Title: The exploratory study to investigate the effect of Ramelteon for insomnia patients with major depressive disorder by using actigraphy

NCT Number: NCT02669082

Statistical analysis plan Approve Date: 26-Feb-2018

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Note; This document was translated into English as the language on original version was Japanese.

The exploratory study to investigate the effect of Ramelteon for insomnia patients with major depressive disorder by using actigraphy

(Protocol number: Ramelteon-4002)

Statistical Analysis Plan

(Ver.2.0: 26 Feb 2018)

Sponsor: Takeda Pharmaceutical Company Limited

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Contents

1. DEFINITIONS of TERMS

- TEAE: Treatment-emergent adverse event
- Summary Statistics: Number of subjects, mean, standard deviations (SDs), maximum values, minimum values and quartiles
- Treatment Group: Ramelteon group

2. TIME WINDOW

[Actigraphy, Sleep diary]

Since the response data of actigraphy and sleep diary at each time point are the mean of data which collected in the previous 7 days, a set of data before each time point will be evaluated if they meet in the time window. For example, if a set of data belongs to the both time windows at week 4 and week 8, a set of data will be divided into two groups, which are for Week 4 and Week 8.

When there are two or more sets of data in the same time window, the one with the nearest visit date to the reference date will be selected, and if the time differences from the reference date are the same, the later data will be adopted.

Assessment time point	Reference Date	Time window
		Days after the first administration
At the start of the treatment period (baseline)	Day 1	Day -7 to Day 1
Week 4 of the treatment period	Day 29	Day 2 to Day 32
Week 8 of the treatment period	Day 57	Day 33 to Day 60
At the end of the treatment period	The latest set of the data group during the treatment period	Day 2 to Day 60

The day before the first day of the administration will be referred to as Day -1, and the first day of administration as Day 1.

[PGI, HAM-D17, 3DSS, Weight]

When there are two or more data in the same time window, the one with the nearest assessment date to the reference date will be selected, and if the time differences from the reference date are the same, the later data will be adopted.

Assessment time point	Reference Date	Time window
		Days after the first administration
At the start of the treatment period (baseline)	Day 1	Day -7 to Day 1
Week 4 of the treatment period	Day 29	Day 2 to Day 32
Week 8 of the treatment period	Day 57	Day 33 to Day 60
At the end of the treatment period	The latest day during the treatment period	Day 2 to Day 60

The day before the first day of the administration will be referred to as Day -1, and the first day of administration as Day 1.

3. ANALYSIS SET

- Full Analysis Set

  Full Analysis set consists of the subjects who are given at least one dose of the study drug.

4. CONSIDERATIONS for ANALYSIS

- Confidence coefficient

  95% (two-sided)
- Level of significance

  5% (two-sided)

- Display digit

  [Mean, Confidence Intervals (CIs), Quartiles]

  Round down to the one digit lower than significant digits of the data.

  [Standard Deviation]

  Round down to the two digits lower than significant digits of the data.

  [Minimum and Maximum Values]

  Display the data at the significant digits.

  [Proportion, Percentage]

  Round to one decimal place.

5. OTHER DATA HANDLING

[Study Drug]

- Study drug exposure in days will be calculated as follows:

  Date of last dose – date of first dose +1

[Actigraphy]

- Daily variation of sleep latency will be calculated at each assessment time point as follows:

  Maximum value of sleep latency – minimum value of sleep latency

[Sleep Diary]

- Total nocturnal sleep time will be derived at each assessment time point as follows:

  (Awaking hour – bedtime hour) – sleep latency

- Daily variation of sleep latency will be calculated at each assessment time point as follows:

  Maximum value of sleep latency – minimum value of sleep latency

[HAM-D17]

- HAM-D17 total score (excluding sleep related score):

  HAM-D17 total score – total score of sleep related score (question number 06, 07, 08)

- HAM-D17 total score (sleep related score only):

  Total score of sleep related score (question number 06, 07, 08)

[Demographic Characteristics]

- Disease Duration (year)

  Duration of insomnia or depression = (date of first dose – onset date of insomnia or depression + 1) / 365.25

For calculation, the onset date is regarded as the first of the month.

