
Has at least one good friend	○ Not true ○ Somewhat true ○ Certainly true
Often fights with other children or bullies them	○ Not true ○ Somewhat true ○ Certainly true
Often unhappy, depressed or tearful	○ Not true ○ Somewhat true ○ Certainly true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 2 – 4

Generally liked by other children	○ Not true ○ Somewhat true ○ Certainly true
Easily distracted, concentration wanders	○ Not true ○ Somewhat true ○ Certainly true
Nervous or clingy in new situations, easily loses confidence	○ Not true ○ Somewhat true ○ Certainly true
Kind to younger children	○ Not true ○ Somewhat true ○ Certainly true
Often argumentative with adults	○ Not true ○ Somewhat true ○ Certainly true
Picked on or bullied by other children	○ Not true ○ Somewhat true ○ Certainly true
Often offers to help others (parents, teachers, other children)	○ Not true ○ Somewhat true ○ Certainly true
Can stop and think things out before acting	○ Not true ○ Somewhat true ○ Certainly true
Can be spiteful to others	○ Not true ○ Somewhat true ○ Certainly true
Gets along better with adults than with other children	○ Not true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 2 – 4

	○ Somewhat true ○ Certainly true
Many fears, easily scared	○ Not true ○ Somewhat true ○ Certainly true
Good attention span, sees tasks through to the end	○ Not true ○ Somewhat true ○ Certainly true
Total difficulties score (calculated)	
Do you have any other comments or concerns?	○ Yes ○ No
If yes, please provide details:	
Overall, do you think that that your child has difficulties in one or more of the following areas: emotions, concentration, behavior or being able to get on with other people?	○ No ○ Yes – minor difficulties ○ Yes – definite difficulties ○ Yes – severe difficulties
If you have answered yes, please answer the following questions about these difficulties:	
How long have these difficulties been present?	○ Less than 1 month ○ 1-5 months ○ 6-12 months ○ Over a year
Do the difficulties upset or distress your child?	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Do the difficulties interfere with your child's everyday life in the	

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 2 – 4

following areas?	
Home life	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Friendships	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Learning	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Leisure activities	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Do the difficulties put a burden on you or the family as a whole?	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Impact score (calculated)	

Age 4 – 10

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 4 - 10

Was the Strengths and Difficulties Questionnaire performed?	○ Yes ○ No
Age range	○ Age 4 - 10 years
Date of birth	
Gender	○ Male ○ Female
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Date of assessment	
Considerate of other people's feelings	○ Not true ○ Somewhat true ○ Certainly true
Restless, overactive, cannot stay still for long	○ Not true ○ Somewhat true ○ Certainly true
Often complains of headaches, stomach-aches or sickness	○ Not true ○ Somewhat true ○ Certainly true
Shares readily with other children, for example toys, treats, pencils	○ Not true ○ Somewhat true ○ Certainly true
Often loses temper	○ Not true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 4 - 10

	○ Somewhat true ○ Certainly true
Rather solitary, prefers to play alone	○ Not true ○ Somewhat true ○ Certainly true
Generally well behaved, usually does what adults request	○ Not true ○ Somewhat true ○ Certainly true
Many worries or often seems worried	○ Not true ○ Somewhat true ○ Certainly true
Helpful if someone is hurt, upset or feeling ill	○ Not true ○ Somewhat true ○ Certainly true
Constantly fidgeting or squirming	○ Not true ○ Somewhat true ○ Certainly true
Has at least one good friend	○ Not true ○ Somewhat true ○ Certainly true
Often fights with other children or bullies them	○ Not true ○ Somewhat true ○ Certainly true
Often unhappy, depressed or tearful	○ Not true ○ Somewhat true ○ Certainly true
Generally liked by other children	○ Not true ○ Somewhat true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 4 - 10

