

## **STATISTICAL ANALYSIS PLAN**

Final Version 1.00, dated 03-Sep 2018

Gabapentin Enacarbil post-marketing clinical study

- A Randomized, Double-blind, Placebo-controlled, Parallel-group Study  
in Subjects With Restless Legs Syndrome -

ISBN: 8825-CL-0101

Astellas Pharma Inc. (API)

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## I. LIST OF ABBREVIATIONS AND KEY TERMS

### List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANCOVA	Analysis of covariance
API	Astellas Pharma Inc.
AST	Aspartate aminotransferase (GOT)
CI	Confidence interval
CRF	Case report form
Dev	Development
eCRF	Electronic case report form
FAS	Full analysis set
H	High
ICGI	Investigator-rated clinical global impression
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRLS	International restless legs scale
ISN	International study number
L	Low
LOCF	Last observation carried forward
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
MI	Multiple imputation
MMRM	Mixed model of repeated measurements
MNAR	Missing not at random
N	Normal
PCGI	Patient-rated clinical global impression
PD	Pharmacodynamic
PK	Pharmacokinetics
PMM	Pattern mixture model
PPS	Per protocol set
PSQI	Pittsburgh sleep quality index
PT	Prothrombin time (second)
QOL	Quality of life
RLS	Restless legs syndrome
SAE	Serious adverse event
SAF	Safety analysis set
SAS	Statistical Analysis Software
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
ULN	Upper limit of normal
WHODDE	WHO drug dictionary enhanced

### List of Key Terms

Term	Definition of terms
Follow-up period	The period from the start of administration of the study drug for the follow-up period to the final observation
Gabapentin	An antiepileptic drug synthesized in Germany in 1973; the active metabolite of gabapentin enacarbil
Gabapentin enacarbil	The active substance of Regnite Tablets; nonproprietary name of the drug
Registration failure	A subject who provided informed consent but did not fulfill the inclusion/exclusion criteria for formal registration and thus was not randomized or did not receive open-label study drug, or who withdrew consent during the run-in period.
Study period	The period from informed consent of the subject to completion of protocol-specified last evaluation/observation in the subject
Screening	A process of active consideration of potential subjects for enrollment in the study, conducted during the run-in period to determine the eligibility for the study
Enroll	To register or enter a patient into a clinical trial as a subject; NOTE: Once a subject is enrolled into the study, the clinical study protocol applies to the subject.
Subject	Study participant
Subject ID number	A number assigned to a subject who provided consent to participate in the study by signing the consent form
Endpoint	An attribute, phenomenon, or event that varies in quality or quantity and serves as a variable
Baseline	Measurement or finding obtained at a time point judged to be initiation of observation for comparison
Run-in period	The period from the start of administration of the study drug for the run-in period to before the start of administration of the study drug for the treatment period
Randomization	A process of assigning study subjects to treatment or control groups in which an element of chance is used in the determination of assignments to reduce bias
Regnite® Tablets	Alternative name for the study drug gabapentin enacarbil; brand name of the drug product approved for marketing in January 2012
ASP8825	Alternative name for the study drug gabapentin enacarbil; a drug substance code used by Astellas Pharma Inc.
GSK1838262	Alternative name for the study drug gabapentin enacarbil; a drug substance code used by GlaxoSmithKline K.K.
XP13512	Alternative name for the study drug gabapentin enacarbil; a Drug substance code used by XenoPort, Inc.

## **1 INTRODUCTION**

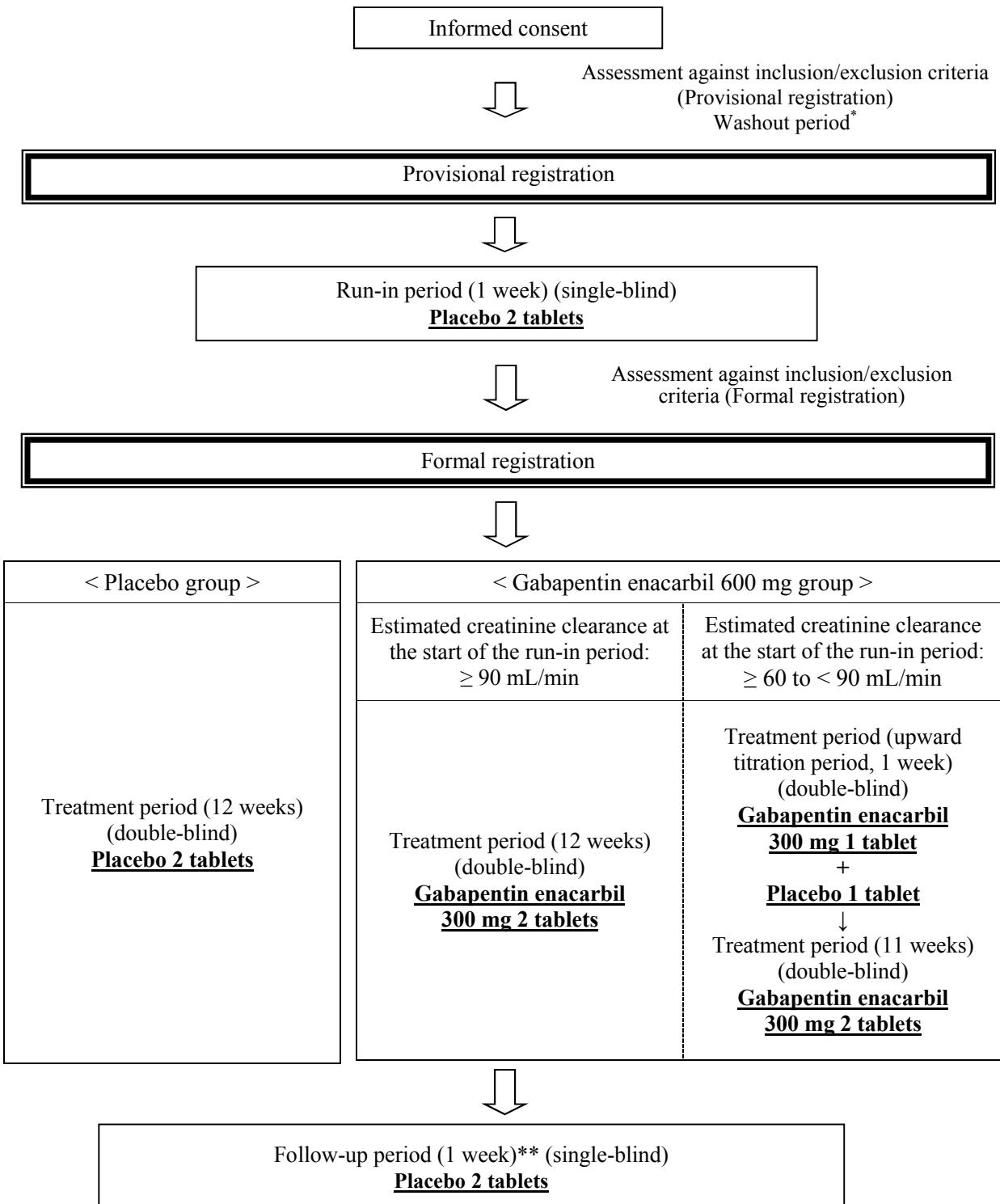
This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to unblinding.

This statistical analysis is coordinated by the responsible biostatistician of Dev, API. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

## 2 FLOW CHART AND VISIT SCHEDULE

### Flow Chart



- \* Subjects using the following drugs before the start of the run-in period will require the specified washout period:
  1. Dopamine agonists, dopamine preparations, gabapentin, pregabalin:  $\geq 7$  days
  2. Opioids, benzodiazepines (for only if used to treat RLS), long-acting dopamine agonists:  $\geq 14$  days
- \*\* For the subjects discontinued during the treatment period, the tests/observations required at discontinuation will be performed and then post-treatment follow-up will be performed as far as possible, but this does not require the use of placebo during the follow-up period.

