STATISTICAL ANALYSIS PLAN

Neurim Pharmaceuticals Ltd

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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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Abbreviations

Abbreviation	Meaning
AE	adverse events
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CGAS	Children Global Assessment Scale
CI	Confidence Interval
CSDI	Composite Sleep Disturbance Index
CSR	clinical study report
eCRF	electronic case report form
ESS	Epworth Sleepiness Scale
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect repeated measures model
PP	Per Protocol
PSQI	Pittsburgh Sleep Quality Index
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SB	single blind
SD	standard deviation
SDQ	Strength and Difficulties Questionnaire
SND	Sleep and Nap Diary (Sleep Log)
TESS	Treatment-Emergent Signs and Symptoms Questionnaire
TST	total sleep time
WHO	World Health Organization
WHO-5	World Health Organization Well-Being Index

1 Version Control

This Statistical Analysis Plan (SAP) is based on the protocol version 6.0 Amendment 5 dated 19th May 2015 and case report form, (CRF) dated 18th March 2015.

All results 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. This will constitute the final analysis of data up to that point and no statistical adjustment of significance tests is required.

The data from the second open-label period will be summarized on the completion of the study and reported as an appendix to the CSR.

2 Study Rationale

Prolonged release melatonin (PRM) may be the response to the unmet need in the field of insomnia in the paediatric population and, specifically, in children with neurodevelopmental disorders, as currently there is no approved drug that is proven to be both effective and safe for this population and thus there is no approved drug indicated for insomnia in the paediatric population.

The optimal profile of a hypnotic is:

(a) high oral bioavailability;

(b) short elimination half-life;

(c) rapid onset of action;

(d) once-nightly dosing;

(e) low risk for dependence, abuse, tolerance, withdrawal, and rebound, without daytime residual effects.

These agents should also carry favourable side-effect profiles, and show no significant reductions in REM and NREM sleep stages and SWS.

PRM fulfils all these pharmacokinetic and pharmacodynamic properties. Importantly, PRM has been found to be effective in primary insomnia patients $\geq$55 with no impairment of morning alertness and memory, lack of withdrawal and rebound effects and no tolerance in primary insomnia patients aged 18-80 in the long-term. In particular, PRM 4-6 mg demonstrated a safe and effective therapy in the long-term for the treatment of sleep disorders in children with neurodevelopmental disorders.

In a recent publication it was found that children with autism that suffer from sleep disturbances, have decreased melatonin levels as compared to age match controls, as indicated by urine levels of the primary melatonin metabolite, 6-sulfatoxymelatonin (6-SMT). The relationship between 6-SMT levels and sleep architecture in children with ASD was investigated. Some publications indicate that higher urinary 6-SMT excretion rates were associated with increased N3 sleep, decreased N2 sleep, and decreased daytime sleepiness. Indeed, another therapeutic benefit of PRM, although not tested in paediatric population is its lack of effect on sleep architecture and improved morning alertness and vigilance. This is opposed to other sleep medication like benzodiazepines or benzodiazepine-like drugs that are known to affect sleep architecture specifically by reducing SWS and REM. Indeed a recent study comparing PRM, temazepam and zolpidem, demonstrated that the effects of PRM on the nocturnal sleep EEG (NREM and REM sleep) were

minor and were different from those of temazepam and zolpidem; this is likely due to the different mechanisms of action of the medications [Arbon 2015].

In addition to this favourable profile of PRM meeting the desired hypnotic profile, using PRM also addresses the physiological background of insomnia in children with neurodevelopmental disorders and not only the symptom. In children with neurodevelopmental disorders specifically ASD and SMS there may be low endogenous melatonin secretion caused by inadequate regulation and metabolism of melatonin, contributing to impairment in both the initiation of sleep and sleep maintenance. Hence, melatonin substitution therapy is proposed to be effective for insomnia in children with impaired endogenous melatonin levels.

Details of references may be found in the Protocol.

3 Objectives

To compare and evaluate safety, tolerability and efficacy of Circadin® 2/5 mg (prolonged release mini-tablet age appropriate oral solid dosage form) to that of placebo after 13 weeks of double blind treatment period as detailed below:

3.1 Primary Objective

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

3.2 Secondary Objectives

The secondary objectives of the study are:

- 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 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
- Sub-analysis to evaluate the impact of shortening latency time versus increasing sleep time after sleep onset on the primary endpoint - TST.
- To assess the treatment effect of Circadin® 2/5 mg to that of placebo on sleep disturbance as assessed by Composite Sleep Disturbance Index (CSDI) 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) 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) 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)
- To assess vital signs and physical examinations in Circadin® and placebo groups

3.3 Exploratory Objective

The exploratory objectives of the study are:

- 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 5), 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 CSDI score after 3 weeks of double-blind treatment (Week 5), 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 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 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) 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) 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 at Weeks 0, 2, 5, 15, 28, 41, 54, 106, and 108
- To determine the proportion of children using a maximum of 2 or 5 mg in the Circadin® and placebo groups

- 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 using the Tanner scale 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

4 Endpoints

4.1 Primary Endpoint

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

4.2 Secondary 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
- Total time in bed from the Sleep and Nap Diary after 13 weeks (Week 15) of double-blind treatment
- Sleep disturbance as assessed by CSDI 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
- TST time as assessed by actigraphy after the 13-week, double-blind treatment period.
- Sleep latency as assessed by actigraphy after 13 weeks (Week 15) of double-blind treatment

- Duration of wake after sleep onset period as assessed by actigraphy after 13 weeks (Week 15) of double-blind treatment
- Number of awakenings as assessed by actigraphy after 13 weeks (Week 15) of double-blind treatment
- Longest sleep period as assessed by actigraphy after 13 weeks (Week 15) of double-blind treatment
- Sleep efficiency as assessed by actigraphy after 13 weeks (Week 15) of double-blind treatment
- 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

4.3 Exploratory 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 weeks of double-blind treatment (Week 5), 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)
- Dosage received by visit and maximum dosage received overall
- 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

5 Study Design

This is a randomized placebo-controlled study in children diagnosed with Autism Spectrum Disorders 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 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 subjects who are still on 2 mg or an increase to 10 mg for subjects 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 two efficacy assessment time points at Weeks 41 and 54. The study will end with a 2-week SB placebo run-out period.

6 Statistical Considerations

6.1 Sample Size

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 subjects are required per combined group. Therefore, 90 subjects in total are required to complete Visit 5. These estimations are based on previous studies conducted with Circadin®.

6.2 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 subjects 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 (up to Week 28). A minimum of 50 children are expected to complete the second open-label safety follow-up period.

7 Protocol Deviations

Major protocol deviations are defined as those deviations from the study protocol that may have the ability to impact the efficacy results. As such, subjects with major deviations occurring up to the end of the double-blind phase will be excluded from the per-protocol (PP) population (as defined in Section 8.5).

Major protocol deviations include (but are not limited to):

- Deviation from inclusion/exclusion criteria
- Withdrawal criteria met during the study but subject was not withdrawn
- Prohibited concomitant medications
- Substantial deviations from the dosing schedule (Subjects received at least 5 of 7 doses in the week prior to the scheduled visit and treatment compliance is within the range >60%)
- Substantial deviations in the completion of the sleep and nap diary (Subjects must have completed the diary at least 3 out of 7 nights per week over the two weeks prior to the scheduled visit and have a valid mean TST value at Visit 4)

Where possible, major deviations will be programmatically verified by Datatrial. Listings of concomitant medications in Excel format will be provided to the sponsor by Datatrial for review to identify prohibited medications prior to unblinding.

Major protocol deviations occurring up to the end of the first open-label phase will be identified during a Blinded Data Review Meeting (BDRM) prior to database lock and unblinding.

The purpose of the BDRM will be two-fold; It will be used to review and confirm the data identified as protocol deviations as detailed above. It will also be used to review the Sleep and Nap diary and confirm that the data is correct and/or identify implausible values and document any changes that are made to the source data. Blinded SAS listings of the Sleep and Nap diary data including derivation of mean TST will be provided by

Datatrial in advance of the BDRM to aid this review. Any changes to the source data may require a further review of the protocol deviations.

8 Analysis Populations

8.1 All Enrolled Set

The All Enrolled Set will include all subjects who have given written informed consent. This set will be used for subject disposition and demographic characteristic summaries, and disposition, eligibility and demographic listings.

8.2 All Randomized Set

The All Randomized Set will include the subjects from the All Enrolled Subset who have been randomized. Subjects will be classified according to randomized treatment. This set will be used for demographic characteristic, and baseline characteristic summaries, and all listings excluding disposition, eligibility and demographic listings.

Furthermore, the All Randomized Set will be used for the sensitivity analyses of missing efficacy data as detailed in Section 11.4.

8.3 Safety Set

Safety analyses will be performed on the Safety Analysis Set, which includes all subjects randomized to treatment who take at least one dose of study medication. Subjects will be classified according to actual treatment received. This analysis set will be used for all safety analyses.

8.4 Full Analysis Set

Efficacy analyses will be performed on the Full Analysis Subset (FAS), and will include all subjects in the Safety Analysis Set who satisfy all major entry criteria (Inclusion Criteria 1-5) and who have a valid mean TST result recorded for baseline and at least one post-baseline period assessment during the double blind phase. Subjects will be classified according to randomized treatment. This analysis set will be used for all efficacy analyses.

8.5 Per Protocol Set

The Per Protocol (PP) Set is a subset of the FAS, which excludes all subjects for whom there were major violations of the protocol as detailed in Section 7. Subjects will be classified according to randomized treatment. This analysis subset will be used for sensitivity analyses of the primary endpoint and select secondary endpoints.

9 Data Reporting Conventions

9.1 Descriptive Statistics

Unless otherwise stated, all continuous parameters will be summarized using standard summary statistics as appropriate (n, mean, standard deviation, minimum, median and maximum). In presentations of summary statistics, the minimum and maximum will be displayed to the same number of decimal places as the variable being summarized was recorded to. The mean and median will be displayed to one extra decimal place; the standard deviation (SD) will be displayed to two extra decimal places.

Categorical variables (e.g., gender) will summarized using frequency counts and percentages. Unless otherwise stated, these presentations will consist of the number of subjects in a particular category and the percentage of the total number of subjects. Percentages will be presented to one decimal place.

Unless otherwise noted, all analyses will be conducted using the validated statistical software Statistical Analysis System (SAS) version 9.3.

9.2 Reporting of Phases

Unless otherwise specified, tables will be reported separately for the Double Blind and Open Label phases. Tables reporting the Double Blind phase will be presented by treatment group.

In addition, baseline demographic and history tables will include an Overall column.

Tables reporting data from the Open Label phases will be presented by the original Double Blind treatment group and will also include an 'All Circadin' group. Unless otherwise specified, the two Open Label phases will be reported in the same table. For the main analysis, the Open Label tables will only include data for Visit 5. On completion of the study, the open label tables will be re-run to include all data up to the end of the study.