	○ Certainly true
Easily distracted, concentration wanders	○ Not true ○ Somewhat true ○ Certainly true
Nervous or clingy in new situations, easily loses confidence	○ Not true ○ Somewhat true ○ Certainly true
Kind to younger children	○ Not true ○ Somewhat true ○ Certainly true
Often lies or cheats	○ Not true ○ Somewhat true ○ Certainly true
Picked on or bullied by other children	○ Not true ○ Somewhat true ○ Certainly true
Often offers to help others (parents, teachers, other children)	○ Not true ○ Somewhat true ○ Certainly true
Thinks things out before acting	○ Not true ○ Somewhat true ○ Certainly true
Steals from home, school or elsewhere	○ Not true ○ Somewhat true ○ Certainly true
Gets along better with adults than with other children	○ Not true ○ Somewhat true ○ Certainly true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 4 - 10

Many fears, easily scared	○ Not true ○ Somewhat true ○ Certainly true
Good attention span, sees chores or homework through to the end	○ Not true ○ Somewhat true ○ Certainly true
Total difficulties score (calculated)	
Do you have any other comments or concerns?	○ Yes ○ No
If yes, please provide details:	
Overall, do you think that that your child has difficulties in one or more of the following areas: emotions, concentration, behavior or being able to get on with other people?	○ No ○ Yes – minor difficulties ○ Yes – definite difficulties ○ Yes – severe difficulties
If you have answered yes, please answer the following questions about these difficulties:	
How long have these difficulties been present?	○ Less than 1 month ○ 1-5 months ○ 6-12 months ○ Over a year
Do the difficulties upset or distress your child?	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Do the difficulties interfere with your child's everyday life in the following areas?	
Home life	○ Not at all ○ Only a little

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 4 - 10

	○ Quite a lot ○ A great deal
Friendships	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Classroom learning	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Leisure activities	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Do the difficulties put a burden on you or the family as a whole?	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Impact score (calculated)	

Age 11 – 17

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 11 - 17

Was the Strengths and Difficulties Questionnaire performed?	○ Yes ○ No
Age range	○ Age 11 - 17 years
Date of birth	
Gender	○ Male ○ Female
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Date of assessment	
Considerate of other people's feelings	○ Not true ○ Somewhat true ○ Certainly true
Restless, overactive, cannot stay still for long	○ Not true ○ Somewhat true ○ Certainly true
Often complains of headaches, stomach-aches or sickness	○ Not true ○ Somewhat true ○ Certainly true
Shares readily with other youth, for example CD's, games, food	○ Not true ○ Somewhat true ○ Certainly true
Often loses temper	○ Not true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 11 - 17

	○ Somewhat true ○ Certainly true
Would rather be alone than with other youth	○ Not true ○ Somewhat true ○ Certainly true
Generally well behaved, usually does what adults request	○ Not true ○ Somewhat true ○ Certainly true
Many worries or often seems worried	○ Not true ○ Somewhat true ○ Certainly true
Helpful if someone is hurt, upset or feeling ill	○ Not true ○ Somewhat true ○ Certainly true
Constantly fidgeting or squirming	○ Not true ○ Somewhat true ○ Certainly true
Has at least one good friend	○ Not true ○ Somewhat true ○ Certainly true
Often fights with other children or bullies them	○ Not true ○ Somewhat true ○ Certainly true
Often unhappy, depressed or tearful	○ Not true ○ Somewhat true ○ Certainly true
Generally liked by other youth	○ Not true ○ Somewhat true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 11 - 17

	○ Certainly true
Easily distracted, concentration wanders	○ Not true ○ Somewhat true ○ Certainly true
Nervous in new situations, easily loses confidence	○ Not true ○ Somewhat true ○ Certainly true
Kind to younger children	○ Not true ○ Somewhat true ○ Certainly true
Often lies or cheats	○ Not true ○ Somewhat true ○ Certainly true
Picked on or bullied by other youth	○ Not true ○ Somewhat true ○ Certainly true
Often offers to help others (parents, teachers, other children)	○ Not true ○ Somewhat true ○ Certainly true
Thinks things out before acting	○ Not true ○ Somewhat true ○ Certainly true
Steals from home, school or elsewhere	○ Not true ○ Somewhat true ○ Certainly true
Gets along better with adults than with other youth	○ Not true ○ Somewhat true ○ Certainly true