[3DSS]

3DSS Questionnaire Instructions

- Choose the best number which describes yourself over the past one month.
- The question is for your daily life, and you don't need to consider any special cases.
- Please fill in the number, or mark it.
- Pen, pencil, marker pen can be used.
- If you correct your answer, please erase it or mark "x" on your previous answer.

No.		Strongly Agree	Agree	Disagree	Strongly Disagree
1	I sleep for less than 6 hours on weekdays.	[1]	[2]	[3]	[4]
2	I cannot get enough sleep even though I want to.	[1]	[2]	[3]	[4]
3	I go to bed at a fixed, regular time on weekdays and weekends.	[1]	[2]	[3]	[4]
4	I wake up at a fixed, regular time on weekdays and weekends.	[1]	[2]	[3]	[4]
5	I have a well-balanced breakfast every day.	[1]	[2]	[3]	[4]
6	It takes me more than 30 minutes to fall asleep.	[1]	[2]	[3]	[4]
7	I wake up more than twice a night.	[1]	[2]	[3]	[4]
8	I wake up earlier than usual (for over 2 hours), and cannot fall asleep again.	[1]	[2]	[3]	[4]
9	I don't sleep soundly.	[1]	[2]	[3]	[4]
10	I worry that I cannot fall asleep.	[1]	[2]	[3]	[4]
11	I don't feel free from sleepiness or fatigue when I wake up.	[1]	[2]	[3]	[4]
12	I feel sleepy not only in the afternoon, but also in the morning and/or evening.	[1]	[2]	[3]	[4]
13	I often doze off.	[1]	[2]	[3]	[4]
14	"Morningness" is better suited to me than "Eveningness".	[1]	[2]	[3]	[4]

No.		Strongly Agree	Agree	Disagree	Strongly Disagree
15	What time do you wake up on weekdays? [1] --> 6 A.M. or earlier [2] --> Around 6:30 A.M. [3] --> Around 7 A.M. [4] --> Later than 7 A.M.	[1]	[2]	[3]	[4]

- Phase scale score

  Phase scale score is the total score of the question number 3, 4, 5, 14 and 15, and each score is assigned according to the answers as below.

  [1]=3, [2]=2, [3]=1, [4]=0

- Quality scale score

  Quality scale score is the total score of the question number 6 to 10, and each score is assigned according to the answers as below.

  [1]=0, [2]=1, [3]=2, [4]=3

- Quantity scale score

  Quantity scale score is the total score of the question number 1, 2, 11, 12 and 13, and the score for each answer is assigned as below.

  [1]=0, [2]=1, [3]=2, [4]=3

[TEAE]

- A TEAE is an adverse event for which the date of onset occurred after the first dose of study drug.

[Non-serious TEAE]

- Non-serious TEAE is an adverse event experienced by more than 5 % of subjects, excluding serious AE (defined in the section 10.1.3 in the protocol).

6. SUBJECTS, DEMOGRAPHIC and OTHER BASELINE CHARACTERISTICS

6.1. Subject Disposition

6.1.1. Study Information

Analysis set: All subjects who are obtained informed consent

Analysis Items: The earliest date of informed consent

The latest date of the last date of administration

Version of MedDRA

Version of SAS

Analysis Methods: For the above analysis items, the following analysis will be performed.

(1) The above items will be listed.

6.1.2. Eligibility of Subjects

Analysis set: All subjects who are obtained informed consent

Analysis Items: Randomization into the treatment period of the study

[Yes, No (and the reason)]

Analysis Methods: For the above analysis items, the following analysis will be performed.

(1) The number of subjects and the percentage will be calculated.

6.1.3. Subject Disposition

6.1.3.1. Status at the End of Study

Analysis set: All subjects who enter the treatment period

Analysis Items: Status at the end of study

[Complete, Incomplete (and the reason)]

Analysis Methods: For the above analysis items, the following analysis will be performed.

(1) The number of subjects and the percentage will be calculated.