< Start and end of the post-marketing clinical study >

The time of the start of this post-marketing clinical study is defined as the time at which informed consent is obtained from the first subject. The time of the end of this post-marketing clinical study is defined as the time at which protocol-specified final assessment is implemented in the last subject.

## Schedule of Assessments

	Run-in period	Treatment period									Follow-up period	Discontinuation <sup>*5</sup>
		W-1	W0	W1	W2	W4	W6	W8	W10	W12		
Day of observation	-7		1	8	15	29	43	57	71	85	Last dosing of the study drug for the treatment period + 8 days <sup>*4</sup>	
Allowed visit window	-10 to -7		1	5 to 11	12 to 18	26 to 32	40 to 46	54 to 60	68 to 74	82 to 88	Last dosing of the study drug for the treatment period + 5 to 11 days <sup>*4</sup>	
Visit	●	●	●	●	●	●	●	●	●	●	●	●
Informed consent	●											
Subject characteristics	●											
Assessment against inclusion/exclusion criteria	●	●										
Patient registration	● Provisional	● Formal										● Discontinuation
Prescription of the study drug	●	●	● <sup>*3</sup>	●	●	●	●	●	●	●		
Compliance status		●	●	●	●	●	●	●	●	●	●	●
Concomitant medication monitoring	●	●	●	●	●	●	●	●	●	●	●	●
IRLS score	●	●	●	●	●	●	●	●	●	●	●	●
ICGI		●	●	●	●		●	●	●	●	●	●
PCGI		●	●	●	●		●	●	●	●	●	●
Pittsburgh Sleep Quality Index		●			●		●		●			●
Athens Insomnia Scale		●			●		●		●			●
EQ-5D-5L		●			●		●		●			●
RLS Pain score	●	●	●	●	●	●	●	●	●	●	●	●
Epworth Sleepiness Scale		●	●	●	●	●	●	●	●	●	●	●
Laboratory tests	◎	◎		◎	◎		◎		◎		◎	◎
Thyroid function tests (TSH, Free T <sub>4</sub> )			◎						◎			◎
HbA1c	◎											
Ferritin	◎											
Estimated creatinine clearance	●											
Pregnancy test <sup>*1</sup>	●								●			●
Height	●											
Body weight	●	●			●		●		●			●
Vital signs	●	●	●	●	●	●	●	●	●	●		●
Adverse event monitoring <sup>*2</sup>	●	●	● <sup>*3</sup>	●	●	●	●	●	●	●	●	●

◎Central measurements

\*<sup>1</sup> Not required in men, postmenopausal women (no menstruation for at least 1 year), or other women with a history of hysterectomy, bilateral oophorectomy, etc. in whom a possibility of pregnancy is clearly excluded.

\*<sup>2</sup> A medical interview should determine any occurrence of eye disorders such as blurred vision or accommodation disorder.

\*<sup>3</sup> In subjects with an estimated creatinine clearance of  $\geq 60$  to  $< 90$  mL/min at the start of the run-in period randomized to the gabapentin enacarbil group, in whom the dose is titrated from 300 mg to 600 mg, any occurrence of AEs should be carefully assessed and the subject's condition should be adequately observed, based on which whether the subject can continue with the study should be carefully determined.

\*<sup>4</sup> Follow-up observation will occur on the day of "last dosing of the study drug for the treatment period +8 days," which will be Day 92 in subjects who take the study drug for the treatment period up to Day 84 per protocol.

\*<sup>5</sup> For the subjects discontinued during the run-in period, the compliance status and any AEs will be investigated.

For the subjects discontinued during the treatment period, the tests/observations required at discontinuation will be performed, and then post-treatment follow-up (i.e., the Week 13 procedure) will be performed as far as possible, but this does not require the use of placebo during the follow-up period.

For the subjects discontinued during the follow-up period, the Week 13 procedure will be performed as the tests/observations at discontinuation.

### **3 STUDY OBJECTIVE AND DESIGN**

#### **3.1 Study Objective**

- To verify the efficacy of oral gabapentin enacarbil 600 mg once daily compared with placebo on the basis of the change from baseline in IRLS score in patients with moderate to severe idiopathic restless legs syndrome (RLS), using a multicenter, randomized, double-blind, parallel-group, comparative design.
- To evaluate the safety of gabapentin enacarbil 600 mg.

#### **3.2 Study Design**

Gabapentin enacarbil 600 mg or placebo will be administered orally once daily after the evening meal. Patients meeting the inclusion and exclusion criteria at provisional registration will receive single-blind placebo for 1 week (run-in period). Of these, patients meeting the inclusion and exclusion criteria at formal registration will be randomized to receive double-blind treatment with either gabapentin enacarbil 600 mg or placebo for 12 weeks (treatment period). After the end of the 12-week treatment period, single-blind placebo will be given for 1 week (follow-up period) for follow-up observation.

However, of the patients meeting the inclusion and exclusion criteria at formal registration, those with an estimated creatinine clearance of  $\geq 60$  to  $< 90$  mL/min at the start of the run-in period will receive randomized double-blind treatment initially with either gabapentin enacarbil 300 mg or placebo for 1 week (upward titration period) followed by gabapentin enacarbil 600 mg or placebo for 11 weeks, totaling 12 weeks (treatment period including the upward titration period).

#### **3.3 Randomization**

The person responsible for study drug randomization will prepare the treatment codes for randomization of the study drug for the double-blind period, and retain them under lock and key until the time of treatment code breaking.

Stratified allocation will be performed with stratification factors of age ( $< 50$  years and  $\geq 50$  years) at the start of the run-in period and estimated creatinine clearance ( $\geq 60$  to  $< 90$  mL/min and  $\geq 90$  mL/min) at the start of the run-in period, to minimize imbalance in subject characteristics between the treatment groups to allow for proper comparison. The patient registration center will assign the drug numbers to the subjects in accordance with the patient registration procedures.

### **4 SAMPLE SIZE**

180 subjects per group (360 subjects in the two groups) as participants in the treatment period.

[Rationale for sample size]

The Japanese phase II/III study [CL-0003] demonstrated the change in IRLS score (mean and standard deviation) at the end of treatment period (Week 12) as shown in Table 1. Of the randomized subjects, 11.8% in the placebo group and 17.5% in the 600 mg group were discontinued during the treatment period.

**Table 1: Change in IRLS score (mean and standard deviation) at the end of treatment period (i.e., Week 12 of study treatment) in the Japanese phase II/III study [CL-0003]: FAS**

	Placebo		ASP8825 600 mg	
	N	Mean (SD)	N	Mean (SD)
Week 12 (LOCF)	116	-8.96 (7.286)	120	-11.10 (7.921)
Week 12 (Treatment period completers)	105	-9.27 (6.996)	98	-11.54 (7.793)

SD: Standard Deviation. LOCF: Last Observation Carried Forward

In addition, a repeated measures analysis of variance of the data from the patients given placebo or ASP8825 600 mg in the Japanese phase II/III study [CL-0003] and included in the Full Analysis Set showed that the adjusted means of the change from baseline in IRLS score at the end of treatment period (Week 12) were -9.15 in the placebo group and -11.71 in the 600 mg group. The difference between the adjusted means from the two groups was -2.56.

On the basis of these results, the difference between treatment groups in the change from baseline in IRLS score at the end of treatment period (Week 12) as the primary endpoint of this study was assumed to be -2.56, with a standard deviation of 8.000 in both groups. Under these assumptions, to detect a statistically significant difference between gabapentin enacarbil and placebo using a 2-sample t-test with a two-sided significance level of 0.05 and a power of 80%, 155 subjects per group would be required. Assuming the discontinuation rate during the treatment period was approximately 15.0% in each group, the sample size has been set to 180 per group.

## **5 ANALYSIS SETS**

In principle, the analysis sets below will be used. However, the final decision on handling of cases for analyses will be made in a case review before the treatment code breaking, in light of opinions/advice from medical expert, statistical advisor, and others.

### **5.1 Full Analysis Set (FAS)**

The Full Analysis Set (FAS) will consist of all subjects who received the study drug for the treatment period and were evaluated for at least one efficacy (either primary or secondary) endpoint during the treatment period. The FAS will be the primary analysis set for efficacy analyses.