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 11 - 17

Many fears, easily scared	○ Not true ○ Somewhat true ○ Certainly true
Good attention span, sees chores or homework through to the end	○ Not true ○ Somewhat true ○ Certainly true
Total difficulties score (calculated)	
Do you have any other comments or concerns?	○ Yes ○ No
If yes, please provide details:	
Overall, do you think that that your child has difficulties in one or more of the following areas: emotions, concentration, behavior or being able to get on with other people?	○ No ○ Yes – minor difficulties ○ Yes – definite difficulties ○ Yes – severe difficulties
If you have answered yes, please answer the following questions about these difficulties:	
How long have these difficulties been present?	○ Less than 1 month ○ 1-5 months ○ 6-12 months ○ Over a year
Do the difficulties upset or distress your child?	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Do the difficulties interfere with your child's everyday life in the following areas?	
Home life	○ Not at all ○ Only a little

Site:

Subject number:

Visit number:

NEU_CH_7911 - Strength and Difficulties Questionnaire – Blank CRF - Age 11 - 17

	○ Quite a lot ○ A great deal
Friendships	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Classroom learning	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Leisure activities	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Do the difficulties put a burden on you or the family as a whole?	○ Not at all ○ Only a little ○ Quite a lot ○ A great deal
Impact score (calculated)	

Appendix 5: Treatment Emergent Signs and Symptoms

This is to be completed by Investigator with the parent/caregiver's input.

Site:

Subject number:

NEU_CH_7911 - Treatment Emergent Signs and Symptoms (TESS)

Was a Treatment Emergent Signs and Symptoms assessment performed?	○ Yes ○ No
Date of assessment	
Select a response for the symptoms and sensations:	
If a score of 1 or above is selected please record a corresponding Adverse Event (only if this is a new symptom or if there is an increase in severity of an existing symptom from the first visit)	
1. Somnolence	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
2. Fatigue	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
3. Increased excitability/activity	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
4. Dizziness	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
5. Hangover feelings	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
6. Mood swings	○ 0 - No Symptoms

Site:

Subject number:

NEU_CH_7911 - Treatment Emergent Signs and Symptoms (TESS)

	○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
7. Tremor	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
8. Seizures	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
9. Headache	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
10. Nausea and/or vomiting	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
11. Rash	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
12. Hypothermia	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
13. Coughing / breathlessness	○ 0 - No Symptoms ○ 1 - Mild

Site:

Subject number:

NEU_CH_7911 - Treatment Emergent Signs and Symptoms (TESS)

	○ 2 - Moderate ○ 3 – Severe ○ Not Done
14. Other adverse effects not listed	○ Yes ○ No
Please specify other adverse effects below:	
Adverse effect	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
Response	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
Please specify other adverse effects below:	
Adverse effect	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
Response	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
Please specify other adverse effects below:	
Adverse effect	○ 0 - No Symptoms ○ 1 - Mild ○ 2 - Moderate ○ 3 – Severe ○ Not Done
Response	○ 0 - No Symptoms ○ 1 - Mild

Site:

Subject number:

NEU_CH_7911 - Treatment Emergent Signs and Symptoms (TESS)

	○ 2 - Moderate ○ 3 – Severe ○ Not Done

Appendix 6: Composite Sleep Disturbance Index

This is to be completed by the site coordinator/Investigator with the parent/caregiver's input.

Site:

Subject number:

NEU_CH_7911 - Composite Sleep Disturbance Index (CSDI)

Was a Composite Sleep Disturbance questionnaire assessment performed?	○ Yes ○ No
Date of assessment	
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Child's sleep habits since last month or visit	
How often does your child have problems settling at bed time?	○ Less than once a week ○ 1 or 2 nights a week ○ 3 or more nights a week
How long does it take them to settle to sleep?	○ Few minutes ○ Up to 30 minutes ○ More than 30 minutes
How often does your child wake in the night?	○ Less than once a week ○ 1 or 2 nights a week ○ 3 or more nights a week
How long does it usually take to resettle him/her?	○ Few minutes ○ Up to 30 minutes ○ More than 30 minutes
How often does your child wake before 5am in the morning and remain awake?	○ Less than once a week ○ 1 or 2 nights a week ○ 3 or more nights a week