6.1.4. Protocol Deviations and Analysis Datasets

6.1.4.1. Protocol Deviations

6.1.4.1.1 Protocol Deviations on the treatment period

Analysis set: All subjects who enter the treatment period

Analysis Items: Protocol Deviations

[Major GCP violations, Deviations of protocol entry criteria, Deviations of discontinuation criteria, Deviations related to treatment procedure or dose, Deviations concerning excluded medication or therapy, Deviations to avoid emergency risk, Other deviations]

Analysis Methods: For the above analysis items, the following analysis will be performed.

The number of subjects with any protocol deviations will be calculated, and classified into the above categories. Subjects with two or more deviations will be counted for each deviation.

(1) The number of subjects and the percentage will be calculated.

6.1.4.2. Datasets Analyzed

6.1.4.2.1 Datasets Analyzed

Analysis set: All subjects who enter the treatment period

Analysis Items: Protocol deviations [Inclusion, Exclusion]

Full Analysis Set

Analysis Methods: For the above analysis items, the following analysis will be performed.

(1) The number of subjects and the percentage will be calculated. Subjects with two or more deviations will be counted for each deviation.

(2) The number of subjects in Full Analysis Set and the percentage will be calculated based on the subjects who enter the treatment period.

6.2. Demographics and Other Baseline Characteristics

6.2.1. Distribution of Demographics

Analysis set: All subjects who are given at least one dose of the study drug

Analysis Items:

Age (years) [Min<= - <65, 65<= - <=Max]

Gender [Male, Female]

Height (baseline) (cm)

[Min<= - <150, 150<= - <160, 160<= - <170,
170<= - <=Max]

Weight (baseline) (kg)

[Min<= - <40.0, 40.0<= - <50.0,
50.0<= - <60.0, 60.0<= - <70.0, 70.0<= - <=Max]

BMI (baseline) (kg/m^2)

[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]

Alcohol consumption per week

[0 day, 1-2 days, 3-5 days, 6-7 days]

Daily smoking status

[Non-smoking, Less than 20 cigarettes, 20 cigarettes or more]

Insomnia

- Duration of disease (years)
- Initial episode/recurrence [Initial episode, Recurrence]
- Non-pharmacological therapy [Yes, No]

Depression

- Duration of disease (years)
- Initial episode/recurrence [Initial episode, Recurrence]
- Psychotherapy [Yes, No]

Sleep latency by actigraphy (baseline)

Sleep latency by sleep diary (baseline)

Total nocturnal sleep time by actigraphy (baseline)

Nocturnal wake time by actigraphy (baseline)

Number of nocturnal awakenings by actigraphy (baseline)

Sleep efficiency by actigraphy (baseline)

Total nocturnal sleep time by sleep diary (baseline)

Number of nocturnal awakenings by sleep diary (baseline)

Daytime activity level by actigraphy (steps) (baseline)

Analysis Methods: For the above analysis items, the following analysis will be performed.

(1) The number of subjects and the percentage will be calculated for discrete variables, and summary statistics will be calculated for continuous variables.

6.2.2. Medical History and Concurrent Medical Conditions

Analysis set: All subjects who are given at least one dose of the study drug

Analysis Items: Medical history, Concurrent medical conditions

Analysis Methods: History events and concurrent medical conditions will be coded using the MedDRA dictionary and tabulated by System Organ Class (SOC) and Preferred Term (PT). SOCs will be sorted in alphabetical order, and PTs will be sorted in decreasing frequency order.

(1) The number of subjects and the percentage will be calculated for medical history by SOC/PT.

(2) The number of subjects and the percentage will be calculated for medical conditions by SOC/PT.

Subjects with one or more events within a level of MedDRA term is counted only once in that level.

6.2.3. Medication History and Concomitant Medications

Analysis set: All subjects who are given at least one dose of the study drug

Analysis Items: Medication history

Previous use of hypnotics

[Yes (previous use of Benzodiazepine hypnotics, previous use of Non-benzodiazepine hypnotics, previous use of other hypnotics), No]

Concomitant Medications

Analysis Methods: The number of subjects and the percentage will be calculated for the above analysis items. Medications will be coded using the WHO (World Health Organization) Drug. Coded medications will be sorted in decreasing frequency order. Medications used more than once within a subject will be counted only once for the coded medication.

6.3. Study Drug Compliance and Exposure

6.3.1. Study Drug Compliance

Analysis set: All subjects who are given at least one dose of the study drug.