9.3 Baseline Derivation

For all efficacy and safety variables, the baseline value will be calculated as the last recorded value prior to the start of randomized treatment.

9.4 Missing Dates

For partial date of births, where the day and month are missing, they will be replaced with 30/06.

The following will be applied to start and end dates for baseline histories, concomitant medications and adverse events where required for calculation of durations and assignment to phases. No imputed values will appear in the listings.

• If the day is unknown and the month and the year are known, it will be replaced by 01 in the case of a start date or by the last day of the month in the case of an end date.

• If the day and the month are unknown, they will be replaced by 01/01 in the case of a start date or 31/12 in the 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.

10 Subject Disposition, and Demographic and Baseline Characteristics

10.1 Subject Disposition

Study completion and discontinuation details, eligibility, treatment allocation, population assignment, and protocol deviations will be listed.

The number of subjects screened, randomized, receiving and completing double-blind treatment and the primary reasons for any study treatment discontinuations in the double-blind phase will be tabulated. A subject is considered to have completed the double-blind phase if they have attended Visit 4 without having discontinued the study.

The number of subjects starting and completing each of the open-label phases and the primary reasons for discontinuation in each of the open-label phases will be tabulated. A subject is considered to have started the first (second) open-label phase if they have been supplied with study treatment at Visit 4 (Visit 5). They are considered to have completed the first (second) open-label phase if they have attended Visit 5 (Visit 8) without having discontinued the study.

The number and percentage of subjects in each analysis population will be tabulated. The number and percentage of subjects in each center and in each geographic region (US and Europe) will be tabulated.

10.2 Demographic and Baseline Characteristics

Demographic parameters will include date of birth, age, sex, race, ethnicity and screening body weight, height and BMI.

Age will be derived from the birth date and screening date as using the following SAS code:

Age=floor ((intck('month',birth,screen) - (day(screen) < day(birth))) / 12)

Body weight and height will be measured at Screening. Body mass index (BMI) at screening will be programmatically calculated in the eCRF.

Demographics will be listed and tabulated using descriptive statistics.

The following baseline characteristics will also be tabulated:

- ADHD (Yes, No; identified from the medical history)
- Epilepsy (Yes, No)
- Prior Anti-Epileptic Treatment (ATC code N03)
- Prior Anti-Depressant Treatment (selective serotonin reuptake inhibitor [SSRIs] ATC code N06AB)
- Prior Beta-Blockers Use (ATC code C07)
- Prior Stimulant Use (ATC code N06B)
- Prior ADHD Treatment (Ritalin ATC code N06BA04)
- Prior Clonidine Use (ATC code C02AC01)

10.3 Neurodevelopmental Disability

Details of the diagnosis of neurodevelopmental disability will be listed and tabulated. The time since first diagnosis of neurodevelopmental disability (in months) will be calculated from date of informed consent and summarized descriptively.

10.4 Melatonin Use

Details of melatonin use will be listed and tabulated.

10.5 Medical History

Details of medical history will be listed including condition, start and stop dates. Partial dates may be recorded in the electronic data capture system and no imputations will be made for missing or partial dates in the listing.

Medical histories will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18 or higher. A summary of medical histories and number of subjects with a medical history will be presented by System Organ Class and Preferred Term.

10.6 Prior and Concomitant Medications

Concomitant medications recorded during the study will be coded using World Health Organization (WHO)-Drug. Details of concomitant medication will be listed.

Concomitant medications will be summarized according to whether they were being taken pre-study (prior medications) and/or during the study (concomitant medication). Prior medications are any that were being taken prior to the first dose of study medication (medication stop date prior to the first dose of study medication). Concomitant medications are any that were being taken on or after the first dose of study medication. If the start and stop dates of the concomitant medications do not clearly define the period during which a medication was taken, it will be assumed to be a concomitant medication.

Concomitant medications will be assigned to the phase they were taken: Double-Blind, first Open-Label, second Open-Label. If a concomitant medication starts or is ongoing between Visit 2 and Visit 4, it will be assigned to the Double-Blind phase. If a concomitant medication starts or is ongoing between Visit 4 + 1 day and Visit 5, it will be assigned to the first Open-Label phase. If a concomitant medication starts or is ongoing between Visit 5 + 1 day and Visit 8, it will be assigned to the second Open-Label phase. If the start and stop dates of the concomitant medications do not clearly define the phase during which a medication was taken, it will be assumed to be taken across all phases.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 2 term and preferred term.

Details of non-pharmacological concomitant measures will be listed.

11 Efficacy

Subjects will be classified and summarized by randomized treatment. For all efficacy assessments, the baseline values will be calculated as the last recorded value prior to the start of randomized treatment. Change from baseline values will be calculated as the assessment score minus the baseline value. For questionnaires the change from baseline values will be calculated for each item and total/subscale score as applicable.

All summaries and analyses will be performed on the FAS set. The primary efficacy endpoint and select secondary efficacy endpoints will also be analyzed on the PP set. Analyses looking at the impact missing data on the primary efficacy endpoint will also be performed on the All Randomized set.

11.1 Primary Efficacy Variable

11.1.1 Total Sleep Time (TST)

TST will be assessed by a Sleep and Nap Diary.

Daily TST will be calculated programmatically as follows:

the time the child woke up in the morning *minus*

the time the child went to bed *minus*

the time taken to fall asleep *minus*

the total duration of any night awakenings

If the time the child went to bed and the time they woke up in the morning are the same, the TST will be set to 0.

The number of daily diaries with data recorded and the number of daily diaries with a valid mean TST will be tabulated by scheduled visit.

For each subject the mean TST will then be calculated as the mean of the last 14 days prior to each scheduled visit. A subject will be required to have a minimum of 3 nightly TST values per week (6 nights in total) in order to have a valid mean TST after baseline. A subject will be required to have a minimum of 6

nightly TST values across the 2 weeks in order to have a valid mean TST at baseline. The mean TST and change from baseline in mean TST will be summarized by scheduled visit using descriptive statistics. The change from baseline in mean TST will be plotted over time. Empirical cumulative distribution functions by treatment group will be plotted for change from baseline in mean TST at Visit 4 (Week 15).

The change from baseline in mean TST will be analyzed using a mixed-effects model for repeated-measures (MMRM). The model will contain the TST at Visit 3 (Week 5) and Visit 4 (Week 15) as the dependent variable, with fixed effects for visit, the mean baseline TST, randomized treatment and the mean baseline TST and randomised treatment both nested within visit. Visit-to-visit repeated measures will assume a general (unstructured) covariance structure. Standard errors and degrees of freedom for significance tests will be derived using the Kenward-Roger method [1].

From this model, the adjusted mean change from baseline (and standard error) in TST after 13 weeks of treatment for each treatment group will be calculated and the associated 95% confidence intervals (CI) for the change presented. Furthermore, the estimated difference (and standard error) between treatments will be estimated, the associated 95% CI presented and the null hypothesis that these means are equal will be tested.

Example SAS code for this analysis is given below:

```
proc mixed data=tst method=reml;
  class subjid trtp avisitn;
  model chg=trtp avisitn base trtp(avisitn) base(avisitn)/ddfm=kr;
  repeated avisitn/subject=subjid type=un;
  lsmeans trtp(avisitn)/diff cl om;
  ods output lsmeans=lsm(where=(avisitn=4)) diffs=diff(where=(avisitn=4));
run;
```

In addition, the effect size will be calculated based on Cohen's d (mean difference between groups/pooled standard deviation) where the mean difference is adjusted for other model factors using MMRM and the pooled standard deviation is evaluated using the model standard errors as follows:

$sd_{pool}=\sqrt{(((se_{circ}*se_{circ}*(n_{circ}-1)*n_{circ})+(se_{plac}*se_{plac}*(n_{plac}-1)*n_{plac}))/(n_{circ}+n_{plac}-2)}$.

where n_{circ} and n_{plac} are the number of subjects with a measurement at Visit 4 (Week 15) and se_{circ} and se_{plac} are the standard errors of the adjusted means in the Circadin and Placebo groups respectively.

11.2 Secondary Efficacy Variables

11.2.1 Sleep and Nap Diary

11.2.1.1 Sleep Latency

Sleep latency as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. If the time the child went to bed and the time they woke up in the morning are the same, the sleep latency for that night will be set to 360 minutes. Mean sleep latency and the change from baseline in mean sleep latency will be summarized by scheduled visit using descriptive statistics. The change from baseline in sleep latency will be plotted over time. The change from baseline in mean sleep latency at 13 weeks will be analysed as detailed above for TST.

11.2.1.2 Duration of Wake

Duration of wake after sleep onset period as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. Mean duration of wake and the change from baseline in mean duration of wake will be summarized by scheduled visit using descriptive statistics. The change from baseline in duration of wake will be plotted over time. The change from baseline in mean duration of wake at 13 weeks will be analysed as detailed above for TST.

11.2.1.3 Number of Awakenings

The number of awakenings as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. The mean number of awakenings and change from baseline in the mean number of awakenings will be summarized by scheduled visit using descriptive statistics. The change from baseline in number of awakenings will be plotted over time. The change from baseline in the mean number of awakenings at 13 weeks will be analysed as detailed above for TST.

11.2.1.4 Longest Sleep Period

The longest sleep period as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. The mean longest sleep period and the change from baseline in the mean longest sleep period will be summarized by scheduled visit using descriptive statistics. The change from baseline in longest sleep period will be plotted over time. The change from baseline in the mean longest sleep period at 13 weeks will be analysed as detailed above for TST.

11.2.1.5 Total Time in Bed

In order to evaluate the impact of shortening latency time versus increasing sleep time after sleep onset on the primary endpoint, TST, a new parameter will be further analysed by removing sleep latency from the TST calculation. This will be referred to as the total time in bed.

That is, total time in bed is defined as follows:

the time the child woke up in the morning *minus*

the time the child went to bed *minus*

the total duration of any night awakenings

The total time in bed as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit.

The mean total time in bed and the change from baseline in the mean total time in bed will be summarized by scheduled visit using descriptive statistics. The change from baseline in total time in bed will be plotted over time. The change from baseline in the mean total time in bed at 13 weeks will be analysed as detailed above for TST.

11.2.2 CSDI

Sleep disturbance as assessed by the CSDI and change from baseline will be summarized by scheduled visit for each treatment group using descriptive statistics for the total score. The change from baseline in the total CSDI score at 13 weeks will be analysed as detailed above for TST.

11.2.3 CGAS

The CGAS score and change from baseline will be summarized by scheduled visit for each treatment group using descriptive statistics. The change from baseline in CGAS score at 13 weeks will be analysed as detailed above for TST.