Site:

Subject number:

NEU_CH_7911 - Composite Sleep Disturbance Index (CSDI)

How often does your child insist on sleeping with someone else for most/all of the night?	○ Less than once a week ○ 1 or 2 nights a week ○ 3 or more nights a week
How satisfied are you with your child's current sleep pattern?	○Completely satisfied ○Mostly satisfied, although some aspects still cause problems ○Neither satisfied nor dissatisfied ○Mostly dissatisfied, although some aspects are OK ○Completely dissatisfied
Total sleep problem subscale score (calculated)	

Appendix 7: Epworth Sleepiness Scale

This is to be completed by the site coordinator/Investigator with the parent/caregiver's input. Note: The ESS is to assess sleepiness of the **parent/caregiver** and NOT the child.

Site:

Subject number:

NEU_CH_7911 - Epworth Sleepiness Scale (ESS)

Was the Epworth Sleepiness Scale questionnaire completed?	○ Yes ○ No
Date of assessment	
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Likelihood of dozing or falling asleep:	
Sitting and reading	○ Would never doze ○ Slight chance of dozing ○ Moderate chance of dozing ○ High chance of dozing
Watching TV	○ Would never doze ○ Slight chance of dozing ○ Moderate chance of dozing ○ High chance of dozing
Sitting, inactive in a public place (e.g., a theatre or a meeting)	○ Would never doze ○ Slight chance of dozing ○ Moderate chance of dozing ○ High chance of dozing
As a passenger in a car for an hour without a break	○ Would never doze ○ Slight chance of dozing ○ Moderate chance of dozing ○ High chance of dozing
Lying down to rest in the afternoon when circumstances permit	○ Would never doze

Site:

Subject number:

NEU_CH_7911 - Epworth Sleepiness Scale (ESS)

	○ Slight chance of dozing ○ Moderate chance of dozing ○ High chance of dozing
Sitting and talking to someone	○ Would never doze ○ Slight chance of dozing ○ Moderate chance of dozing ○ High chance of dozing
Sitting quietly after a lunch without alcohol	○ Would never doze ○ Slight chance of dozing ○ Moderate chance of dozing ○ High chance of dozing
In a car, while stopped for a few minutes in the traffic	
Total (calculated)	

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991 Dec;14(6):540-5 (PubMed abstract). ESS © MW Johns 1990-1997. Used under license. ESS contact information and permission to use: MAPI Research Trust, Lyon, France. E-mail: PROinformation@mapi-trust.org – Internet: www.mapi-trust.org.

Appendix 8: Pittsburgh Sleep Quality Index

This is to be completed by the site coordinator/Investigator with the parent/caregiver's input. Note: The PSQI is to assess the well-being of the **parent/caregiver** and NOT the child.

Site:

Subject number:

NEU_CH_7911 - Pittsburgh Sleep Quality Index (PSQI)

Was the Pittsburgh Sleep Quality Index questionnaire completed?	○ Yes ○ No
Date of assessment	
Time of questionnaire	
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
1. During the past two weeks, what time have you usually gone to bed at night?	
2. During the past two weeks, how long (in minutes) has it usually taken you to fall asleep each night?	
3. During the past two weeks, what time have you usually gotten up in the morning?	
4. During the past two weeks, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed)	
5. During the past two weeks how often have you had trouble sleeping because you…	
a. cannot get to sleep within 30 minutes	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
b. wake up in the middle of the night or early morning	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week

Site:

Subject number:

NEU_CH_7911 - Pittsburgh Sleep Quality Index (PSQI)

c. have to get up to use the bathroom	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
d. cannot breath comfortably	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
e. cough or snore loudly	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
f. feel too cold	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
g. feel too hot	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
h. had bad dreams	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
i. have pain	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
j. other reason(s), please describe	
k. how often during the past two weeks have you have had trouble sleeping because of this?	○ Not during the past two weeks