Analysis Items:

Study drug compliance [Properly (90% or more), Generally (70% or more), Half (50% or more), Less than half (less than 50%)]

Antidepressants Compliance [Properly (90% or more), Generally (70% or more), Half (50% or more), Less than half (less than 50%)]

Change of antidepressants dosage regimen [Yes, no]

Time point: Week 4, Week 8

Analysis Methods: For the above analysis items, the following analysis will be performed.

(1) The number of subjects and the percentage will be calculated for each category.

6.3.2. Study Drug Exposure

Analysis set: All subjects who are given at least one dose of the study drug.

Analysis Items:

Duration of study drug exposure (days) [1<=-<29, 29<=-<58, 58<=-<=Max]

Analysis Methods: For the above analysis items, the following analysis will be performed.

(1) The number of subjects and the percentage will be calculated for discrete variables, and summary statistics will be calculated for continuous variables.

7. EFFICACY EVALUATIONS

7.1. Primary Endpoint and the Analytical Methods

7.1.1. Change from Baseline in Sleep Latency by Actigraphy

Analysis set: Full Analysis Set

Analysis items: Sleep latency by actigraphy

Time point: Baseline, Week 4, Week 8, End of the treatment period

Analysis methods: For the above analysis items, the following analysis will be performed.

(1) As the analyses for primary endpoint, summary statistics and two-sided 95% confidence interval (CI) of the mean will be calculated for both change and percentage change from baseline to the end of treatment period, and one sample t-test will be conducted to assess the change within a subject. The same analyses as described above will be performed for change and percentage change at Week 4 and Week 8. In addition, mean plots with +/- SD for change and percentage change will be displayed at each time point.

(2) For change and percentage change from baseline to each time point, case plots will be illustrated at each time point.

(3) For observed value at each time point, case plots will be displayed, and summary statistics and two-sided 95% CI of the mean will be calculated. Mean plots with +/- SD will be also displayed at each time point.

7.2. Secondary Endpoints and the Analytical Methods

7.2.1. Secondary Endpoints and the Analytical Methods

Analysis set: Full Analysis Set

Analysis items:

Sleep latency by actigraphy

Total nocturnal sleep time by actigraphy

Nocturnal wake time by actigraphy

Number of nocturnal awakenings by actigraphy

Sleep efficiency by actigraphy

Total nocturnal sleep time by sleep diary

Number of nocturnal awakenings by sleep diary

Daytime activity level by actigraphy (steps)

Time Point: Baseline, Week 4, Week 8, End of the treatment period

Analysis Methods: For the above analysis items, the same analyses as described in 7.1.1. will be performed for secondary endpoints.

7.3. Other Analyses

7.3.1. Patient Global Impression of Improvement (PGI)

Analysis set: Full Analysis Set

Analysis items: PGI [Very much worse, Much worse, A little worse, No change, A little improved, Much improved, Very much improved]

Time Point: End of the treatment period

Analysis Methods: For the above analysis items, the following analysis will be performed

(1) The number of subjects and the percentage will be calculated for each category.

7.3.2. Hamilton Rating Scale for Depression-17 (HAM-D17)

Analysis set: Full Analysis Set

Analysis items:

01. Depressed mood (Sadness, hopeless, helpless, worthless)	[0, 1, 2, 3, 4]
02. Work and activities	[0, 1, 2, 3, 4]
03. Genital symptoms	[0, 1, 2]
04. Somatic symptoms gastrointestinal	[0, 1, 2]
05. Loss of weight (Rated by A or B)	
A. Rating by history	[0, 1, 2, 3]
B. Rating weekly by measuring weight by ward psychiatrist	[0, 1, 2, 3]
06. Insomnia early	[0, 1, 2]
07. Insomnia middle	[0, 1, 2]
08. Insomnia late	[0, 1, 2]
09. Somatic symptoms general	[0, 1, 2]
10. Feelings of guilt	[0, 1, 2, 3, 4]
11. Suicide	[0, 1, 2, 3, 4]
12. Anxiety psychic	[0, 1, 2, 3, 4]
13. Anxiety somatic	[0, 1, 2, 3, 4]
14. Hypochondriasis	[0, 1, 2, 3, 4]