### **5.2 Per Protocol Set (PPS)**

The Per Protocol Set (PPS) will consist of the subjects in the FAS who meet the following criteria:

- Subjects meeting the inclusion criteria
- Subjects not meeting any of the exclusion criteria that can affect efficacy assessments
- Subjects not using excluded concomitant medications or therapies that can affect efficacy assessments
- Subjects given the study drug for the treatment period for at least 2 weeks from the start of the treatment period
- Subjects with  $\geq 70\%$  compliance with study treatment during the treatment period

### **5.3 Safety Analysis Set (SAF)**

The Safety Analysis Set (SAF) will consist of all subjects given at least one dose of the study drug for the treatment period.

## **6 ANALYSIS VARIABLES**

### **6.1 Efficacy Endpoints**

#### **6.1.1 Primary Efficacy Endpoint**

Change from baseline in IRLS score at the end of treatment period (Week 12)

#### **6.1.2 Secondary Efficacy Endpoints**

The secondary efficacy endpoints are as follows:

- Change from baseline in IRLS score at each time point
- ICGI responder rate at each time point
- PCGI responder rate at each time point
- Change from baseline in Pittsburgh Sleep Quality Index at each time point
- Change from baseline in Athens Insomnia Scale at each time point
- Change from baseline in RLS Pain score at each time point
- Change from baseline in EQ-5D-5L at each time point

##### **6.1.2.1 ICGI and PCGI**

In terms of Investigator-rated Clinical Global Impression (ICGI) and Patient-rated Clinical Global Impression (PCGI), a subject with “Very much improved” or “Much improved” is defined as “Responder”; otherwise, “Non-responder”.

##### **6.1.2.2 Pittsburgh Sleep Quality Index**

The Pittsburgh Sleep Quality Index (PSQI) is a self-administered questionnaire to assess subjective sleep quality during the previous month (see [Appendix 1: Pittsburgh Sleep Quality Index](#)). The self-rated items of the PSQI generate seven component scores (range of subscale scores, 0-3): sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction. The sum of these seven component scores yields one global score of subjective sleep quality (range, 0-21); higher scores represent poorer subjective sleep quality. For more details and description of the component and global scores, refer to [Appendix 1: Pittsburgh Sleep Quality Index](#)

### **6.1.2.3 EQ-5D-5L**

The EQ-5D-5L is an international standardized non-disease specific (i.e. generic) instrument for describing and valuing health status, and a multi-dimensional measure of health-related QOL.

EQ-5D-5L includes two main components: (1) a VAS scale rating perception of overall health and (2) 5 qualitative domains: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. No imputation will be performed in case of a missing item.

## **6.2 Safety Variables**

Safety will be assessed by evaluation of the following variables:

- Vital signs
- Adverse events
- Laboratory tests
- Body weight
- Epworth Sleepiness Scale

### **6.2.1 Adverse Events**

TEAE is defined as an adverse event observed after starting administration of the study drug in the treatment period. If the adverse event occurs on the date of first dose of study drug (treatment period) and the onset check box is marked “ONSET BETWEEN FIRST DOSE OF STUDY DRUG IN TREATMENT PERIOD AND FIRST DOSE OF STUDY DRUG IN FOLLOW UP PERIOD”, then the adverse event will be considered treatment-emergent.

A drug-related TEAE is defined as any TEAE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

## **6.3 Other Variables**

### **6.3.1 Variables Related to Study Drugs**

#### **Treatment Groups**

Table 2 below presents the groups to which subjects are randomized.

**Table 2 Treatment groups**

<b>Randomization Arm Code (ARMCD)</b>	<b>Randomization Arm (ARM)</b>	<b>Treatment Group (Labels in TLFs)</b>	
G600	GABAPENTIN ENACARBIL 600 mg QD	Gabapentin enacarbil	Total
P	PLACEBO	Placebo	

#### **Analysis Date of First Dose**

Dates of first dose of study drug in run-in period, treatment period and follow-up period are collected in the Study Drug Dosing 3 eCRF. Analysis dates of first dose in run-in period, treatment period and follow-up period are defined as Date of First Dose of Study Drug

(RUN-IN PERIOD), Date of First Dose of Study Drug (TREATMENT PERIOD) and Date of First Dose of Study Drug (FOLLOW UP PERIOD), respectively.

### **Analysis Date of Last Dose**

Dates of last dose of study drug in run-in period, treatment period and follow-up period are collected in the Study Drug Dosing 3 eCRF. Analysis dates of last dose in run-in period, treatment period and follow-up period are defined as Date of Last Dose of Study Drug (RUN-IN PERIOD), Date of Last Dose of Study Drug (TREATMENT PERIOD) and Date of Last Dose of Study Drug (FOLLOW UP PERIOD), respectively.

### **Duration of Exposure in Treatment Period**

For each subject, duration of exposure in treatment period will be calculated in days, using the following formula:

(‘Analysis Date of Last Dose in Treatment Period’ - ‘Analysis Date of First Dose in Treatment Period’) + 1

### **Duration of Exposure in Entire Period**

For each subject, duration of exposure in entire period will be calculated in days, using the following formula:

(‘Analysis Date of Last Dose in Follow-up Period’ - ‘Analysis Date of First Dose in Run-in Period’) + 1

If subjects do not take any study drugs in follow-up period, ‘Analysis Date of Last Dose in Follow-up Period’ will be replaced with ‘Analysis Date of Last Dose in Treatment Period’.

### **Compliance in Treatment Period**

For each subject, compliance of study drug in treatment period will be calculated in %, using the following formula:

$$\frac{\text{Total number of study drugs actually taken in treatment period}}{\text{Duration of Exposure in Treatment Period} \times 2} \times 100$$

where

‘Total number of study drugs actually taken in treatment period’ =  
(Sum of “Number Dispensed” for 0WEEK, 1WEEK, 2WEEK, 4WEEK, 6WEEK, 8WEEK and 10WEEK in the Study Drug Accountability 2 eCRF) minus (Sum of “Number Returned” for 0WEEK, 1WEEK, 2WEEK, 4WEEK, 6WEEK, 8WEEK and 10WEEK in the Study Drug Accountability 2 eCRF) minus (Sum of “Number Lost” for 0WEEK, 1WEEK, 2WEEK, 4WEEK, 6WEEK, 8WEEK and 10WEEK in the Study Drug Accountability 2 eCRF)

### **Compliance in Entire Period**

For each subject, compliance of study drug in entire period will be calculated in %, using the following formula:

$$\frac{\text{Total number of study drugs actually taken in entire period}}{\text{Duration of Exposure in Entire Period} \times 2} \times 100$$

where

‘Total number of study drugs actually taken in entire period’ =  
(Sum of “Number Dispensed” for -1WEEK, 0WEEK, 1WEEK, 2WEEK, 4WEEK,  
6WEEK, 8WEEK, 10WEEK and 12WEEK in the Study Drug Accountability 2 eCRF)  
minus (Sum of “Number Returned” for -1WEEK, 0WEEK, 1WEEK, 2WEEK, 4WEEK,  
6WEEK, 8WEEK, 10WEEK and 12WEEK in the Study Drug Accountability 2 eCRF)  
minus (Sum of “Number Lost” for -1WEEK, 0WEEK, 1WEEK, 2WEEK, 4WEEK,  
6WEEK, 8WEEK, 10WEEK and 12WEEK in the Study Drug Accountability 2 eCRF)

### 6.3.2 Demographic Characteristic Variables

#### Duration of Onset of Restless Legs Syndrome

Duration of Onset of Restless Legs Syndrome in years is defined as:

$$(\text{‘Date of Visit of Run-in Period’} - \text{‘Date of Diagnosis’})/365.25$$

where ‘Date of Diagnosis’ is imputed by the following rules;

<b>Reported Date (from the eCRF)</b>	<b>Date of Diagnosis (Derived)</b>
MM/YYYY	01/MM/YYYY
--/YYYY	01/01/YYYY
MM/----, or --/---- (Unknown)	No imputation

### 6.3.3 Previous and Concomitant Medication

Previous medication is defined as medication with at least one dose taken before ‘Date of Visit of Run-in Period’ (exclusive).