Site:

Subject number:

NEU_CH_7911 - Pittsburgh Sleep Quality Index (PSQI)

	○ Less than once a week ○ Once or twice a week ○ Three or more times a week
6. During the past two weeks, how would you rate your sleep quality overall?	○ Very good ○ Fairly good ○ Fairly bad ○ Very bad
7. During the past two weeks, how often have you taken medicine to help you sleep (prescribed or "over the counter")?	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
8. During the past two weeks, how often have you had trouble staying awake while driving eating meals, or engaging in social activity?	○ Not during the past two weeks ○ Less than once a week ○ Once or twice a week ○ Three or more times a week
9. During the past two weeks, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	○ No problem at all ○ Only a very slight problem ○ Somewhat of a problem ○ A very big problem
Scoring	
Component 1 Score (calculated)	
Component 2 Score (calculated)	
Component 3 Score (calculated)	
Component 4 Score (calculated)	
Component 5 Score (calculated)	
Component 6 Score (calculated)	
Component 7 Score (calculated)	
Global PSQI Score (calculated)	

Appendix 9: WHO-5 Well-being Index

This is to be completed by the site coordinator/Investigator with the parent/caregiver's input. Note: The WHO-5 is to assess the quality of sleep of the **parent/caregiver** and NOT the child.

Site: Subject number: **NEU_CH_7911 - WH0-5 Well-being Index**	
Was the WH0-5 Wellbeing Index questionnaire completed	○ Yes ○ No
Date of assessment	
Questionnaire completed by	○ Mother ○ Father ○ Guardian ○ Caregiver ○ Other
If completed by other, please specify	
Over the last two weeks	
1. I have felt cheerful and in good spirits	○ All of the time ○ Most of the time ○ More than half of the time ○ Less than half of the time ○ Some of the time ○ At no time
2. I have felt calm and relaxed	○ All of the time ○ Most of the time ○ More than half of the time ○ Less than half of the time ○ Some of the time ○ At no time

Site:

Subject number:

NEU_CH_7911 - WH0-5 Well-being Index

3. I have felt active and vigorous	○ All of the time ○ Most of the time ○ More than half of the time ○ Less than half of the time ○ Some of the time ○ At no time
4. I woke up feeling fresh and rested	○ All of the time ○ Most of the time ○ More than half of the time ○ Less than half of the time ○ Some of the time ○ At no time
5. My daily life has been filled with things that interest me	○ All of the time ○ Most of the time ○ More than half of the time ○ Less than half of the time ○ Some of the time ○ At no time
Total Score (calculated)	
Scoring the WHO-5 Well-being Index:	
The raw score is calculated by totalling the figures of the five answers.	
All of the time = 5	
Most of the time = 4	
More than half of the time = 3	
Less than half of the time = 2	
Some of the time = 1	
At no time = 0	

Appendix 10: Epilepsy Seizures Diary

This is to be completed only by the patient's parent/caregiver after each seizure.

Site:

Subject number:

NEU_CH_7911 - Epileptic Seizure Diary

Did the child have any seizures since the last visit?	○ Yes ○ No
If yes, please provide details for all seizures	
Date of seizure	
Day or Night	○ Day ○ Night
Duration of seizure (minutes)	
Seizure type	○ G1 - absence seizure ○ G2 - myoclonic seizure ○ G3 - atonic seizure ○ G4 - tonic seizure ○ G5 - clonic seizure ○ G6 - tonic-clonic convulsion ○ G7 - other with unconsciousness ○ F1 - aura ○ F2 - other with consciousness retained
Was emergency medication given?	○ Yes ○ No
If yes, please provide details for all seizures	
Date of seizure	
Day or Night	○ Day ○ Night
Duration of seizure (minutes)	
Seizure type	○ G1 - absence seizure ○ G2 - myoclonic seizure ○ G3 - atonic seizure ○ G4 - tonic seizure ○ G5 - clonic seizure

Site:

Subject number:

NEU_CH_7911 - Epileptic Seizure Diary

	○ G6 - tonic-clonic convulsion ○ G7 - other with unconsciousness ○ F1 - aura ○ F2 - other with consciousness retained
Was emergency medication given?	○ Yes ○ No
If yes, please provide details for all seizures	
Date of seizure	
Day or Night	○ Day ○ Night
Duration of seizure (minutes)	
Seizure type	○ G1 - absence seizure ○ G2 - myoclonic seizure ○ G3 - atonic seizure ○ G4 - tonic seizure ○ G5 - clonic seizure ○ G6 - tonic-clonic convulsion ○ G7 - other with unconsciousness ○ F1 - aura ○ F2 - other with consciousness retained
Was emergency medication given?	○ Yes ○ No

Appendix 11: Prohibited Medication List

Active compound	Trade name	Class	Reason for Exclusion
Agomelatine	Valdoxan Melitor Thymanax	Melatonin agonist	Major depressive disorder
Ramelteon	Rozerem	Melatonin agonist	Anxiolytic,myorelaxant, and amnesic
Zopiclone	Imovane Zopiclone Nocturno Nocturno S.L.	Z-Drugs	Hypnotic
Zaleplon	Sonata Starnoc	Z-Drugs	Sedative/hypnotic
Zolpidem	Zodorm Stilnox	Z-Drugs	Hypnotic
Eszopiclone	Lunesta	Z-Drugs	Sedative/hypnotic
Brotizolam	Bondormin Brotizolam	Benzodiazepine	Hypnotic
Clonazepam*	Clonex Rivotril Klonopin	Benzodiazepine	Hypnotic
Diazepam	Assival Diaz Valium Stesolid	Benzodiazepine	Hypnotic
Flunitrazepam	Hypnodorm	Benzodiazepine	Hypnotic
Lorazepam	Lorivan Ativan	Benzodiazepine	Hypnotic
Lormetazepam	Loramet Noctamid	Benzodiazepine	Sedative/hypnotic
Nitrazepam	Numbon	Benzodiazepine	Sedative
Oxazepam	Vaben Alepam Medopam Alopam Sobril Oxascand	Benzodiazepine	Sedative/hypnotic
Midazolam	Dormicum Hypnovel Versed	Benzodiazepine	Hypnotic
Trialzolam	Trialzolam	Benzodiazepine	Hypnotic
Temazepam	Restoril Normison	Benzodiazepine	Hypnotic
Oxazepam	Vaben	Benzodiazepine	Hypnotic
Loprazolam	Dormonoct Havlane Sonin Somnovit	Benzodiazepine derivative	Sedative
Estazolam	ProSom Eurodin	Benzodiazepine derivative	Sedative
Triprolidine hydrochloride		Anti-histamine	Sedative/hypnotic
Diphenhydramine hydrochloride		Anti-histamine	Sedative/hypnotic
Chlorpheniramine maleate		Anti-histamine	Sedative/hypnotic

Dexchlorpheniramine maleate		Anti-histamine	Sedative/hypnotic
Diphenhydramine		Anti-histamine	Sedative
Promethazine	Phenergan Promethegan Romergan Farganesse Lergigan	Anti-histamine	Sedative
Doxylamine	Unisom	Anti-histamine	Sedative
Niaprazine	Nopron	Phenylpiperazine class	Sedative/hypnotic
Clomethiazole		Thiamine- vitamin B1 like	Sedative/hypnotic
Phenobarbital	Phenobarbital Phenobarbitone Philinet Philinal Pacetal	Barbiturate	Sedative
Chloral hydrate			Sedative/hypnotic
Triclofos			Sedative
Alimemazine	Nedeltran, Panectyl, Repeltin, Therafene, Theraligene, Theralen, Theralene, Vallergan, Vanectyl, and Temaril	Antipruritic	Sedative/hypnotic
Valerian		Herbal	
Fluvoxamine	Luvox	Antidepressant	Interact with endogenous melatonin and increases melatonin levels by inhibiting its metabolism

* If a child receives a single dose of Clonazepam to treat seizures he should not be withdrawn from the study but a deviation should be recorded.