15. Insight [0, 1, 2]

16. Retardation (Slowness of thought and speech, impaired ability to concentrate, decreased motor activity) [0, 1, 2, 3, 4]

17. Agitation [0, 1, 2, 3, 4]

HAM-D17 total score [0<=-<8, 8<=-<17, 17<=-<24, 24<=]

HAM-D17 total score (except for sleep related score)

HAM-D17 total score (sleep related score)

Time Point: Baseline, Week 4, Week 8, End of the treatment period

Analysis Methods: For the above analysis items, the following analysis will be performed

(1) The number of subjects and the percentage will be calculated for each category.

(2) For HAM-D17 total score, HAM-D17 total score (except for sleep related) and HAM-D17 total score (sleep related), summary statistics will be calculated and case plots will be displayed.

(3) For HAM-D17 total score, HAM-D17 total score (sleep related) and HAM-D17 total score (except for sleep related), summary statistics and two-sided 95% CI of the mean will be calculated for both change and percentage change from baseline to each time point, and one sample t-test will be conducted to assess the change within a subject.

7.3.3. 3 Dimensional Sleep Scale (3DSS)

Analysis set: Full Analysis Set

Analysis items:

01. I sleep for less than 6 hours on weekdays.

02. I cannot get enough sleep even though I want to.

03. I go to bed at a fixed, regular time on weekdays and weekends.

04. I wake up at a fixed, regular time on weekdays and weekends.

05. I have a well-balanced breakfast every day.

06. It takes me more than 30 minutes to fall asleep.

07. I wake up more than twice a night.

08. I wake up earlier than usual (for over 2 hours), and cannot fall asleep again.

09. I don’t sleep soundly.

10. I worry that I cannot fall asleep.

11. I don’t feel free from sleepiness or fatigue when I wake up.

12. I feel sleepy not only in the afternoon, but also in the morning and/or evening.
13. I often doze off.
14. “Morningness” is better suited to me than “Eveningness”.

[Strongly Agree, Agree, Disagree, Strongly Disagree] for the question 1 - 14.

15. What time do you wake up on weekdays?

[6 A.M. or earlier, Around 6:30 A.M., Around 7 A.M., Later than 7 A.M.]

Phase scale score

Quality scale score

Quantity scale score

Time Point: Baseline, Week 4, Week 8, End of the treatment period

Analysis Methods: For the above analysis items, the following analysis will be performed

(1) The number of subjects and the percentage will be calculated for each category.
(2) For phase scale score, quality scale score and quantity scale score, summary statistics will be calculated and case plots will be displayed.
(3) For phase scale score, quality scale score and quantity scale score, summary statistics and two-sided 95% CI of the mean will be calculated for both change and percentage change from baseline to each time point, and one sample t-test will be conducted to assess the change within a subject.

7.3.4. Correlation between Endpoints

Analysis set: Full Analysis Set

Analysis items: Sleep latency by actigraphy
Sleep latency by sleep diary
Total nocturnal sleep time by actigraphy
Total nocturnal sleep time by sleep diary

Time Point: End of the treatment period

Analysis Methods: Correlation charts between the items below will be illustrated and Spearman’s correlation coefficient will calculated.

Sleep latency by actigraphy vs. sleep diary

Total nocturnal sleep time by actigraphy vs. sleep diary

8. SAFETY EVALUATION

8.1. Evaluation of Adverse Event

8.1.1. Brief Summary of TEAE

Analysis set: Full Analysis Set

Analysis items: TEAE

Category Classification:

Causal relationship with study drug	[related, unrelated]
Severity	[Mild, Moderate, Severe]
Date of onset	[1<= - <29, 29<= - <58, 58<= - <=Max]

For the above analysis items, the following analyses will be performed.

(1) Brief summary of TEAE

1) All TEAEs
2) TEAEs related to study drug
3) TEAEs by severity
4) TEAEs related to study drug by severity
5) TEAEs leading to study drug discontinuation
6) Serious TEAEs
7) Serious TEAEs related to study drug
8) Serious TEAEs leading to study drug discontinuation
9) TEAEs leading to death
10) TEAEs by date of onset

Incidence rates will be calculated based on the following rules.