Concomitant medication is defined as medication with at least one dose taken between ‘Date of Visit of Run-in Period’ (inclusive) and ‘Date of Last Study Evaluation’ (inclusive).

## 7 STATISTICAL METHODOLOGY

### 7.1 General Considerations

- For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum.
- The number of digits to be used for the mean, standard deviation and median will be added one more digit to raw data with rounding off. The minimum and maximum will be presented with the same number of digit(s) as raw data.
- Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.
- Frequencies and percentages will be rounded to one decimal place.

- For time-to-event variables, the number and percentage of subjects with the event using Kaplan-Meier method, the cumulative event rate will be estimated and a plot will be constructed.
- All data processing, summarization, and analyses will be performed using SAS Drug Development version 4.5 and SAS version 9.4. Specifications for tables, figures, and data listing formats can be found in the TLF specifications for this study.
- For continuous variables that are recorded as “< X” or “> X”, the value of “X” will be used in the calculation of summary statistics. The original values will be used for the listings.
- MedDRA/J (version 19.0) will be used as the coding dictionary for adverse event and medical history.
- WHODDE (J-Drug(2016H1)) will be used as the coding dictionary for previous and concomitant medication.
- All statistical results will be presented, as appropriate, by treatment group, and by scheduled visit; the schedule of assessments is provided in section [7.10](#)
- For the definition of subgroups of interest please refer to section [7.8](#)

## 7.2 Study Population

### 7.2.1 Disposition of Subjects

The following subject data will be summarized and presented:

[Analysis population: All subjects with informed consent, Analysis group: Total]

- Number of subjects with informed consent, discontinued before run-in period, administered at least one dose of study drug in run-in period, discontinued in run-in period, randomized, and
- Number and percentage of subjects discontinued before run-in period, by primary reason for study discontinuation.

[Analysis population: All subjects with administered at least one dose of study drug in run-in period, Analysis group: Total]

- Number and percentage of subjects discontinued in run-in period, by primary reason for study discontinuation.

[Analysis population: All randomized subjects, Analysis group: Placebo, Gabapentin enacarbil, Total]

- Number and percentage of subjects randomized in each analysis set, administered at least one dose of study drug in treatment period,
- Number and percentage of subjects completed and discontinued the treatment period, by primary reason for study discontinuation, and
- Number and percentage of subjects excluded from FAS, PPS and SAF by reason for exclusion defined in section [5.1](#) [5.2](#) and [5.3](#)

Following data will be presented graphically by treatment group for the all randomized subjects. Subjects who complete the study will be censored at the date of last evaluation.

- Time to study discontinuation using a Kaplan-Meier plot.

[Analysis population: All subjects with administered at least one dose of study drug in follow up period, Analysis group: Placebo, Gabapentin enacarbil, Total]

- Number and percentage of subjects completed and discontinued the follow up period, by primary reason for study discontinuation.

### **7.2.2 Demographic and Other Baseline Characteristics**

Demographic and other baseline characteristics will be summarized by descriptive statistics and frequency tabulations (Table 3), by treatment group for the SAF, FAS and PPS.

Baseline values of efficacy variables will be summarized by descriptive statistics and frequency tabulations (Table 4), by treatment group for the FAS and PPS.

Medical history is coded in MedDRA, and will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group for the SAF.

**Table 3 Demographic and baseline characteristics**

Item	Classification
Sex	1: Male 2: Female
Age (Years) [Informed Consent]	Measurement value 1: < 65 2: >= 65
Height (cm) [Run-in Period]	Measurement value
Weight (kg) [Run-in Period]	Measurement value 1: < 60 2: >= 60
BMI (kg/m <sup>2</sup> ) [Run-in Period]	Measurement value 1: < 25 2: >= 25
Duration of Onset of Restless Legs Syndrome (Years)	Measurement value 1: < 1 2: >= 1 to < 5 3: >= 5 to < 10 4: >= 10 5: Unknown
Family History of RLS	1: No 2: Yes
Age (Years) [Run-in Period]	Measurement value 1: < 50 2: >= 50
Estimated creatinine clearance (mL/min) [Run-in Period]	Measurement value 1: >= 60 to < 90 2: >= 90

**Table 4 Baseline values of efficacy variables**

Item	Classification
IRLS score	Measurement value 1: <= 20 2: > 20 to <= 30 3: > 30 to <= 40
PSQI Sleep Quality	Measurement value
PSQI Sleep Latency	Measurement value
PSQI Sleep Duration	Measurement value
PSQI Habitual Sleep Efficiency	Measurement value
PSQI Sleep Disturbance	Measurement value
PSQI Use of Sleeping Medication	Measurement value
PSQI Daytime Dysfunction	Measurement value
PSQI Global Score	Measurement value
Total Score of Athens Insomnia Scale	Measurement value
RLS pain score	Measurement value
EQ-5D-5L VAS Score	Measurement value
EQ-5D-5L Mobility	1: I have no problems in walking about 2: I have slight problems in walking about 3: I have moderate problems in walking about 4: I have severe problems in walking about 5: I am unable to walk about
EQ-5D-5L Self-Care	1: I have no problems washing or dressing myself 2: I have slight problems washing or dressing myself 3: I have moderate problems washing or dressing myself 4: I have severe problems washing or dressing myself 5: I am unable to wash or dress myself
EQ-5D-5L Usual Activities	1: I have no problems doing my usual activities 2: I have slight problems doing my usual activities 3: I have moderate problems doing my usual activities 4: I have severe problems doing my usual activities 5: I am unable to do my usual activities
EQ-5D-5L Pain/Discomfort	1: I have no pain or discomfort 2: I have slight pain or discomfort 3: I have moderate pain or discomfort 4: I have severe pain or discomfort 5: I have extreme pain or discomfort
EQ-5D-5L Anxiety/Depression	1: I am not anxious or depressed 2: I am slightly anxious or depressed 3: I am moderately anxious or depressed 4: I am severely anxious or depressed 5: I am extremely anxious or depressed

### 7.2.3 Previous and Concomitant Medications

Previous and concomitant medications are coded with WHODDE, and will be summarized by preferred WHO name, by treatment group for the SAF.

The following specific medications uses will be summarized by frequency tabulations, by treatment group for the SAF, FAS and PPS.

Prior Dopamine agonists Use	No, Yes
-----------------------------	---------

## **7.3 Study Drugs**

### **7.3.1 Exposure**

Durations of exposure in treatment and entire period will be summarized by descriptive statistics and frequency tabulations, by treatment group for the SAF. The following categories of the durations of exposure (days) will be defined:

- < 29 (4 weeks)
- >= 29 (4 weeks) to < 57 (8 weeks)
- >= 57 (8 weeks) to < 85 (12 weeks)
- >= 85 (12 weeks)

### **7.3.2 Study drug Compliance**

Study drug compliances in treatment and entire period will be summarized by descriptive statistics and frequency tabulations, by treatment group for the SAF. The following categories of the study drug compliances (%) will be defined:

- < 50
- >= 50 to < 75
- >= 75 to < 90
- >= 90
- Unknown

## **7.4 Analysis of Efficacy**

### **7.4.1 Analysis of Primary Endpoint**

#### **7.4.1.1 Primary Analysis**

The primary analysis will be performed using the FAS.

The primary efficacy endpoint is the change from baseline in IRLS score at the end of treatment period. Using a repeated measures analysis of variance model, so-called Mixed Model of Repeated Measurements (MMRM) model, having the following average structure, the adjusted mean in each treatment group and its difference (gabapentin enacarbil group - placebo group) at the end of treatment period (Week 12) will be calculated, with comparison between the placebo group and the gabapentin enacarbil group:

Change in IRLS score at each time point

$$= \text{Baseline IRLS score} + \text{Age category}^{\ast 1} + \text{Estimated creatinine clearance category}^{\ast 2} + \\ \text{Treatment group} + \text{Time point} + \text{Treatment group} \times \text{Time point}$$

$\ast^1$  Age category: < 50 years and  $\geq$  50 years

$\ast^2$  Estimated creatinine clearance category:  $\geq$  60 to < 90 mL/min and  $\geq$  90 mL/min

Compound symmetry will be used as the covariance structure for repeated measures of the response variable. A two-sided significance level of 0.05 will be used for statistical tests.