11.2.4 SDQ

The SDQ consists of 25 items which are divided into 5 subscales:

1) emotional symptoms (5 items)

2) conduct problems (5 items)

3) hyperactivity/inattention (5 items)

4) peer relationship problems (5 items)

5) prosocial behaviour (5 items).

Subscales 1 to 4 added together generate a total difficulties score (20 items). An impact score will also be calculated as part of the SDQ.

The following website provides SAS syntax to enable scoring of the 5 subscales: http://www.sdqinfo.com/c2.html. (Appendix A)

The total difficulties score, impact score and the subscale total scores and corresponding changes from baseline will be summarized by scheduled visit for each treatment group using descriptive statistics. The change from baseline in the scores at 13 weeks will also be analysed as detailed above for TST.

11.2.5 Number of Dropouts

The proportion of subjects dropping out in the double-blind phase will be compared between the treatment groups using a chi-square test with continuity correction.

Example SAS code for this analysis is given below:

```
proc freq data=drop;
  table drop*trtp/chisq;
  ods output chisq=chi(where=(statistic='Continuity Adj. Chi-Square'));
run;
```

11.2.6 Actigraphy

Sleep parameters (Total Sleep Time, Sleep Latency, Duration of Wake and Number of Awakenings, Longest Sleep Period and Sleep Efficiency) as measured by actigraphy will be calculated as the mean of the last 14 days prior to each scheduled visit. The sleep parameters and corresponding changes from baseline will be summarized by scheduled visit using descriptive statistics. The sleep parameters at 13 weeks will be analysed as detailed above for TST.

11.3 Exploratory Efficacy Variables

11.3.1 Sleep and Nap Diary by Visit

The change from baseline at 3 weeks of double-blind treatment is analysed in the same model as the change from baseline at 13 weeks. From that model, the adjusted mean change from baseline (and standard error) in TST after 3 weeks of treatment for each treatment group will be calculated and the associated 95% CI for the change presented. Furthermore, the estimated difference (and standard error) between treatments will be estimated, the associated 95% confidence interval presented and the null hypothesis that these means are equal will be tested.

For the TST during open-label treatment the estimated change from baseline (and standard error) will be calculated and associated 95% CI for the change will be presented for each visit. A paired t-test will be performed comparing the mean TST at visit to the baseline mean.

Example SAS code for this analysis is given below:

```
proc means data=tst mean stderr lclm uclm probt;
  var chg;
run;
```

These analyses will be repeated for the other sleep variables derived from the Sleep and Nap diary.

A subject is defined as a TST responder if the mean change from baseline in TST is 45 minutes or greater (increase in TST) over the 14 days prior to each scheduled visit. A subject is defined as a sleep latency responder if the mean change from baseline in sleep latency is 15 minutes or greater (reduction in SL) over the 14 days prior to each scheduled visit. Frequency tables of TST response and sleep latency response will be presented by scheduled visit.

For Visits 3 and 4, the TST response rate and sleep latency response rate will be analysed using logistic regression. Subjects without a mean TST (or mean sleep latency) at a visit will be taken to be non-responders in this analysis. The model will include terms for treatment and mean baseline value of TST and sleep latency respectively. From the model the estimated odds of responding will be calculated, as will estimated odds ratios, associated 95% CI and p-values for testing the null hypothesis of the odds ratio being 1.

Example SAS code for this analysis is given below:

```
proc genmod data=resp;
  class trtp;
  model resp=trtp base/link=logit dist=bin;
  lsmeans trtp/diff cl om exp;
run;
```

The responder analysis will be repeated on all non-missing data. That is, subjects without a mean TST (or mean sleep latency) at a visit will not be included in the analysis.

The time to going to bed will be categorized to the following time slots: < 18:00, 18:00 - < 19:00, 19:00 - <20:00, 20:00 - < 21:00, 21:00 - < 22:00, 22:00 - < 23:00, 23:00 - < 00:00, >= 00:00.

The shift in time to going to bed will be tabulated by scheduled visit for the most frequently occurring time slot over the 14 days at each visit. Where the daily time to going to bed is equally distributed across the time slots, the latest occurring time slot will be selected for inclusion in the shift table.

11.3.2 Sleep Disturbance by Visit

For the sleep disturbance as assessed by the CSDI, the total CSDI score after 3 weeks of double blind treatment and during open-label treatment will be analysed as for TST.

11.3.3 CGAS by Visit

The CGAS score after 3 weeks of double blind treatment and 13 weeks of open-label treatment will be analysed as detailed above for TST.

11.3.4 SDQ by Visit

The SDQ score for total difficulties score, impact score and the subscale total scores after 3 weeks of double blind treatment and 13 weeks of open-label treatment will be analysed as detailed above for TST.

11.3.5 ESS

Caregiver sleepiness as assessed by the ESS total score and the change from baseline in ESS total score will be summarized by scheduled visit using descriptive statistics. The ESS total score after 3 weeks and 13 weeks of double blind treatment and during open-label treatment will be analysed as detailed above for TST.

11.3.6 PSQI

The global PSQI score and corresponding component scores and changes from baseline will be summarized by scheduled visit using descriptive statistics. The global PSQI score after 3 weeks and 13 weeks of double blind treatment and during open-label treatment will be analysed as detailed above for TST.

11.3.7 WHO-5 Well-being Index

WHO-5 Well-being Index total score and change from baseline in the total score will be summarized by scheduled visit using descriptive statistics. The Well-being Index total score after 3 weeks and 13 weeks of double blind treatment and during open-label treatment will be analysed as detailed above for TST.

11.3.8 Actigraphy by Visit

The shift in time to going to bed will be tabulated by scheduled visit. The categories used will be as detailed for Sleep and Nap Diary Time to bed.

The number and percentage of subjects defined as a responder according to actigraphy will be tabulated for the run-in period. A responder is defined as > 6 hours of continuous sleep and < 0.5 hour sleep latency from light off in 3 out of 5 nights.

11.4 Other Efficacy Variables

11.4.1.1 Quality of Sleep

The quality of sleep as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. Quality of sleep will be scored as follows:

Very bad = 1; bad = 2; fair = 3; good = 4; very good = 5; unknown = not scored.

The mean quality of sleep and change from baseline in the mean quality of sleep during the day will be summarized by scheduled visit using descriptive statistics. The change from baseline in the mean quality of sleep at 13 weeks will be analysed as detailed above for TST.

11.4.1.2 Current Alertness

The current alertness as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. Current alertness will be scored as follows:

Very tired = 1; tired = 2; quite alert = 3; alert = 4; very alert = 5; unknown = not scored.

The mean current alertness and change from baseline in the mean current alertness during the day will be summarized by scheduled visit using descriptive statistics. The change from baseline in the mean current alertness at 13 weeks will be analysed as detailed above for TST.

11.4.1.3 Feeling on Awakening

The child's feeling on awakening as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. Feeling on awakening will be scored as follows:

Very fatigued = 1; fatigued = 2; somewhat refreshed = 3; refreshed = 4; very refreshed = 5; unknown = not scored.

The mean feeling on awakening and change from baseline in the mean feeling on awakening during the day will be summarized by scheduled visit using descriptive statistics. The change from baseline in the mean feeling on awakening at 13 weeks will be analysed as detailed above for TST.

11.4.1.4 Number of Naps

The number of naps during the day as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. The mean number of naps during the day and change from baseline in the mean number of naps during the day will be summarized by scheduled visit using descriptive statistics. The change from baseline in the mean number of naps at 13 weeks will be analysed as detailed above for TST.

11.4.1.5 Duration of Naps

The duration of naps during the day as assessed by a Sleep and Nap Diary will be calculated as the mean of the last 14 days prior to each scheduled visit. The mean duration of naps during the day and change from baseline in the mean duration of naps during the day will be summarized by scheduled visit using descriptive statistics. The change from baseline in the mean duration of naps at 13 weeks will be analysed as detailed above for TST.

11.4.2 CSDI

Sleep disturbance as assessed by the CSDI and change from baseline will also be summarized by scheduled visit for each treatment group using descriptive statistics, for each of the individual questions. The change

from baseline in the total CSDI score at 13 weeks for of the individual questions, will be analysed as detailed above for TST.

Individual questions will be scored as follows:

Questions 1, 3, 5 and 6 - 3 or more nights a week = 2; 1 or 2 nights a week = 1; less than once a week = 0;

Questions 2 and 4 - More than 30 minutes = 2; up to 30 minutes = 1; few minutes = 0;

Question 7 - Completely dissatisfied = 1; mostly dissatisfied = 2; neither satisfied nor dissatisfied = 3; mostly satisfied = 4; completely satisfied = 5.

11.5 Missing Efficacy Data

11.5.1 Multiple Imputation

For the primary efficacy variable and the secondary efficacy variables collected using the Sleep and Nap Diary, an analysis will be undertaken to assess the effect of missing data arising on the estimated treatment effects. This will be done using a pattern mixture model where missing data from subjects who are withdrawn is imputed with observations imitating the placebo response [2].

Specifically, using the absolute values for baseline, Week 5 and Week 15, a monotone multiply imputed (1000 imputations) dataset will be initially created. Using this dataset the remaining missing data will then be imputed (1 imputation) using an imputation model based on sequential regression methodology. Starting at Week 5, values for subjects that have missing data will be imputed based on all placebo-treated subjects having a value at that visit. The effect of this is to mimic the expected response as if the withdrawn subjects had been treated with placebo from the point of withdrawal. Next, at Week 15, values for subjects that have missing data will be imputed based on all placebo-treated subjects having a value at that visit. The change from baseline to Week 15 will then be calculated.

These imputed datasets will be analysed separately using ANCOVA with randomised treatment as a factor and baseline as a covariate. The individual results will then be combined using the method of Rubin [3]. The adjusted mean change from baseline (and standard error) in TST after 13 weeks of treatment for each treatment group, the estimated difference (and standard error) between treatments, the associated 95% CI presented and the p-value for the test of null hypothesis that these means are equal will be presented.