[Frequency of Subjects]

In case of the analysis by severity, subjects with one or more adverse events within a level of MedDRA term is counted only once in that level using the most severe incident. The denominator when calculating the incidence of adverse events is the number of subjects of Full Analysis Set.

In case of the analysis by date of onset, subjects with one or more adverse events are counted once in each category of period when the incident occurred. The denominator when calculating the incidence of adverse events is the number of subjects who are administrated the study drug on and after the period, or the subjects with TEAEs on and after the period. The numerator is the number of subjects with TEAEs on the period.

In the analyses other than the above, subjects with one or more adverse events within a level of MedDRA term is counted only once in that level. The denominator when calculating the incidence of adverse events is the number of subjects of Full Analysis Set.

8.1.2. Display of TEAE

Analysis set: Full Analysis Set

Analysis items: TEAE

Category Classification:

Causal relationship with study drug	[related, unrelated]
Severity	[Mild, Moderate, Severe]
Date of onset	[1<= - <29, 29<= - <58, 58<= - <=Max]

Analysis Methods: For the above analysis items, the following analysis will be performed. The data will be coded using the MedDRA dictionary and be summarized into SOC and PT. SOCs will be sorted in alphabetical order, then PTs will be sorted in decreasing frequency order.

1) All TEAEs (by SOC/PT)
2) TEAEs related to study drug (by SOC/PT)
3) TEAEs by severity (by SOC/PT)
4) TEAEs related to study drug by severity (by SOC/PT)
5) TEAEs leading to study drug discontinuation (by SOC/PT)
6) Serious TEAEs (by SOC/PT)
7) Non-serious TEAEs (by SOC/PT)
8) Serious TEAEs related to study Drug (by SOC/PT)
9) Serious TEAEs leading to study drug discontinuation (by SOC/PT)
10) TEAEs leading to death (by SOC/PT)
11) TEAEs by date of onset (by SOC/PT)

The number of subjects and incidence rates will be calculated in the same manner as mentioned in 8.1.1.

8.2. Other Evaluation

8.2.1. Evaluation of Weight

Analysis set: Full Analysis Set

Analysis items: Weight

Time Point: Baseline, Week 4, Week 8, End of the treatment period

Analysis Methods: For the above analysis items, the following analysis will be performed

(1) Summary statistics for observed values and post-treatment changes (post-treatment value – baseline value) will be calculated at each time point.

(2) For observed value, case plots will be illustrated at each time point.

9. LISTING

Listing of the following data will be presented.

- Demographic Data
- Medication History
- Medical History, Concurrent Medical Conditions
- Insomnia History
- Depression History
- Weight, BMI
- HAM-D17
- 3DSS
- Actigraphy
- Eligibility
- Study Drug Compliance
- Status at the end of Study
- PGI
- Sleep Diary
- Adverse Event
- Concomitant Medications
- Overdose

10. CONSIDERATIONS on STATISTICAL ANALYSIS

10.1. Adjustments for Covariates

Adjustments for covariates will not be performed.

10.2. Handling of Dropouts or Missing Data

Any imputation for missing data will not be performed.

10.3. Criteria for Interim Analysis and Early Discontinuation

No interim analyses will be performed.

10.4. Multicenter Studies

No statistical adjustments will be made to compensate for multi-center study.

10.5. Multiple Comparisons/Multiplicity

No statistical adjustments will be made for multiple comparisons.

10.6. Examination of Subgroups

The subgroup analyses will be performed to examine the primary endpoints using the same analysis methods as 7.1.1(1). The analyses will be performed for the data at the end of treatment period only.