The least-squares mean estimates of the change from baseline in IRLS score at Week 12, the estimates of treatment effect (e.g., least-squares mean change from baseline in IRLS score for gabapentin enacarbil group minus the least-squares mean change from baseline in IRLS score for placebo group) and the corresponding 95% CIs will be reported.

## **MMRM**

The SAS procedure will be similar to the following:

```
proc mixed;  
  class SUBJECT GROUP VISIT AGE ECC;  
  model CHANGE = GROUP BASE VISIT AGE ECC GROUP*VISIT / ddfm=sat;  
  repeated VISIT /subject = SUBJECT type = cs;
```

```
lsmestimate  
  GROUP*VISIT  
  "GABAPENTIN ENACARBIL v.s. PLACEBO"  
  0 0 ... 0 1 0 0 ... 0 1 / cl alpha=0.05 om;  
  where VISIT in ('Week1', 'Week2', ... , 'Week12');  
run;
```

### **7.4.1.2 Secondary Analysis**

The primary analysis will be repeated on the PPS. Additionally, the analysis to confirm the robustness will be presented.

### **7.4.1.3 Sensitivity Analysis**

The primary endpoint will be analyzed using the following approaches:

- Analysis of Covariance (ANCOVA) model with Last Observation Carried Forward (LOCF),
- Analysis of Covariance (ANCOVA) model with Multiple Imputation (MI), and
- Pattern Mixture Model (PMM) with different assumptions for missing patterns.

For all sensitivity analyses, confidence intervals will be presented.

Table 5 summarizes all sensitivity analyses to be performed with the primary endpoint.

**Table 5 Primary, Secondary and Sensitivity Analyses for Primary Endpoint**

<b>Code</b>	<b>Set</b>	<b>Endpoint</b>	<b>Model</b>	<b>Covariates</b>
Primary	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	MMRM	Treatment group, Visit, Baseline IRLS score, Age category, Estimated creatinine clearance category, Visit by Treatment group interaction
Secondary	PPS	Change from baseline in IRLS score at the end of treatment period (Week 12)	MMRM	Treatment group, Visit, Baseline IRLS score, Age category, Estimated creatinine clearance category, Visit by Treatment group interaction
S1	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	ANCOVA with LOCF	Treatment group, Baseline IRLS score, Age category, Estimated creatinine clearance category
S2	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	ANCOVA with MI	Treatment group, Baseline IRLS score, Age category, Estimated creatinine clearance category
S3	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	PMM (Last Mean Carried Forward)	Treatment group, Baseline IRLS score, Age category, Estimated creatinine clearance category
S4	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	PMM (Last Mean Carried Forward for Gabapentin Enacarbil and Randomized Arm MAR for Placebo)	Treatment group, Baseline IRLS score, Age category, Estimated creatinine clearance category
S5	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	PMM (Copy Reference)	Treatment group, Baseline IRLS score, Age category, Estimated creatinine clearance category
S6	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	PMM (Jump to Reference)	Treatment group, Baseline IRLS score, Age category, Estimated creatinine clearance category
S7	FAS	Change from baseline in IRLS score at the end of treatment period (Week 12)	PMM (Copy Increment from Reference)	Treatment group, Baseline IRLS score, Age category, Estimated creatinine clearance category

### **ANCOVA with MI**

The MI ANCOVA model will be used to compare gabapentin enacarbil and placebo group in a fixed sequence procedure:

1. Generate 1000 datasets, using seed 394852, where intermittent missing IRLS score will be imputed for each treatment relying on non-missing data from all subjects within each treatment group using the Monte Carlo Markov Chain (MCMC) imputation model with treatment and the available non-missing IRLS score for each scheduled Week. The MCMC statement in the SAS PROC MI procedure with monotone option will be used. As a result, each dataset will only have missing ending data, or a monotone missing data pattern.
2. For each dataset from step 1, missing ending data (IRLS score up through end of treatment period) will be imputed using seed 394852. As a result, 1000 imputed complete datasets will be generated.
  - Missing data at Week 1 will be imputed using the regression imputation model with the stratification factors, baseline and IRLS score from Week 1, using the SAS PROC MI procedure with the REGRESSION option in the MONOTONE statement.
  - The SAS PROC MI procedure will use data separately from each treatment subjects to impute the missing data for a specific Week (i.e., only those that need the imputation for the Week). Since subjects from the different treatment groups for that Week are excluded from the step, they will not contribute to the imputation for the Week.
  - Repeat for all other scheduled Weeks sequentially (Week 2 to the end of evaluation period). Subjects whose missing data were imputed for previous Weeks will contribute to the imputation for the current Week.

The regression imputation model includes an intercept and the slopes of the IRLS score from previous Weeks and the stratification factors.

3. Analyze each imputed dataset using the ANCOVA using the observed or imputed IRLS score at Week 12. The model will contain terms for baseline IRLS score measurement as a covariate and treatment group and the other stratification factors as fixed effects.
4. Combine estimates from the results of each of the 1000 ANCOVA runs using SAS PROC MIANALYZE.

The least-squares mean estimates of the change from baseline in IRLS score at Week 12, the estimates of treatment effect (e.g., least-squares mean change from baseline in IRLS score for gabapentin enacarbil group minus the least-squares mean change from baseline in IRLS score for placebo group) and the corresponding 95% CIs will be reported.

### **Pattern Mixture Models (PMM)**

PMMs will be used as an alternative to impute missing values, using different assumptions for missing patterns.

PMMs provide a general and flexible framework for sensitivity analyses that allows formulating assumptions regarding missing data in a transparent and clinically interpretable manner. This is expected to address the possibility of the data being missing not at random (MNAR).

The following aspects of data missingness, may affect the estimates.

- Timing and extent of missingness
- Assumed underlying mechanism for data missingness

#### **A. Timing and Extent of Missing Data**

To assess the potential effect of data missingness on the estimate of treatment effect, subjects will be classified as full data or missing data cases. Patterns of missingness will be based on non-missing IRLS score before the end of the treatment period.

- Full data cases are defined as subjects with non-missing IRLS score for all scheduled weeks of the treatment period.
- Missing data cases are defined as subjects with a missing IRLS score on at least one scheduled Week of the treatment period. The missing data cases are further grouped into intermittent missing and monotone missing cases.
  - Intermittent missing hemoglobin cases are defined as subjects with a missing IRLS score for at least one scheduled week of but not on consecutive scheduled weeks up to end of the treatment period.
  - Monotone missing IRLS score cases are defined as subjects who have consecutive scheduled Weeks with missing IRLS score up to the end of treatment period. A subject who is a Monotone missing case could have intermittent missing IRLS score prior to the ending Week.

Subjects will be grouped as follows:

- Full data cases
- Intermittent missing data cases
- Monotone missing data cases

Should the incidence of Monotone missing data cases and intermittent missing data cases be relatively small, then those cases will be combined so that the groups are full data cases and missing data cases.

#### **B. Assumptions on Missing Data Mechanism**

In addition to the extent of data missingness, the mechanism under which missing data occur may affect the estimate of the parameter of interest.

The potential impact of missing efficacy endpoints on the estimates of treatment effects will be assessed using alternative statistical models with different underlying assumptions on the missing data mechanism for MNAR (Little and Rubin, 2002).

#### **C. PMM - Last Mean Carried Forward**

A pattern-mixture model using a last mean carried forward multiple imputation method (Carpenter *et al.*, 2013) will be used as another sensitivity analysis to explore the robustness of the MMRM, ANCOVA with LOCF and ANCOVA with MI results for the primary efficacy variables. Using this method, missing data after ending week will be imputed based on the last non-missing mean from its own treatment group.