Example SAS code for this analysis is given below:

```
* Create monotone dataset;
proc mi data=tst out=mi_mono nimpute=1000 seed=5635245;
  by trtp;
  var week_0 week_3 week_13;
  mcmc impute=monotone;
run;

* Pattern mixture model with placebo-based imputation;
* Impute week 3;
data mi_imp1 mi_rest1;
  set mi_mono;
```

```
  if trtp='Circadin' and lastwk>=3 then output mi_rest1;
  else output mi_imp1;
run;

proc mi data=mi_imp1 out=mi_reg_imp1 nimpute=1 seed=8254340;
  class gender disease;
  var week_0 week_3;
  monotone regression;
  by _imputation_;
run;

data midata_2;
  set mi_rest1 mi_reg_imp1;
  by _imputation_;
run;

* Impute week 13;
data mi_imp2 mi_rest2;
  set midata_2;
  if trtp='Circadine' and lastwk=13 then output mi_rest2;
  else output mi_imp2;
run;

proc mi data=mi_imp2 out=mi_reg_imp2 nimpute=1 seed=1066436;
  class gender disease;
  var week_0 week_3 week_13;
  monotone regression;
  by _imputation_;
run;

data tst_mi;
  set mi_rest2 mi_reg_imp2;
  by _imputation_;
  chg=week_13-week_0;
  base=week_0;
run;

* Perform analysis;
proc mixed data=tst_mi;
  class trtp gender disease;
  model chg=trtp base;
  lsmeans trtp/cl diff;
  by _imputation_;
  ods output Diffs=est LSMeans=lsm;
run;

* Combine estimates of adjusted means from each imputation;
proc sort data=lsm;
  by trtp;
run;

proc mianalyze data=lsm;
  by trtp;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=milsm;
run;
```

```
* Combine estimates of treatment difference from each imputation;
proc mianalyze data=est;
  modeleffects estimate;
  stderr stderr;
  ods output ParameterEstimates=midiff;
run;
```

11.5.2 Baseline Observation Carried Forward

In addition to using the MI method, the effect of missing data will also be assessed using the Baseline Observation Carried Forward (BOCF) method. For the primary efficacy variable and the secondary efficacy variables collected using the Sleep and Nap Diary, the analysis will be repeated to assess the effect of missing data arising on the estimated treatment effects by imputing the missing values with the subject's baseline observation. The analysis will be done using the substantive (ANCOVA) model used in the MI approach.

11.6 Subgroup Analysis

11.6.1 Inclusion of Additional Factors in MMRM Analysis

The effect of treatment in subgroups of interest will be assessed by repeating the analysis of the primary efficacy variable by including the following factors in the model, one at a time.

- Geographic region (US v Europe)
- Center
- Age (2-<6 yrs, 6-<12 yrs, >-12 yrs)
- Gender
- ADHD (Yes, No; identified from the medical history)
- Austim Type
- Epilepsy (Yes, No)
- Prior Anti-Epileptic Treatment
- Prior Anti-Depressant Treatment
- Prior Beta-Blockers Use
- Prior Stimulant Use
- Prior ADHD Treatment
- Prior Clonidine Use

From this model, within each subgroup, the adjusted mean change from baseline (and standard error) in TST after 13 weeks of treatment for each treatment group will be calculated and the associated 95% CI for the change presented. Furthermore for each subgroup, the estimated difference (and standard error) between treatments will be estimated, the associated 95% CI presented and the null hypothesis that these means are equal will be tested.

Example SAS code for this analysis is given below:

```
proc mixed data=tst method=reml;
  class subjid trtp avisitn geog;
  model chg=trtp avisitn base geog trtp*geog trtp(avisitn) base(avisitn)
geog(avisitn) trtp*geog(avisitn)/ddfm=kr;
  repeated avisitn/subject=subjid type=un;
```

```
  lsmeans trtp*geog(avisitn)/diff cl om;
  ods output lsmeans=lsm(where=(avisitn=4)) diffs=diff(where=(avisitn=4 and
geog=_geog));
run;
```

The above analysis will be repeated for CSDI, CGAS and Total SDQ at 13 weeks incorporating the following factors into the model:

- ADHD (Yes, No)
- Epilepsy (Yes, No)
- Prior ADHD Treatment
- Prior Clonidine Use

11.6.2 SND Summaries by Final Dose

The summary tables for the SND parameters will be presented separately for the double blind and open label phases by the final dose that the subject received at the end of each phase respectively.

11.7 Agreement between Sleep and Nap Diary and Actigraphy

An analysis will be performed to assess the agreement of the following sleep parameters collected via the Sleep and Nap Diary and actigraphy:

- Total Sleep Time
- Sleep Latency
- Duration of Wake
- Number of Awakenings
- Longest Sleep Duration
- Total Time in Bed
- Number of Responders at baseline, Visit 2 (defined as > 6 hours of continuous sleep and < 0.5 hour sleep latency from light off in 3 out of 5 nights.)

The analysis will use data from Visits 2 and 4. Agreement will be assessed using the methods described by Bland and Altman ([4], [5]). Bland and Altman plots (plotting the difference in the measurements from the two sources versus the average of the measurements from the two sources) will be produced and the 95% limits of agreement calculated.

Example SAS code for the calculation of the limits of agreement is given below:

```
proc mixed data=agree method=type1;
  class subjid;
  model diff=/solution ddfm=sat;
  random subjid;
  ods output CovParms=covparms;
run;

proc means data=agree noprint;
  var diff;
  output out=meandiff mean=meandiff;
run;
```

```
data loa;
  merge meandiff covparms(where=(covparm='SUBJID') rename=(estimate=between))
covparms(where=(covparm='Residual') rename=(estimate=within));
  std=sqrt(within+between);
  upper_loa=meandiff+(1.96*std);
  lower_loa=meandiff-(1.96*std);
run;
```

For number of responders, a 2 x 2 table will be presented tabulating responders according to the sleep and nap diary against responders according to actigraphy. Agreement between the sleep and nap diary and actigraphy responders will be summarised using Cohen's kappa statistic. The hypothesis that Cohen's kappa differs from 0 will be tested. A 95% confidence interval for Cohen's kappa will also be presented.

11.8 Correlation between Sleep and Nap Diary and Actigraphy versus Daytime Endpoints

Scatterplots will be presented for selected sleep parameters collected via the Sleep and Nap Diary and actigraphy against CSDI, CGAS and SDQ Total score as follows:

- SND TST versus CSDI
- SND TST versus CGAS
- SND TST versus SDQ Total Score
- SND Sleep Latency versus CSDI
- SND Sleep Latency versus CGAS
- SND Sleep Latency versus SDQ Total Score
- SND WASO versus CSDI
- SND WASO versus CGAS
- SND WASO versus SDQ Total Score
- Actigraphy TST versus CSDI
- Actigraphy TST versus CGAS
- Actigraphy TST versus SDQ Total Score
- Actigraphy Sleep Latency versus CSDI
- Actigraphy Sleep Latency versus CGAS
- Actigraphy Sleep Latency versus SDQ Total Score
- Actigraphy WASO versus CSDI
- Actigraphy WASO versus CGAS
- Actigraphy WASO versus SDQ Total Score

Spearman's rank correlations will be calculated and presented on the scatterplot for each correlation. In addition, the null hypothesis of zero correlation will be tested.

12 Safety

Subjects will be classified and summarized by actual treatment.

Safety will be assessed using TESS, AEs, vital signs, BMI and physical development data.

12.1 Treatment Exposure

Details of study drug compliance, dose modifications and dose increases will be listed.

The time on treatment will be listed and summarized descriptively.

Time on treatment (days) in DB Phase = Last dose date of DB phase – first dose date of DB phase +1

Time on treatment (days) in OL Phase = Last dose date of OL phase – first dose date of OL phase +1

Time on active treatment (days) = Last dose date of active treatment – first dose date of active treatment +1

The number of subjects having a decrease in dose or an increase in dose will be tabulated by visit. % compliance will be summarized descriptively.

The dosage achieved (2/5/10mg) will be tabulated by scheduled visit and the maximum dose achieved will also be tabulated.

12.2 Treatment Emergent Signs and Symptoms

TESS are recorded throughout the study. At Visit 1, the TESS questionnaire is completed and the information is used to assess medical history. All symptoms that are score of 1 or more will be recorded in the medical history. At Visit 2 and all subsequent visits thereafter, the TESS questionnaire will be used to report all treatment-emergent signs and symptoms that may have occurred since Visit 1. A given sign and symptom will be reported as a corresponding AE 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 will not be reported.

A frequency table of TESS results will be presented by sign/symptom and scheduled visit for the thirteen hypothecated events.

12.3 Adverse Events

AEs will be coded according to MedDRA® version 18.0 or higher.

An overall AE summary will be presented for the following pre-defined subsets of events:

- Any TEAEs
- Any TEAEs considered related to treatment
- Any TEAEs leading to study drug discontinuation
- Any SAEs
- Any deaths
- Any SAEs considered related to treatment
- Any SAEs leading to study drug discontinuation

Listings by subject will be presented for the following subsets:

- Any TEAEs

- Any SAEs

All TEAEs will be summarized and grouped by MedDRA® System Organ Class (SOC) and specific AE preferred term (PT). Results will be displayed in order of decreasing frequency by SOC and PT.

Summaries will also be produced of SAEs, treatment related AEs and TEAEs leading to study drug discontinuation by SOC and PT terms. In addition, a summary will be provided by severity (mild, moderate, severe).

For all summary tables, both number of events and number of subjects will be tabulated. For subjects, percentages will be calculated from the total number of subjects per treatment group. Related to treatment is defined as any adverse events considered either "possibly", "probably" or "definitely" related to study drug.

Tables will be presented for the double blind and open-label phases separately.

In addition a cumulative summary will also be presented for all subjects on active treatment for all TEAEs, SAEs and TESAEs leading to discontinuation of study drug grouped by SOC and PT terms occurring in either the double blind or open-label phase.

For the purposes of the interim analysis reporting, an AE cut-off point will be defined as any AE starting on or before Visit 5.

12.4 Vital Signs

Vital signs include systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, oral temperature (°C)

The result, change from baseline and % change from baseline for all vital sign parameters will be listed and summarized descriptively by scheduled visit.

12.5 BMI and Z-scores

Weight, height and BMI will be recorded throughout the study.

The result, change from baseline and % change from baseline for weight, height and BMI will be listed and summarized descriptively by scheduled visit. Descriptive statistics will also be presented for the following age groups: 2 to ≤5 years, > 5 to < 8 years and ≥8 years.

The BMI percentiles 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 percentiles 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 (CDC).

A SAS program and reference data can be downloaded from the following webpage:

http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. (Appendix B)

The program will calculate the percentiles and z-scores (standard deviations) for a child's sex and age for BMI, weight, height, and head circumference based on the CDC growth charts. The reference data contains the L, M, and S parameters needed to generate the percentiles and z-scores.

An input file should be setup containing AGEMOS (age in months), SEX (coded as 1 for boys and 2 for girls) and BMI. An output file will be generated containing BMIPCT (BMI percentile) and BMIZ (BMI Z-Score).

The BMI percentiles will be used to categorize the subject's weight as follows:

Weight Status Category	**Percentile Range**
Underweight	Less than the 5th percentile
Normal or Healthy Weight	5th percentile to less than the 85th percentile
Overweight	85th to less than the 95th percentile
Obese	Equal to or greater than the 95th percentile

A shift table will be presented for the change in weight status category from baseline to end of double-blind treatment, to the end of the first open-label phase and to the end of study.

The Z-score and change from baseline will be listed and summarized descriptively by scheduled visit.

BMI and Z-score after 3 weeks and 13 weeks of double blind treatment and during open-label treatment will be analysed as for TST.