Subgroups:

- Medication history
  [Previous use of Benzodiazepine hypnotics,
  No previous use of Benzodiazepine hypnotics (Previous use of Non-benzodiazepine hypnotics),
  No previous use of Benzodiazepine hypnotics (No previous use of Non-benzodiazepine hypnotics and previous use of other hypnotics),
  No previous use of hypnotics]
- Concomitant use of Benzodiazepine anxiolytics [Yes, No]
- Concomitant use of SSRI or SNRI [Yes, No]
- Duration of insomnia [< 3years, 3years<=]
- Duration of depression [< 3years, 3years<=]
- Phase scale score in 3DSS at Baseline [< 9, 9<=]

11. REVISION HISTORY

Ver.	Date	Author	Revised Content	Reason for Revision
1.0	3 JUN 2016	PPD	-	
2.0	26 FEB 2018	PPD	5.OTHER DATA HANDLING Add the endpoints below: [Actigraphy] ・ Daily variation of sleep latency [Sleep Diary] ・ Daily variation of sleep latency [HAM-D17] ・ HAM-D17 total score (excluding sleep related score) ・ HAM-D17 total score (sleep related score only) [Demographic Characteristics] ・ Disease Duration (year) [Non-serious TEAE]	To add the endpoints.
			6.1.3. Subject Disposition Modify the title below: (Before) 6.1.3.1. Status at the End of Treatment Period (After) 6.1.3.1. Status at the End of Study Modify the endpoint below: (Before) Status at the end of treatment (After) Status at the end of study	To specify the contents of analysis.
			6.1.4.2.1. Datasets Analyzed Delete the underlined part below: For the above analysis items, the following analysis will be performed for merged treatment group.	To correct the clerical error.

Ver.	Date	Author	Revised Content	Reason for Revision
			6.2.1. Distribution of Demographics Add the endpoints below: Insomnia ・ Duration of disease (years) ・ Initial episode/recurrence ・ Non-pharmacological therapy Depression ・ Duration of disease (years) ・ Initial episode/recurrence ・ Psychotherapy	To add the endpoints.
			6.2.3. Medication History and Concomitant Medications Add the endpoints below: Analysis items: Previous use of hypnotics [Yes (previous use of Benzodiazepine hypnotics, previous use of Non-benzodiazepine hypnotics, previous use of other hypnotics), No]	To add the endpoints.

Ver.	Date	Author	Revised Content	Reason for Revision
			7.1.1. Change from Baseline in Sleep Latency by Actigraphy (1) Add the underlined part below: As the analyses for primary endpoints, summary statistics and two-sided 95% confidence interval (CI) of the mean will be calculated for <u>both</u> change <u>and percentage change</u> from baseline to the end of treatment period (2) Add this section. (3) Add the underlined parts below: For observed value at each time point, <u>case plots will be displayed, and</u> summary statistics and two-sided 95% CI of the mean will be calculated. Mean plots with +/- SD will be also displayed at each time point.	To add the endpoints and analysis methods.

Ver.	Date	Author	Revised Content	Reason for Revision
			7.2.1. Secondary Endpoints and the Analytical Methods (1) Add the underlined part below: As the analyses for primary endpoints, summary statistics and two-sided 95% confidence interval (CI) of the mean will be calculated for <u>both</u> change <u>and percentage change</u> from baseline to the end of treatment period (2) Add this section. (3) Add the underlined parts below: For observed value at each time point, <u>case plots will be displayed, and</u> summary statistics and two-sided 95% CI of the mean will be calculated. Mean plots with +/- SD will be also displayed at each time point.	To add the endpoints and analysis methods.
			7.3.2. Hamilton Rating Scale for Depression-17 (HAM-D17) Modify the categories below: (Before) HAM-D17 total score [0<=-<8, 8<=-<17, 17<=-<<u>23</u>, 24<=] (After) HAM-D17 total score [0<=-<8, 8<=-<17, 17<=-<<u>24</u>, 24<=] Add the endpoints below: ・ HAM-D17 total score (except for sleep related score) ・ HAM-D17 total score (sleep related score)	To correct the clerical error and add the endpoints.

Ver.	Date	Author	Revised Content	Reason for Revision
			7.3.3. 3 Dimensional Sleep Scale (3DSS) (2) Add the underlined parts below: For phase scale score, quality scale score and quantity scale score, summary statistics will be calculated and case plots will be displayed. (3) Add this section	To add the endpoints.
			7.3.4. Correlation between Endpoints Add this whole section.	To add the analysis.
			8.1.2. Display of TEAE 7) Add this section.	To add the analysis.
			9. LISTING Add this whole section.	To add the analysis.
			10.6. Examination of Subgroups Add this whole section.	To add the analysis.