#### **D. PMM - Last Mean Carried Forward for Gabapentin Enacarbil and Randomized Arm MAR for Placebo**

This method is a combination of PMM-Last Mean Carried forward for gabapentin enacarbil and PMM-Randomized Arm MAR for placebo group. The imputation data will be generated based on last mean carried forward method described above for the gabapentin enacarbil group, while for the placebo group, the imputation data will be generated using the Randomized Arm MAR group described below.

The Randomized Arm MAR is similar to PMM-Last Mean Carried Forward except that the joint distribution of the patient's observed and missing data is multivariate normal with mean and covariance matrix from their randomized arms.

#### **E. PMM - Copy Reference**

For the purpose of imputing the missing response data, a patient's whole distribution, both pre- and post-discontinuation, is assumed to be the same as placebo group. Post-discontinuation data in the placebo group will be imputed under Randomized Arm MAR.

#### **F. PMM - Jump to Reference**

For post-discontinuation, subject's mean response distribution is assumed to be the same as that of the placebo group. Such a change may be seen as extreme, and choosing the placebo group might be used as a worst-case scenario in terms of reducing any treatment effect since withdrawn patients on active will lose the effect of their period on treatment. Post-discontinuation data in the reference arm will be imputed under Randomized Arm MAR.

#### **G. PMM - Copy Increment from Reference**

After the subject discontinuation, the subject's post-discontinuation mean increments copy those from the placebo group. Post-discontinuation data in the placebo arm will be imputed under Randomized Arm MAR.

#### **H. Analysis Model and Reporting**

The ANCOVA model will then be performed for each combined imputed complete data set. Similarly, the Rubin's method will be then used to combine the estimates and the differences between the least square mean differences between the two treatment groups from each of the ANCOVA analyses.

The least-squares mean estimates of the change from baseline in IRLS score at Week 12, the estimates of treatment effect (e.g., least-squares mean change from baseline in IRLS score for gabapentin enacarbil group minus the least-squares mean change from baseline in IRLS score for placebo group) and the corresponding 95% CIs will be reported.

## **7.4.2 Analysis of Secondary Endpoints**

The analyses of secondary endpoints will be performed using the FAS.

### **7.4.2.1 Change from baseline in IRLS score at each time point**

The baseline visit is the measurement at Week 0.

IRLS score and its change from baseline will be summarized by descriptive statistics, by treatment group and visit.

Least square mean difference (gabapentin enacarbil group minus placebo group) of the changes in IRLS score from baseline will be calculated by visit, using ANCOVA model with the baseline value as a covariate. 95% CI and two-sided p-value of the difference will be presented.

Change from baseline in IRLS score will be summarized by subgroups defined in section 7.8.

Following data will be presented graphically by treatment group:

- IRLS score using mean (+/- SD) plot,
- Change in IRLS score from baseline using mean (+/- SD) plot.

### **7.4.2.2 ICGI responder rate at each time point**

The ICGI responder rate will be presented by treatment group. 95% CIs of the responder rate will be calculated using Clopper-Pearson method.

Difference (gabapentin enacarbil group minus placebo group) of the ICGI responder rates and its 95% CI (normal approximation with continuity correction) will be calculated. The two treatment groups will be compared using Fisher's exact test.

Following data will be presented graphically by treatment group:

- ICGI responder rate (+/- 95% CI) plot.

### **7.4.2.3 PCGI responder rate at each time point**

The PCGI responder rate will be presented by treatment group. 95% CIs of the responder rate will be calculated using Clopper-Pearson method.

Difference (gabapentin enacarbil group minus placebo group) of the PCGI responder rates and its 95% CI (normal approximation with continuity correction) will be calculated. The two treatment groups will be compared using Fisher's exact test.

Following data will be presented graphically by treatment group:

- PCGI responder rate (+/- 95% CI) plot.

### **7.4.2.4 Change from baseline in Pittsburgh Sleep Quality Index at each time point**

The baseline visit is the measurement at Week 0.

PSQI component scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction) and PSQI

global score, and their change from baseline will be summarized by descriptive statistics, by treatment group and visit.

Least square mean difference (gabapentin enacarbil group minus placebo group) of the changes in PSQI component and global scores from baseline will be calculated by visit, using the ANCOVA model with the baseline value as a covariate. 95% CI and two-sided p-value of the difference will be presented.

Following data will be presented graphically by treatment group:

- PSQI component scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction) and PSQI global score using mean (+/- SD) plot,
- Change in PSQI component scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction) and PSQI global score from baseline using mean (+/- SD) plot.

#### **7.4.2.5 Change from baseline in Athens Insomnia Scale at each time point**

The baseline visit is the measurement at Week 0.

Total score of Athens insomnia scale and its change from baseline will be summarized by descriptive statistics, by treatment group and visit.

Least square mean difference (gabapentin enacarbil group minus placebo group) of the changes in total score of Athens insomnia scale from baseline will be calculated by visit, using the ANCOVA model with the baseline value as a covariate. 95% CI and two-sided p-value of the difference will be presented.

Following data will be presented graphically by treatment group:

- Total score of Athens insomnia scale using mean (+/- SD) plot,
- Change in total score of Athens insomnia scale from baseline using mean (+/- SD) plot.

#### **7.4.2.6 Change from baseline in RLS Pain score at each time point**

The baseline visit is the measurement at Week 0.

RLS pain score and its change from baseline will be summarized by descriptive statistics, by treatment group and visit.

Least square mean difference (gabapentin enacarbil group minus placebo group) of the changes in RLS pain score from baseline will be calculated by visit, using the ANCOVA model with the baseline value as a covariate. 95% CI and two-sided p-value of the difference will be presented.

Following data will be presented graphically by treatment group:

- RLS pain score using mean (+/- SD) plot,
- Change in RLS pain score from baseline using mean (+/- SD) plot.

#### **7.4.2.7 Change from baseline in EQ-5D-5L at each time point**

The baseline visit is the measurement at Week 0.

Descriptive statistics for EQ-5D-5L VAS score and change from baseline at each visit will be presented by treatment group. For the EQ-5D-5L qualitative domains, the number and percentage of subjects in each response level value will be reported by treatment group and visit. In addition, a plot for EQ-5D-5L VAS score of mean (+/- SD) and that of change from baseline will be produced.

### **7.5 Analysis of Safety**

All analysis of safety will be presented by treatment group for the SAF, unless specified otherwise.

#### **7.5.1 Adverse Events**

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to withdrawal of treatment,
- Number and percentage of subjects with TEAEs leading to withdrawal of treatment,
- Number of drug related TEAEs leading to withdrawal of treatment,
- Number and percentage of subjects with drug related TEAEs leading to withdrawal of treatment, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment group. Summaries will be provided for:

- TEAEs,
- Drug related TEAEs,
- Serious TEAEs,
- Serious drug related TEAEs,
- TEAEs leading to withdrawal of treatment,
- Drug related TEAEs leading to withdrawal of treatment,
- TEAEs excluding serious adverse event that equal to or exceed a threshold of 5.0% in any treatment group,
- Common TEAEs that equal to or exceed a threshold of 5.0% in any treatment group,
- Common drug related TEAEs that equal to or exceed a threshold of 5.0% in any treatment group.

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by severity and by relationship to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity or relationship, then the subject will be counted only once with the worst severity or highest degree of relationship, however, if any of the severity or relationship values are missing then the subject will be counted only once with missing severity or relationship. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs will be presented in a similar way by severity only.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by time interval. For each adverse event in a particular interval, a subject will be counted if there is an onset of TEAEs regardless of onset in other intervals. Time intervals will be categorized according to the following categories (days from the first dosing of study drug in the treatment period):

- $\geq 1$  (0 weeks) to  $\leq 29$  (4 weeks)
- $> 29$  (4 weeks) to  $\leq 57$  (8 weeks)
- $> 57$  (8 weeks) to  $\leq 85$  (12 weeks)
- $> 85$  (12 weeks)

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by subgroups defined in section 7.8.