12.6 Tanner Assessment of Pubertal Development

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

Two measures are collected for males (genital development (5 stages G1–G5) and pubic hair (6 stages PH1–PH6)) and females (breast development (5 stages B1–B5), pubic hair (6 stages PH1–PH6)) respectively.

Tanner scores for pubertal assessment in subjects ≥8 years of age during the study will be analyzed using the web application (http://vps.stefvanbuuren.nl/puberty). The Tanner scores for each measure will be uploaded to the website as a .csv file. The file will contain the subject's sex and age in months to two decimal places. An example file is available to ensure the correct format for uploading the file to the site. This tool will calculate SD scores of individual observations of Tanner scores for each assessment.

Results from the Tanner assessment will be tabulated for each measure by scheduled visit.

For subjects ≥8 years of age the SD score and change from baseline in the SD score for each pubertal assessment will be listed and summarized descriptively by scheduled visit.

The result, change from baseline and % change from baseline for head circumference will be listed and summarized descriptively by scheduled visit. Descriptive statistics will also be presented for the following age group: 2 to ≤5 years, > 5 to < 8 years and ≥8 years.

12.7 Epilepsy

Number and type of epilepsy seizures in children diagnosed with epilepsy will be tabulated, using the Epilepsy Seizures Diaries that are completed by parents at the time of the seizures. For the number of epilepsy seizures, percentages will be based on the number of children diagnosed with epilepsy.

The median number of epilepsy seizures will be summarized by scheduled visit and across all visits. At each visit Wilcoxon rank-sum test will be performed to compare the number of seizures occurring between the two groups.

Example SAS code for this analysis is given below:

```
proc NPAR1WAY data=epil wilcoxon;
      class trtp;
      var numepil;
      exact wilcoxon;
run;
```

12.8 Other Data

12.8.1 Pregnancy Test

All subjects will be tested for pregnancy by urine dipstick at Screening, Week 2, Week 15 and Week 108. Details of pregnancy test results will be listed.

12.8.2 Physical Examination

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 and recorded on the adverse event eCRF. The date of the physical examination will be listed.

12.8.3 Visit Dates

Visit dates will be listed.

13 Interim Analysis

All results 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. This will constitute the final analysis of data up to that point and no statistical adjustment of significance tests is required.

The data from the second open-label period will be summarized on the completion of the study and reported as an appendix to the CSR.

14 Changes to Planned Methodology

The analysis of total CSDI score at 13 weeks has been moved from an exploratory endpoint to a secondary endpoint to reflect the greater importance being placed on this endpoint at the present time.

15 References

[1] Kenward, M. G. and Roger, J. H. (1997), Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood, Biometrics, 53, 983–997

[2] Ratitch, B. and O'Kelly, M. (2011), Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures, in Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group), SP04, Nashville.

[3] Rubin, D. B. (1987), Multiple Imputation for Nonresponse in Surveys, New York: John Wiley & Sons.

[4] Bland, J.M., Altman, D.G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement, Lancet, i: 307-310.

[5] Bland, J.M., Altman, D.G. (2007). Agreement between methods of measurement with multiple observations per individual, J. Biopharmaceutical Statistics, 17: 571-582.

16 Tables, Figures and Listings

Tables and listings will be presented landscape. A font size of 8 and a font of courier new will be used throughout for tables and listings. Tables and listings will be provided as a bookmarked pdf. Figures will be provided as individual files.

The subject population being utilized in the table will be indicated in the table title. Page numbers and dates of production will be included in an appropriate place at the bottom of the output. Listings which support the table will also be detailed in an appropriate place at the bottom of the output.

Tables will only be generated where there is sufficient data to warrant the inclusion of the table.

16.1 List of Tables

Table Number	Table Title	Population
Table 14.1.1.1	Patient Disposition: Double Blind Phase	All Enrolled Set
Table 14.1.1.2	Patient Disposition: First Open Label Phase	All Enrolled Set
Table 14.1.1.3	Patient Disposition: Second Open Label Phase	All Enrolled Set
Table 14.1.2.1	Demographic Characteristics	All Enrolled Set
Table 14.1.2.2	Demographic Characteristics	All Randomized Set
Table 14.1.3	Baseline Characteristics	All Randomized Set
Table 14.1.4	Diagnosis of Neurodevelopmental Disability	All Randomized Set
Table 14.1.5	Melatonin Use	All Randomized Set
Table 14.1.6	Medical History	All Randomized Set
Table 14.1.7	Prior Medications	All Randomized Set
Table 14.1.8	Concomitant Medications - Double Blind Phase	All Randomized Set
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Table 14.2.1.1	Number of Sleep and Nap Diaries with Data Recorded	FAS Set
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Table 14.2.1.26	SND Feeling on Awakening Change from Baseline at 13 Weeks Double Blind – MMRM Analysis	FAS Set
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Table 14.2.18.9	SND Number of Awakenings and Change from Baseline – Open Label - Descriptive Statistics by Final Dose	FAS Set
Table 14.2.18.10	SND Longest Sleep Period and Change from Baseline – Open Label - Descriptive Statistics by Final Dose	FAS Set
Table 14.2.19	Summary of Level of Agreement between Sleep and Nap Diary and Actigraphy Assessment of Responder	FAS Set
Table 14.3.1.1	Summary of Study Drug Exposure	Safety Set
Table 14.3.1.2	Summary of Study Drug Modifications	Safety Set
Table 14.3.1.3	% Compliance by Scheduled Visit	Safety Set
Table 14.3.1.4	Dosage Achieved by Scheduled Visit	Safety Set
Table 14.3.1.5	Number of Dropouts -Chi-Square Test	Safety Set
Table 14.3.2.1	Summary of TESS by Scheduled Visit	Safety Set

Table Number	Table Title	Population
Table 14.3.2.2	Overall Adverse Event Summary: Double Blind Phase	Safety Set
Table 14.3.2.3	Overall Adverse Event Summary: Open Label Phase	Safety Set
Table 14.3.2.4	Treatment Emergent Adverse Events by System Organ Class and Preferred Term: Double Blind Phase	Safety Set
Table 14.3.2.5	Treatment Emergent Adverse Events by System Organ Class and Preferred Term: Open Label Phase	Safety Set
Table 14.3.2.6	Serious Adverse Events by System Organ Class and Preferred Term: Double Blind Phase	Safety Set
Table 14.3.2.7	Serious Adverse Events by System Organ Class and Preferred Term: Open Label Phase	Safety Set
Table 14.3.2.8	Treatment Related Adverse Events by System Organ Class and Preferred Term: Double Blind Phase	Safety Set
Table 14.3.2.9	Treatment Related Adverse Events by System Organ Class and Preferred Term: Open Label Phase	Safety Set
Table 14.3.2.10	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity: Double Blind Phase	Safety Set
Table 14.3.2.11	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity: Open Label Phase	Safety Set
Table 14.3.2.12	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term: Double Blind Phase	Safety Set
Table 14.3.2.13	Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term: Open Label Phase	Safety Set
Table 14.3.2.14	Treatment Emergent Adverse Events on Active Treatment by System Organ Class and Preferred Term: Cumulative	Safety Set
Table 14.3.2.15	Serious Adverse Events on Active Treatment by System Organ Class and Preferred Term: Cumulative	Safety Set
Table 14.3.2.16	Treatment Emergent Adverse Events Study Drug Discontinuation on Active Treatment by System Organ Class and Preferred Term: Cumulative	Safety Set
Table 14.3.3	Vital Sign Parameters and Change from Baseline – Descriptive Statistics	Safety Set
Table 14.3.4.1	Weight and Change from Baseline – Descriptive Statistics	Safety Set
Table 14.3.4.2	Weight and Change from Baseline by Age Group – Descriptive Statistics	Safety Set
Table 14.3.4.3	Height and Change from Baseline – Descriptive Statistics	Safety Set
Table 14.3.4.4	Height and Change from Baseline by Age Group – Descriptive Statistics	Safety Set
Table 14.3.5.1	BMI and Change from Baseline – Descriptive Statistics	Safety Set
Table 14.3.5.2	BMI and Change from Baseline by Age Group – Descriptive Statistics	Safety Set
Table 14.3.5.3	Shift Table of Change in BMI Weight Status	Safety Set

Table Number	Table Title	Population
Table 14.3.5.4	BMI Change from Baseline at 3 Weeks Double Blind – MMRM Analysis	FAS Set
Table 14.3.5.5	BMI Change from Baseline at 13 Weeks Double Blind – MMRM Analysis	FAS Set
Table 14.3.5.6	BMI Change from Baseline Analysis During the Open Label Phase and Run-Out Period	FAS Set
Table 14.3.5.7	BMI Z-Score and Change from Baseline – Descriptive Statistics	Safety Set
Table 14.3.5.8	BMI Z-Score Change from Baseline at 3 Weeks Double Blind – MMRM Analysis	FAS Set
Table 14.3.5.9	BMI Z-Score Change from Baseline at 13 Weeks Double Blind – MMRM Analysis	FAS Set
Table 14.3.5.10	BMI Z-Score Change from Baseline Analysis During the Open Label Phase and Run-Out Period	FAS Set
Table 14.3.6.1	Summary of Tanner Assessment of Pubertal Development - Staging of Pubic Hair Growth	Safety Set
Table 14.3.6.2	Summary of Tanner Assessment of Pubertal Development - Staging of Breast Development	Safety Set
Table 14.3.6.3	Summary of Tanner Assessment of Pubertal Development - Staging of Genitalia Development	Safety Set
Table 14.3.6.4	SD Score and Change from Baseline - Pubic Hair Growth – Descriptive Statistics	Safety Set
Table 14.3.6.5	SD Score and Change from Baseline - Breast Development – Descriptive Statistics	Safety Set
Table 14.3.6.6	SD Score and Change from Baseline - Genitalia Development – Descriptive Statistics	Safety Set
Table 14.3.7.1	Head Circumference and Change from Baseline – Descriptive Statistics	Safety Set
Table 14.3.7.2	Head Circumference and Change from Baseline by Age Group – Descriptive Statistics	Safety Set
Table 14.3.8.1	Number of Epilepsy Seizures in Children Diagnosed with Epilepsy - Categorical Summary	Safety Set
Table 14.3.8.2	Number of Epilepsy Seizures in Children Diagnosed with Epilepsy - Wilcoxon Rank-Sum Test	Safety Set
Table 14.3.8.3	Type of Epilepsy Seizures in Children Diagnosed with Epilepsy	Safety Set