#### **7.5.1.1 Adverse Events of special interest**

For the adverse events of Nervous system disorders, the following analysis will be performed:

- The number and percentage of subjects with TEAEs of Nervous system disorders, as classified by SOC and PT will be summarized for each treatment group,
- Time to first onset of selected TEAE using a Kaplan-Meier plot based on the date of first dosing of study drug in the treatment period. Subjects who complete the study without having any TEAEs of Nervous system disorders will be censored at the date of last evaluation. Subjects who discontinued the study without having any TEAEs of Nervous system disorders will be censored at the date of discontinuation.

The following PT terms are defined as TEAEs of Nervous system disorders:

PT term	PT code
Somnolence	10041349
Dizziness	10013573

#### **7.5.2 Clinical Laboratory Evaluation**

The baseline visit is the measurement at Week 0.

Quantitative clinical laboratory variables, i.e. hematology, biochemistry, and thyroid function tests will be summarized in SI unit, using mean, standard deviation, minimum, maximum and

median, for each treatment group at each visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented for each treatment group at each visit.

For hematology, biochemistry and thyroid function tests, shift tables will be presented for each treatment group:

- Summary shifts of reference range changes from baseline to each visit (shift from normal or high to low, shift from normal or low to high, categorized increase [shift from low to normal or from normal to high], categorized no change [value stays in the same reference range], categorized decrease [shift from high to normal or from normal to low]).

Following data will be presented graphically by treatment group:

- Quantitative clinical laboratory test results using mean (+/- SD) plot.

#### **7.5.2.1 Liver Enzymes and Total Bilirubin**

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value after the date of first dosing will be used.

<u>Parameter</u>	<u>Criteria</u>
ALT	> 3xULN > 5xULN > 10xULN > 20xULN
AST	> 3xULN > 5xULN > 10xULN > 20xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin <sup>(*)</sup>	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

(\*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the investigational period will be presented by treatment group.

### **7.5.3 Vital Signs**

The baseline visit is the measurement at Week 0.

Vital signs (systolic blood pressure, diastolic blood pressure and pulse rate) will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit.

Following data will be presented graphically by treatment group:

- Vital sign results using mean (+/- SD) plot.

### **7.5.4 Body Weight**

The baseline visit is the measurement at Week 0.

Body weight will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit.

Following data will be presented graphically by treatment group:

- Body weight results using mean (+/- SD) plot.

### **7.5.5 Epworth Sleepiness Scale**

The baseline visit is the measurement at Week 0.

Total score of Epworth sleepiness scale will be summarized using mean, standard deviation, minimum, maximum and median by treatment group and visit. Additionally, a within-subject change will be calculated as the post-baseline measurement minus the baseline measurement and summarized by treatment group and visit.

Following data will be presented graphically by treatment group:

- Total score of Epworth sleepiness scale using mean (+/- SD) plot.

## **7.6 Analysis of PK**

Not applicable.

## **7.7 Analysis of PD**

Not applicable.

## **7.8 Subgroups of Interest**

Selected efficacy and safety variables will be summarized by the treatment group for the subgroups defined on the basis of the categorized variables listed in Table 6.

**Table 6 Subgroup factors and their categories**

<b>Item</b>	<b>Classification</b>	<b>Endpoints to be assessed</b>
Sex	1: Male	Change from baseline in IRLS score
	2: Female	TEAE
Age (Years) [Informed Consent]	1: < 65	Change from baseline in IRLS score
	2: >= 65	TEAE
Family History of RLS	1: No 2: Yes	Change from baseline in IRLS score
Baseline IRLS score	1: <= 20 2: > 20 to <= 30 3: > 30 to <= 40	Change from baseline in IRLS score
Previous Dopamine agonists Use	1: No 2: Yes	Change from baseline in IRLS score
Duration of Onset of Restless Legs Syndrome (Years)	1: < 1 2: >= 1 to < 5 3: >= 5 to < 10 4: >= 10	Change from baseline in IRLS score

## **7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)**

No interim analyses are planned.

## **7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information**

Final decision on handling of missing data and outliers for analyses will be made before treatment code breaking, in light of opinions/advice from medical expert, statistical advisor, and others.

### **7.10.1 Missing Data**

As a general principle, no imputation of missing data will be done. Exception is the primary efficacy endpoint. The following imputations will be performed:

- An MMRM model will be run for the purpose of implicit imputation of missing data by using all the available information from the observed data via the within-patient correlation structure for continuous endpoints with inferential analysis (section 7.4.1.1).
- An ANCOVA model with Last Observation Carried Forward (LOCF), an ANCOVA model with multiple imputations (MI) and PMM models with different missingness patterns assumptions will be run as the sensitivity analysis for the primary analysis (section 7.4.1.3).

### **7.10.2 Outliers**

All values will be included in the analyses.

### **7.10.3 Visit Windows**

In terms of the handling of data time points for analysis, if two or more observed values are available for one time interval, the value collected closer to the protocol-specified time point

will be used. If the difference from the reference time point is the same for two values, the value collected at a later point will be used. Day 1 and Day -1 are defined as the day of the formal registration and its prior day, respectively.

#### **7.10.3.1 IRLS score and RLS Pain score**

For the IRLS score and the RLS Pain score, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

<b>Analysis visit</b>	<b>Allowable time window</b>	<b>Reference day</b>
Run-in	Day -10 to Day -7	Day 1
Week 0	Day 1	Day 1
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 6	Day 40 to Day 46	Day 43
Week 8	Day 54 to Day 60	Day 57
Week 10	Day 68 to Day 74	Day 71
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period
Follow-up	Reference day +5 days to Reference day +11 days	Day of last dosing in the treatment period

#### **7.10.3.2 ICGI and PCGI**

For the ICGI and PCGI, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

<b>Analysis visit</b>	<b>Allowable time window</b>	<b>Reference day</b>
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period
Follow-up	Reference day +5 days to Reference day +11 days	Day of last dosing in the treatment period

#### **7.10.3.3 Pittsburgh Sleep Quality Index, Athens Insomnia Scale, and EQ-5D-5L**

For the Pittsburgh Sleep Quality Index, Athens Insomnia Scale, and EQ-5D-5L, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Week 0	Day 1	Day 1
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

#### 7.10.3.4 Laboratory Tests

For laboratory tests, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Run-in	Day -10 to Day -7	Day 1
Week 0	Day 1	Day 1
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

#### 7.10.3.5 Vital Signs

For the vital signs, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

Analysis visit	Allowable time window	Reference day
Run-in	Day -10 to Day -7	Day 1
Week 0	Day 1	Day 1
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 6	Day 40 to Day 46	Day 43
Week 8	Day 54 to Day 60	Day 57
Week 10	Day 68 to Day 74	Day 71
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

#### 7.10.3.6 Body Weight

For body weight, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

<b>Analysis visit</b>	<b>Allowable time window</b>	<b>Reference day</b>
Run-in	Day -10 to Day -7	Day 1
Week 0	Day 1	Day 1
Week 4	Day 26 to Day 32	Day 29
Week 8	Day 54 to Day 60	Day 57
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period

#### 7.10.3.7 Epworth Sleepiness Scale

For the Epworth Sleepiness Scale, the allowed time windows for analyses are shown in the table below. For data in the treatment period, the data obtained up to 7 days after the day of last dosing in the treatment period will be used.

<b>Analysis visit</b>	<b>Allowable time window</b>	<b>Reference day</b>
Week 0	Day 1	Day 1
Week 1	Day 5 to Day 11	Day 8
Week 2	Day 12 to Day 18	Day 15
Week 4	Day 26 to Day 32	Day 29
Week 6	Day 40 to Day 46	Day 43
Week 8	Day 54 to Day 60	Day 57
Week 10	Day 68 to Day 74	Day 71
Week 12	Day 82 to Day 88	Day 85
End of treatment	Day 2 to Reference day +7 days	Day of last dosing in the treatment period
Follow-up	Reference day +5 days to Reference day +11 days	Day of last dosing in the treatment period

## 8 DOCUMENT REVISION HISTORY

<b>Version</b>	<b>Date</b>	<b>Changes</b>	<b>Comment/rationale for change</b>
1.00	03-SEP-2018	NA	Document finalized

## 9 REFERENCES

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ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. ([www.ich.org](http://www.ich.org); Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. ([www.ich.org](http://www.ich.org); Guidelines; "Efficacy" Topics)

Little RJA and Rubin DB. Statistical Analysis with Missing Data, Second Edition. John Wiley & Sons; New Jersey: 2002.

## **10 APPENDICES**

### **10.1 Appendix 1: Pittsburgh Sleep Quality Index**

#### **10.1.1 Pittsburgh Sleep Quality Index Questionnaire**

#### **PITTSBURGH SLEEP QUALITY INDEX**

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##### **INSTRUCTIONS:**

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.

Please answer all questions.

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1. During the past month, what time have you usually gone to bed at night?

BED TIME \_\_\_\_\_

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES \_\_\_\_\_

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME \_\_\_\_\_

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT \_\_\_\_\_

*For each of the remaining questions, check the one best response. Please answer all questions.*

5. During the past month, how often have you had trouble sleeping because you . . .

- a) Cannot get to sleep within 30 minutes

Not during the past month _____	Less than once a week _____	Once or twice a week _____	Three or more times a week _____
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b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
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c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
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d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
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e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
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f) Feel too cold

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
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g) Feel too hot

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

h) Had bad dreams

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____
-----------------------------------	-------------------------------	------------------------------	------------------------------------

i) Have pain

Not during the past month \_\_\_\_\_ Less than once a week \_\_\_\_\_ Once or twice a week \_\_\_\_\_ Three or more times a week \_\_\_\_\_

j) Other reason(s), please describe \_\_\_\_\_

How often during the past month have you had trouble sleeping because of this?

Not during the past month \_\_\_\_\_ Less than once a week \_\_\_\_\_ Once or twice a week \_\_\_\_\_ Three or more times a week \_\_\_\_\_

6. During the past month, how would you rate your sleep quality overall?

Very good \_\_\_\_\_  
Fairly good \_\_\_\_\_  
Fairly bad \_\_\_\_\_  
Very bad \_\_\_\_\_

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month \_\_\_\_\_ Less than once a week \_\_\_\_\_ Once or twice a week \_\_\_\_\_ Three or more times a week \_\_\_\_\_

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month \_\_\_\_\_ Less than once a week \_\_\_\_\_ Once or twice a week \_\_\_\_\_ Three or more times a week \_\_\_\_\_

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all \_\_\_\_\_  
Only a very slight problem \_\_\_\_\_  
Somewhat of a problem \_\_\_\_\_  
A very big problem \_\_\_\_\_

10. Do you have a bed partner or room mate?

No bed partner or room mate \_\_\_\_\_  
Partner/room mate in other room \_\_\_\_\_  
Partner in same room, but not same bed \_\_\_\_\_  
Partner in same bed \_\_\_\_\_

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month \_\_\_\_\_ Less than once a week \_\_\_\_\_ Once or twice a week \_\_\_\_\_ Three or more times a week \_\_\_\_\_

b) Long pauses between breaths while asleep

Not during the past month \_\_\_\_\_ Less than once a week \_\_\_\_\_ Once or twice a week \_\_\_\_\_ Three or more times a week \_\_\_\_\_

c) Legs twitching or jerking while you sleep

Not during the past month \_\_\_\_\_ Less than once a week \_\_\_\_\_ Once or twice a week \_\_\_\_\_ Three or more times a week \_\_\_\_\_

d) Episodes of disorientation or confusion during sleep

Not during the      Less than      Once or twice      Three or more  
past month \_\_\_\_\_    once a week \_\_\_\_\_    a week \_\_\_\_\_    times a week \_\_\_\_\_

e) Other restlessness while you sleep; please describe \_\_\_\_\_

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Not during the      Less than      Once or twice      Three or more  
past month \_\_\_\_\_    once a week \_\_\_\_\_    a week \_\_\_\_\_    times a week \_\_\_\_\_

### 10.1.2 Pittsburgh Sleep Quality Index Scoring

Questions 1 through 9 are not allowed to be missing except as noted below. If these questions are missing, then any scores calculated using missing questions are also missing.

In the event that a range is given for an answer (for example, '30 to 60' is written as the answer to Q2, minutes to fall asleep), split the difference and enter 45.

#### Reference

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer OJ: The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Research* 28:193-213, 1989.

#### Scores - reportable in publications

On May 20, 2005, on the instruction of Dr. Daniel J. Buysse, the scoring of the PSQI was changed to set the score for Q5J to 0 if either the comment or the value was missing. This may reduce the DISTB score by 1 point and the PSQI Total Score by 1 point.

#### 1. Sleep quality

The sleep quality is scored by the response of question 6.

The response of question 6	Sleep quality score
Very good	0
Fairly good	1
Fairly bad	2
Very bad	3

#### 2. Sleep latency

The sleep latency is scored by the sum of scores of question 2 and 5 (a).

The response of question 2	The score of question 2
$\geq 0$ to $\leq 15$ minutes	0
$> 15$ to $\leq 30$ minutes	1
$> 30$ to $\leq 60$ minutes	2
$> 60$ minutes	3

The response of question 5 (a)	The score of question 5 (a)
Not during the past month	0

Less than once a week	1
Once or twice a week	2
Three or more times a week	3

The sum of scores of question 2 and 5(a)	Sleep latency score
0	0
1 to 2	1
3 to 4	2
5 to 6	3

### 3. Sleep duration

The sleep duration is scored by the response of question 4.

The response of question 4	Sleep duration score
$\geq 7$ hours	0
$\geq 6$ to $< 7$ hours	1
$\geq 5$ to $< 6$ hours	2
$< 5$ hours	3

### 4. Habitual sleep efficiency

The habitual sleep efficiency is scored by the sleep efficiency which is calculated from the responses of question 1, 3 and 4, using the following formula:

- Bed time: The response of question 1.
- Getting up time: The response of question 3.
- Diffhour:

If Bed time  $\geq$  Getting up time, then Diffhour = (Getting up time + 24 hours) – Bed time.

If Bed time  $<$  Getting up time, then Diffhour = Getting up time – Bed time.

- Sleep efficiency = (The response of question 4) / Diffhour \* 100.

Sleep efficiency	Sleep duration score
$\geq 85$ %	0
$\geq 75$ to $< 85$ %	1
$\geq 65$ to $< 75$ %	2
$< 65$ %	3

## 5. Sleep disturbance

The sleep disturbance is scored by the sum of scores of question 5 (b) to 5 (j). If question 5 (j) comment is null or question 5 (j) is null, set the value of question 5 (j) to 0.

The response of question 5 (b), (c), (d), (e), (f), (g), (h), (i), (j)	The score of question 5 (b), (c), (d), (e), (f), (g), (h), (i), (j)
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

The sum of scores of question 5 (b) to 5 (j)	Sleep disturbance score
0	0
1 to 9	1
10 to 18	2
19 to 27	3

## 6. Use of sleeping medication

The use of sleeping medication is scored by the response of question 7.

The response of question 7	Use of sleeping medication score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

## 7. Daytime dysfunction

The daytime dysfunction is scored by the sum of scores of question 8 and 9.

The response of question 8	The score of question 8
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

The response of question 9	The score of question 5 (a)
No problem at all	0
Only a very slight problem	1
Somewhat of a problem	2

A very big problem	3
--------------------	---

The sum of scores of question 2 and 5(a)	Sleep latency score
0	0
1 to 2	1
3 to 4	2
5 to 6	3

8. Global score of subjective sleep quality

The global score of subjective sleep quality is the sum of above 7 component scores.

## 10.2 Appendix 2: Key Contributors and Approvers

### List of Key Contributors and Approvers

#### Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

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[REDACTED], [REDACTED] [REDACTED], was the biostatistics peer reviewer of this Statistical Analysis Plan

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