16.2 List of Figures

Figure Number	Figure Title	Population
Figure 14.2.1.1	Change from Baseline in Mean TST over Time	FAS Set
Figure 14.2.1.2	Change from Baseline in Mean Sleep Latency over Time	FAS Set
Figure 14.2.1.3	Change from Baseline in Mean Duration of Wake over Time	FAS Set
Figure 14.2.1.4	Change from Baseline in Mean Number of Awakenings over Time	FAS Set
Figure 14.2.1.5	Change from Baseline in Mean Longest Sleep Duration over Time	FAS Set
Figure 14.2.1.6	SND Total Sleep Time Change from Baseline at 13 Weeks Double Blind - Empirical Cumulative Distribution Plot	FAS Set
Figure 14.2.1.7	SND Sleep Latency Change from Baseline at 13 Weeks Double Blind - Empirical Cumulative Distribution Plot	FAS Set
Figure 14.2.1.8	SND Duration of Wake Change from Baseline at 13 Weeks Double Blind - Empirical Cumulative Distribution Plot	FAS Set
Figure 14.2.1.9	SND Number of Awakenings Change from Baseline at 13 Weeks Double Blind - Empirical Cumulative Distribution Plot	FAS Set
Figure 14.2.1.10	SND Longest Sleep Duration Change from Baseline at 13 Weeks Double Blind - Empirical Cumulative Distribution Plot	FAS Set
Figure 14.2.2.1	Total Sleep Time, Sleep and Nap Diary against Actigraphy – Bland and Altman Plots	FAS Set
Figure 14.2.2.2	Sleep Latency, Sleep and Nap Diary against Actigraphy – Bland and Altman Plots	FAS Set
Figure 14.2.2.3	Duration of Wake, Sleep and Nap Diary against Actigraphy – Bland and Altman Plots	FAS Set
Figure 14.2.2.4	Number of Awakenings, Sleep and Nap Diary against Actigraphy – Bland and Altman Plots	FAS Set

Figure 14.2.2.5	Longest Sleep Duration, Sleep and Nap Diary against Actigraphy – Bland and Altman Plots	FAS Set
Figure 14.2.3.1	Scatterplot of SND TST versus CSDI	FAS Set
Figure 14.2.3.2	Scatterplot of SND TST versus CGAS	FAS Set
Figure 14.2.3.3	Scatterplot of SND TST versus SDQ Total Score	FAS Set
Figure 14.2.3.4	Scatterplot of SND Sleep Latency versus CSDI	FAS Set
Figure 14.2.3.5	Scatterplot of SND Sleep Latency versus CGAS	FAS Set
Figure 14.2.3.6	Scatterplot of SND Sleep Latency versus SDQ Total Score	FAS Set
Figure 14.2.3.7	Scatterplot of SND WASO versus CSDI	FAS Set
Figure 14.2.3.8	Scatterplot of SND WASO versus CGAS	FAS Set
Figure 14.2.3.9	Scatterplot of SND WASO versus SDQ Total Score	FAS Set
Figure 14.2.4.1	Scatterplot of Actigraphy TST versus CSDI	FAS Set
Figure 14.2.4.2	Scatterplot of Actigraphy TST versus CGAS	FAS Set
Figure 14.2.4.3	Scatterplot of Actigraphy TST versus SDQ Total Score	FAS Set
Figure 14.2.4.4	Scatterplot of Actigraphy Sleep Latency versus CSDI	FAS Set
Figure 14.2.4.5	Scatterplot of Actigraphy Sleep Latency versus CGAS	FAS Set
Figure 14.2.4.6	Scatterplot of Actigraphy Sleep Latency versus SDQ Total Score	FAS Set
Figure 14.2.4.7	Scatterplot of Actigraphy WASO versus CSDI	FAS Set
Figure 14.2.4.8	Scatterplot of Actigraphy WASO versus CGAS	FAS Set
Figure 14.2.4.9	Scatterplot of Actigraphy WASO versus SDQ Total Score	FAS Set

16.3 List of Listings

Listings will be sorted by treatment and subject number.

Listing Number	Listing Title	Population
Listing 16.2.1.1	Patient Disposition	All Enrolled Set
Listing 16.2.1.2	Informed Consent and Protocol Version	All Enrolled Set
Listing 16.2.1.3	Eligibility	All Enrolled Set
Listing 16.2.1.4	Inclusion and Exclusion Criteria	All Enrolled Set
Listing 16.2.2	Protocol Deviations	All Randomized Set
Listing 16.2.3	Subset Allocation	All Enrolled Set
Listing 16.2.4.1	Demography	All Enrolled Set
Listing 16.2.4.2	Diagnosis of Neurodevelopmental Disability	All Randomized Set
Listing 16.2.4.3	Melatonin Use	All Randomized Set
Listing 16.2.4.4	Medical History	All Randomized Set
Listing 16.2.4.5	Prior and Concomitant Medications	All Randomized Set
Listing 16.2.4.6	Non-Pharmacological Concomitant Measures	All Randomized Set
Listing 16.2.5.1	Study Drug Administration - IMP Compliance	All Randomized Set
Listing 16.2.5.2	Study Drug Administration - Dose Modification	All Randomized Set
Listing 16.2.5.3	Study Drug Administration - Dose Increase (Visit 3 and Visit 5 only)	All Randomized Set
Listing 16.2.5.4	Study Drug Administration - Overall Summary	All Randomized Set
Listing 16.2.6.1	Sleep and Nap Diary	All Randomized Set
Listing 16.2.6.2	Sleep and Nap Diary - Naps	All Randomized Set
Listing 16.2.6.3	Sleep and Nap Diary - Daily Values	All Randomized Set
Listing 16.2.6.4	Sleep Parameters - Sleep and Nap Diary and Actigraphy	All Randomized Set

Listing Number	Listing Title	Population
Listing 16.2.6.5	Composite Sleep Disturbance Index	All Randomized Set
Listing 16.2.6.6	Children Global Assessment Scale	All Randomized Set
Listing 16.2.6.7	Strength and Difficulties Questionnaire	All Randomized Set
Listing 16.2.6.8	Strength and Difficulties Questionnaire -Scores	All Randomized Set
Listing 16.2.6.9	Actigraphy	All Randomized Set
Listing 16.2.6.10	Pittsburgh Sleep Quality Index	All Randomized Set
Listing 16.2.6.11	Epworth Sleepiness Scale	All Randomized Set
Listing 16.2.6.12	WHO-5 Well-being Index	All Randomized Set
Listing 16.2.7.1	Treatment Emergent Signs and Symptoms	All Randomized Set
Listing 16.2.7.2	Adverse Events	All Randomized Set
Listing 16.2.7.3	Serious Adverse Events	All Randomized Set
Listing 16.2.8	Serum and Urine Pregnancy Test	All Randomized Set
Listing 16.2.9	Vital Signs	All Randomized Set
Listing 16.2.10	BMI and Z-scores	All Randomized Set
Listing 16.2.11	Tanner Assessment of Pubertal Development	All Randomized Set
Listing 16.2.12	Physical Examination	All Randomized Set
Listing 16.2.13	Epileptic Seizure Diary	All Randomized Set
Listing 16.2.14	Visit Dates	All Randomized Set

Appendices

Appendix A - SAS Program to generate SDQ Scores

The scoring algorithm is based on the 25 variables plus impact items for each questionnaire. The algorithm expects to find these variables with specific names: the first letter of each variable name is 'p' for the parent SDQ, 's' for the self-report SDQ and 't' for the teacher SDQ. After this first letter, the variable names are as follows:

consid = Item 1 : considerate

restles = Item 2 : restless

somatic = Item 3 : somatic symptoms

shares = Item 4 : shares readily

tantrum = Item 5 : tempers

loner = Item 6 : solitary

obeys = Item 7 : obedient

worries = Item 8 : worries

caring = Item 9 : helpful if someone hurt

fidgety = Item 10 : fidgety

friend = Item 11 : has good friend

fights = Item 12 : fights or bullies

unhappy = Item 13 : unhappy

popular = Item 14 : generally liked

distrac = Item 15 : easily distracted

clingy = Item 16 : nervous in new situations

kind = Item 17 : kind to younger children

lies = Item 18 : lies or cheats *[for the SDQ for 2-4 year olds, replace 'lies' with 'argues']*

bullied = Item 19 : picked on or bullied

helpout = Item 20 : often volunteers

reflect = Item 21 : thinks before acting

steals = Item 22 : steals *[for the SDQ for 2-4 year olds, replace 'steals' with 'spite']*

oldbest = Item 23 : better with adults than with children

afraid = Item 24 : many fears

attends = Item 25 : good attention

ebddiff = Impact question: oveall difficulties in at least one area

distres = Impact question: upset or distressed

imphome = Impact question: interferes with home life

impfrie = Impact question: interferes with friendships

impclas = Impact question: interferes with learning

impleis = Impact question: interferes with leisure

For each of these items, if the first response category (not true, no, not at all) has been selected, this is coded as zero, the next response category (somewhat true, yes-minor, just a little) is coded as one and so on.

For each informant, the algorithm generates six scores. The first letter of each derived variable is 'p' for parent-based scores, 's' for self-report-based scores and 't' for teacher-based scores. After this first letter, the names of the scores are as follows:

emotion = emotional symptoms

conduct = conduct problems

hyper = hyperactivity/inattention

peer = peer problems

prosoc = prosocial

ebdtot = total difficulties

impact = impact

```
if pconsid ge 0 then ppr1=1;
else ppr1=0;
if pshares ge 0 then ppr2=1;
else ppr2=0;
if pcaring ge 0 then ppr3=1;
else ppr3=0;
if pkind ge 0 then ppr4=1;
else ppr4=0;
if phelpout ge 0 then ppr5=1;
else ppr5=0;
pprotot=sum(pconsid,pshares,pcaring,pkind,phelpout);
pprono=ppr1+ppr2+ppr3+ppr4+ppr5;
pprosoc=round(pprotot*5/pprono,1);
if pprono lt 3 then pprosoc=.;
if ploner ge 0 then ppeer1=1;
else ppeer1=0;
if pfriend ge 0 then ppeer2=1;
else ppeer2=0;
if ppopular ge 0 then ppeer3=1;
else ppeer3=0;
if pbullied ge 0 then ppeer4=1;
else ppeer4=0;
if poldbest ge 0 then ppeer5=1;
else ppeer5=0;
pfrienx=2-pfriend;
ppopulax=2-ppopular;
ppeertot=sum(ploner,pfrienx,ppopulax,pbullied,poldbest);
ppeerno=ppeer1+ppeer2+ppeer3+ppeer4+ppeer5;
ppeer=round(ppeertot*5/ppeerno,1);
if ppeerno lt 3 then ppeer=.;
if prestles ge 0 then pha1=1;
else pha1=0;
if pfidgety ge 0 then pha2=1;
else pha2=0;
if pdistrac ge 0 then pha3=1;
else pha3=0;
if preflect ge 0 then pha4=1;
else pha4=0;
if pattends ge 0 then pha5=1;
else pha5=0;
preflecx=2-preflect;
```

```
pattendx=2-pattends;
phatot=sum(prestles,pfidgety,pdistrac,preflecx,pattendx);
phano=pha1+pha2+pha3+pha4+pha5;
phyper=round(phatot*5/phano,1);
if phano lt 3 then phyper=.;
if psomatic ge 0 then pem1=1;
else pem1=0;
if pworries ge 0 then pem2=1;
else pem2=0;
if punhappy ge 0 then pem3=1;
else pem3=0;
if pclingy ge 0 then pem4=1;
else pem4=0;
if pafraid ge 0 then pem5=1;
else pem5=0;
pemtot=sum(psomatic,pworries,punhappy,pclingy,pafraid);
pemno=pem1+pem2+pem3+pem4+pem5;
pemotion=round(pemtot*5/pemno,1);
if pemno lt 3 then pemotion=.;
if ptantrum ge 0 then pco1=1;
else pco1=0;
if pobeys ge 0 then pco2=1;
else pco2=0;
if pfights ge 0 then pco3=1;
else pco3=0;
if plies ge 0 then pco4=1;
else pco4=0;
if psteals ge 0 then pco5=1;
else pco5=0;
pobeyx=2-pobeys;
pcotot=sum(ptantrum,pobeyx,pfights,plies,psteals);
pcono=pco1+pco2+pco3+pco4+pco5;
pconduct=round(pcotot*5/pcono,1);
if pcono lt 3 then pconduct=.;
pebdtot=pemotion+pconduct+phyper+ppeer;
pdistrez=pdistres-1 ;
if pdistres=0 then pdistrez=0;
pimphomz=pimphome-1 ;
if pimphome=0 then pimphomz=0;
pimpfriz=pimpfrie-1 ;
if pimpfrie=0 then pimpfriz=0;
pimpclaz=pimpclas-1 ;
if pimpclas=0 then pimpclaz=0;
pimpleiz=pimpleis-1 ;
if pimpleis=0 then pimpleiz=0;
pimpact=sum(pdistrez,pimphomz,pimpfriz,pimpclaz,pimpleiz);
if pimpact lt 0 and pebddiff=0 then pimpact=0;
drop ppr1 ppr2 ppr3 ppr4 ppr5 pprotot pprono
ppeer1 ppeer2 ppeer3 ppeer4 ppeer5 pfrienx ppopulax ppeertot ppeerno
pha1 pha2 pha3 pha4 pha5 preflecx pattendx phatot phano
```

```
pem1 pem2 pem3 pem4 pem5 pemtot pemno
pco1 pco2 pco3 pco4 pco5 sobeyx pcotot pcono;

if sconsid ge 0 then spr1=1;
else spr1=0;
if sshares ge 0 then spr2=1;
else spr2=0;
if scaring ge 0 then spr3=1;
else spr3=0;
if skind ge 0 then spr4=1;
else spr4=0;
if shelpout ge 0 then spr5=1;
else spr5=0;
sprotot=sum(sconsid,sshares,scaring,skind,shelpout);
sprono=spr1+spr2+spr3+spr4+spr5;
sprosoc=round(sprotot*5/sprono,1);
if sprono lt 3 then sprosoc=.;
if sloner ge 0 then speer1=1;
else speer1=0;
if sfriend ge 0 then speer2=1;
else speer2=0;
if spopular ge 0 then speer3=1;
else speer3=0;
if sbullied ge 0 then speer4=1;
else speer4=0;
if soldbest ge 0 then speer5=1;
else speer5=0;
sfrienx=2-sfriend;
spopulax=2-spopular;
speertot=sum(sloner,sfrienx,spopulax,sbullied,soldbest);
speerno=speer1+speer2+speer3+speer4+speer5;
speer=round(speertot*5/speerno,1);
if speerno lt 3 then speer=.;
if srestles ge 0 then sha1=1;
else sha1=0;
if sfidgety ge 0 then sha2=1;
else sha2=0;
if sdistrac ge 0 then sha3=1;
else sha3=0;
if sreflect ge 0 then sha4=1;
else sha4=0;
if sattends ge 0 then sha5=1;
else sha5=0;
sreflecx=2-sreflect;
sattendx=2-sattends;
shatot=sum(srestles,sfidgety,sdistrac,sreflecx,sattendx);
shano=sha1+sha2+sha3+sha4+sha5;
shyper=round(shatot*5/shano,1);
if shano lt 3 then shyper=.;
if ssomatic ge 0 then sem1=1;
```

```
else sem1=0;
if sworries ge 0 then sem2=1;
else sem2=0;
if sunhappy ge 0 then sem3=1;
else sem3=0;
if sclingy ge 0 then sem4=1;
else sem4=0;
if safraid ge 0 then sem5=1;
else sem5=0;
semtot=sum(ssomatic,sworries,sunhappy,sclingy,safraid);
semno=sem1+sem2+sem3+sem4+sem5;
semotion=round(semtot*5/semno,1);
if semno lt 3 then semotion=.;
if stantrum ge 0 then sco1=1;
else sco1=0;
if sobeys ge 0 then sco2=1;
else sco2=0;
if sfights ge 0 then sco3=1;
else sco3=0;
if slies ge 0 then sco4=1;
else sco4=0;
if ssteals ge 0 then sco5=1;
else sco5=0;
sobeyx=2-sobeys;
scotot=sum(stantrum,sobeyx,sfights,slies,ssteals);
scono=sco1+sco2+sco3+sco4+sco5;
sconduct=round(scotot*5/scono,1);
if scono lt 3 then sconduct=.;
sebdtot=semotion+sconduct+shyper+speer;
sdistrez=sdistres-1 ;
if sdistres=0 then sdistrez=0;
simphomz=simphome-1 ;
if simphome=0 then simphomz=0;
simpfriz=simpfrie-1 ;
if simpfrie=0 then simpfriz=0;
simpclaz=simpclas-1 ;
if simpclas=0 then simpclaz=0;
simpleiz=simpleis-1 ;
if simpleis=0 then simpleiz=0;
simpact=sum(sdistrez,simphomz,simpfriz,simpclaz,simpleiz);
if simpact lt 0 and sebddiff=0 then simpact=0;
drop spr1 spr2 spr3 spr4 spr5 sprotot sprono
speer1 speer2 speer3 speer4 speer5 sfrienx spopulax speertot speerno
sha1 sha2 sha3 sha4 sha5 sreflecx sattendx shatot shano
sem1 sem2 sem3 sem4 sem5 semtot semno
sco1 sco2 sco3 sco4 sco5 sobeyx scotot scono;

if tconsid ge 0 then tpr1=1;
else tpr1=0;
if tshares ge 0 then tpr2=1;
```

```
else tpr2=0;
if tcaring ge 0 then tpr3=1;
else tpr3=0;
if tkind ge 0 then tpr4=1;
else tpr4=0;
if thelpout ge 0 then tpr5=1;
else tpr5=0;
tprotot=sum(tconsid,tshares,tcaring,tkind,thelpout);
tprono=tpr1+tpr2+tpr3+tpr4+tpr5;
tprosoc=round(tprotot*5/tprono,1);
if tprono lt 3 then tprosoc=.;
if tloner ge 0 then tpeer1=1;
else tpeer1=0;
if tfriend ge 0 then tpeer2=1;
else tpeer2=0;
if tpopular ge 0 then tpeer3=1;
else tpeer3=0;
if tbullied ge 0 then tpeer4=1;
else tpeer4=0;
if toldbest ge 0 then tpeer5=1;
else tpeer5=0;
tfrienx=2-tfriend;
tpopulax=2-tpopular;
tpeertot=sum(tloner,tfrienx,tpopulax,tbullied,toldbest);
tpeerno=tpeer1+tpeer2+tpeer3+tpeer4+tpeer5;
tpeer=round(tpeertot*5/tpeerno,1);
if tpeerno lt 3 then tpeer=.;
if trestles ge 0 then tha1=1;
else tha1=0;
if tfidgety ge 0 then tha2=1;
else tha2=0;
if tdistrac ge 0 then tha3=1;
else tha3=0;
if treflect ge 0 then tha4=1;
else tha4=0;
if tattends ge 0 then tha5=1;
else tha5=0;
treflecx=2-treflect;
tattendx=2-tattends;
thatot=sum(trestles,tfidgety,tdistrac,treflecx,tattendx);
thano=tha1+tha2+tha3+tha4+tha5;
thyper=round(thatot*5/thano,1);
if thano lt 3 then thyper=.;
if tsomatic ge 0 then tem1=1;
else tem1=0;
if tworries ge 0 then tem2=1;
else tem2=0;
if tunhappy ge 0 then tem3=1;
else tem3=0;
if tclingy ge 0 then tem4=1;
```

```
else tem4=0;
if tafraid ge 0 then tem5=1;
else tem5=0;
temtot=sum(tsomatic,tworries,tunhappy,tclingy,tafraid);
temno=tem1+tem2+tem3+tem4+tem5;
temotion=round(temtot*5/temno,1);
if temno lt 3 then temotion=.;
if ttantrum ge 0 then tco1=1;
else tco1=0;
if tobeys ge 0 then tco2=1;
else tco2=0;
if tfights ge 0 then tco3=1;
else tco3=0;
if tlies ge 0 then tco4=1;
else tco4=0;
if tsteals ge 0 then tco5=1;
else tco5=0;
tobeyx=2-tobeys;
tcotot=sum(ttantrum,tobeyx,tfights,tlies,tsteals);
tcono=tco1+tco2+tco3+tco4+tco5;
tconduct=round(tcotot*5/tcono,1);
if tcono lt 3 then tconduct=.;
tebdtot=temotion+tconduct+thyper+tpeer;
tdistrez=tdistres-1 ;
if tdistres=0 then tdistrez=0;
timpfriz=timpfrie-1 ;
if timpfrie=0 then timpfriz=0;
timpclaz=timpclas-1 ;
if timpclas=0 then timpclaz=0;
timpact=sum(tdistrez,timpfriz,timpclaz);
if timpact lt 0 and tebddiff=0 then timpact=0;
drop tpr1 tpr2 tpr3 tpr4 tpr5 tprotot tprono
tpeer1 tpeer2 tpeer3 tpeer4 tpeer5 tfrienx tpopulax tpeertot tpeerno
tha1 tha2 tha3 tha4 tha5 treflecx tattendx thatot thano
tem1 tem2 tem3 tem4 tem5 temtot temno
tco1 tco2 tco3 tco4 tco5 tobeyx tcotot tcono tdistrez timpfriz timpclaz;
```

Appendix B – SAS Program to generate BMI percentiles and Z scores

```
************************************************************
* This sas program calculates CDC percentiles and z-scores based on
* the 2000 cdc growth charts
* (http://www.cdc.gov/growthcharts/cdc_charts.htm.
* The reference population is children examined in NCHS studies
* from 1963-65 to 1988-94.

* Biologically implausible values - based on the 1995 WHO cutpoints - are
flagged,
* but these values are not necessarily incorrect.  Please see the information
* on 'Extreme or biologically implausible values' on the web page.

* Unless you have a very good reason to alter this file (and this is unlikely),
* please do NOT make changes.  This file is meant to be called with a %include
* statement from your SAS program.

* Program was revised in April 2015 to fix problems with labels and formats
************************************************************;

*********************************************;
*********  macros for calculations ***********;
*********************************************;

%macro _zscore(var,l, m, s, z, p, f);
        if &var >0 then do;
                if abs(&L) ge 0.01 then &z=((&var / &M)**&L-1)/(&L * &S);
                  else if .z < abs(&L) < 0.01 then &z=log(&var / &M)/ &S;
                &p=probnorm(&z)*100;

                sdl=((&M - &M*(1 - 2 * &L * &S)**(1 / &L)) / 2);
                sdh=((&M * (1 + 2 * &L * &S)**(1 / &L) - &M) / 2);
                        if &var lt &M then &f= (&var - &M) / sdl; else &f= (&var
- &M) / sdh;
        end;
%mend _zscore;

%macro _cuts(var,out,l,u);
        if &L <= &var <= &u then &out=0;
                else if &var> &u then &out=1; else if .< &var < &L then &out= -1;
%mend _cuts;

************ End of Macros ************;

data _orig _mydata _old; set mydata; _id=_n_; length agemos 8 sex 3;
        * length and stand_ht are used later in deciding to use
    * wt-for-stature or wt-for-len reference;
  if (. < agemos < 24) then do; length=height; end;
        if agemos>=24 then stand_ht=height;

  if agemos lt 240 then output _mydata; else output _old;
  output _orig;


data _cinage _cinlen _cinht; set _mydata;
if agemos ge 0 and agemos lt 0.5 then _agecat=0;
```

```
    else _agecat=int(agemos+0.5)-0.5;
if bmi < 0 & ( weight>0 & height >0 & agemos >=24) then
bmi=weight/(height/100)**2;
output _cinage;

if length > . then do;
    if length >= 45 then _htcat=int(length+0.5)-0.5;
        if 45 <= length < 45.5 then _htcat=45;
        output _cinlen;
       end;
if stand_ht > . then do;
    if stand_ht ge 77.5 then _htcat=int(stand_ht+0.5)-0.5;
        else if 77<= stand_ht < 77.5 then _htcat=77;
        output _cinht;
    end;

*************************************************************************;
*** begin the for-age calcs - note that this calls up the refdir libname;
data crefage; set refdir.CDCref_d; where denom='age';
        *contains all merged LMS data - use 'denom' variable;
        length sex 3;
    proc sort; by sex _agecat;        proc sort data=_cinage; by sex _agecat;

data finfage; merge _cinage (in=a) crefage (in=b); by sex _agecat;  if a;
    ageint = _agemos2-_agemos1; dage=agemos- _agemos1;

array l0  _llg  _mlg  _slg  _lht  _mht  _sht  _lwt  _mwt  _swt _lhc  _mhc  _shc
        _lbmi  _mbmi  _sbmi;
array l1 _llg1 _mlg1 _slg1 _lht1 _mht1 _sht1 _lwt1 _mwt1 _swt1 _lhc1 _mhc1 _shc1
        _lbmi1 _mbmi1 _sbmi1;
array l2 _llg2 _mlg2 _slg2 _lht2 _mht2 _sht2 _lwt2 _mwt2 _swt2 _lhc2 _mhc2 _shc2
        _lbmi2 _mbmi2 _sbmi2;
do over l0; l0= l1 + (dage * (l2 - l1)) / ageint; end;

if agemos < 24 then _mbmi=.; *theres a valid value for 23.5 months! ;

%_zscore(length, _llg, _mlg, _slg, lgz, lgpct, _Flenz);
        %_cuts(_flenz, _bivlg, -5, 3);
%_zscore(stand_ht, _lht, _mht, _sht, stz, stpct, _Fstatz);
        %_cuts(_fstatz, _bivst, -5, 3);
%_zscore(weight, _lwt, _mwt, _swt, waz, wapct, _Fwaz);
        %_cuts(_fwaz, _bivwt, -5, 5);
%_zscore(headcir, _lhc, _mhc, _shc, headcz, headcpct, _Fheadcz);
        %_cuts(_fheadcz, _bivhc, -5, 5);
%_zscore(bmi, _lbmi, _mbmi, _sbmi, bmiz, bmipct, _Fbmiz);
        %_cuts(_fbmiz, _bivbmi, -4, 5);

bmi95 = _mbmi * ((1 + _lbmi*_sbmi*probit(0.95))**(1/_lbmi));
        bmipct95=100 * (bmi/bmi95);
        **% of 95th percentile: m * ((1+l*s*z)^(1/l));

drop _llg1 _mlg1 _slg1 _lht1 _mht1 _sht1 _lwt1 _mwt1 _swt1 _lhc1 _mhc1 _shc1
        _lbmi1 _mbmi1 _sbmi1 _llg2 _mlg2 _slg2 _lht2 _mht2 _sht2 _lwt2 _mwt2
_swt2
        _lhc2 _mhc2 _shc2 _lbmi2 _mbmi2 _sbmi2 _lwht1  _mwht1  _swht1  _lwht2
        _mwht2  _swht2  _lwlg1  _mwlg1  _swlg1 _lwlg2  _mwlg2  _swlg2;
```

```
****************************************;
*** begin for-length and for-stand_ht calcs;
****************************************;

*** begin for-length calcs, birth to 36 mos;
proc sort data=_cinlen; by sex _htcat;
data creflg; set refdir.CDCref_d (keep=denom sex _lg1--_swlg2);
       where denom='length'; _htcat=_lg1;    length sex 3;
    proc sort data=creflg; by sex _htcat;

data finflg; merge _cinlen (in=a) creflg; by sex _htcat;
    if a & (43 < length <104);
    lenint = _lg2- _lg1; dlen=length - _lg1;
array l  _lwl  _mwl  _swl;
array l1  _lwlg1  _mwlg1  _swlg1;
array l2  _lwlg2  _mwlg2  _swlg2;
do over l; l = l1 + (dlen * (l2 - l1)) / lenint; end;

%_zscore(weight, _lwl, _mwl, _swl, wlz, wlpct, _Fwlz);
       %_cuts(_Fwlz,_bivwlg, -4, 5);
keep _id sex _agecat agemos weight _Fwlz _bivwlg wlz wlpct;

*** begin for-stand_ht calcs, zwtstat.xls;
proc sort data=_cinht; by sex _htcat;
data crefht; set refdir.CDCref_d
       (keep=denom sex _ht1 _ht2 _lwht1 _lwht2 _mwht1 _mwht2 _swht1 _swht2);
       where denom='height';  _htcat=_ht1;  length sex 3;
       proc sort data=crefht; by sex _htcat;

data finfht; merge _cinht (in=a) crefht; by sex _htcat;
    if a & (77 < height <122);
    htint = _ht2- _ht1; dht=height - _ht1;
array l   _lwh     _mwh   _swh;
array l1  _lwht1  _mwht1  _swht1;
array l2  _lwht2  _mwht2  _swht2;
do over l; l = l1 + (dht * (l2 - l1)) / htint; end;

%_zscore(weight, _lwh, _mwh, _swh, wstz, wstpct, _Fwstz);
       %_cuts(_Fwstz,_bivwst,-4,5);
keep _id sex _agecat agemos weight _Fwstz _bivwst wstz wstpct;

*** combine the for-age, for-length, and for-height calcs;
proc sort data=finflg; by _id; proc sort data=finfht; by _id;
data lenht; merge finflg finfht; by _id;

proc sort data=finfage; by _id;
data _outdata; **define height vars as max of standing height and lenth vars;
  merge finfage lenht; by _id;

    array a stz  stpct _bivst _fstatz wstz wstpct _bivwst _fwstz ;
    array b lgz  lgpct _bivlg _flenz  wlz  wlpct  _bivwlg _fwlz;
    array c haz  hapct _bivht _Fhaz   whz  whpct  _bivwh _Fwhz;
       do over c; if agemos ge 24 then c=a; else c=b; end;
              /* do over c; c=max(a,b); */
```

```
        if .z < weight< 0.01 then do; waz=.; wapct=.; bmiz=.; bmipct=.; whz=.;
whpct=.; end;
        if .z < height< 0.01 then do; haz=.; hapct=.; bmiz=.; bmipct=.; whz=.;
whpct=.; end;
        if .z < headcir< 0.01 then do; headcz=.; headcpct=.; end;

        min= min(of _bivht _bivwt _bivbmi _bivac _bivhc _bivssf _bivtsf _bivwh);
                if min>=0 then _bivlow=0; else if min= -1 then _bivlow=1;
        max= max(of _bivht _bivwt _bivbmi _bivac _bivhc _bivssf _bivtsf _bivwh);
                if max=0 or max= -1 then _bivhigh=0; else if max= 1 then
_bivhigh=1;

data _outdata; set _outdata;
keep _Fbmiz _Fhaz _Fheadcz _Flenz _Fstatz _Fwaz _Fwhz _fwstz _Fwlz _bivbmi
_bivhc
        _bivhigh _bivht _bivlg _bivlow _bivst _bivwh _bivwlg _bivwst _bivwt
agemos bmi bmipct
        bmipct95 bmiz height haz stz lgz headcir headcpct headcz _id lgpct sex
stpct wapct
        waz whpct whz hapct wstz wstpct _fstatz;

 data _outdata; set _outdata _old; ** combine with older, excluded people;
        label waz='weight-for-age Z'  wapct='weight-for-age percentile'
_fwaz='modified weight-for-age Z'
                        _bivwt='BIV weight-for-age'
                haz='height-for-age Z'  hapct='height-for-age percentile'
_bivht='BIV height-for-age'
                        _fhaz='modified height-for-age Z'
                bmiz='BMI-for-age Z'  bmipct='BMI-for-age percentile'
_fbmiz='modified BMI-for-age Z'
                        _bivbmi='BIV BMI-for-age' bmipct95='% of 95th BMI
percentile'
                whz='weight-for-height Z' whpct='weight-for-height percentile'
        _bivwh='BIV weight-for-height'
                        _fwhz='modified weight-for-height Z'
                headcz='head_circ-for-age Z' headcpct='head_circ-for age perc'
        _Fheadcz='modified head_circ Z'
                        _bivhc='BIV head_circ'
                _bivlow='any low BIV'  _bivhigh='any high BIV';

proc sort data= _outdata; by _id; proc sort data=_orig; by _id;

data _cdcdata; update _outdata _orig; by _id;
        * variables in _orig dataset will overwrite any changes that were made;
        drop _id stz stpct _bivst _fstatz wstz wstpct _fwstz  lgz  lgpct _bivlg
_flenz  _fwlz
                        length stand_ht _bivwst _bivwlg;
```