



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

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

Protocol

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

| | |
|-----------------------|--|
| Sponsor | Takeda Pharmaceutical Company Limited 12-10 Nihonbashi 2-chome, Chuo-ku, Tokyo 103-8668 |
| Study Number | Ramelteon-4002 |
| Version Number | Amendment No. 1 |
| Study Drug | Ramelteon |
| Date | July 31, 2017 |

CONFIDENTIAL

Amendment History:

| Date | Amendment Number | Applicable Sites |
|----------------|-------------------------|-------------------------|
| March 29, 2016 | Initial version | All study sites |
| July 31, 2017 | Amendment No.1 | All study sites |

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1.0 STUDY ADMINISTRATIVE INFORMATION AND STUDY PRINCIPLES

1.1 Contact Information and Responsibilities for Study-Related Activities

See the attachment.

1.2 Clinical Study Principals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, December 22, 2014).
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

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2.0 STUDY SUMMARY

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| Sponsor: Takeda Pharmaceutical Company Limited | Study drug: Ramelteon |
| Study title: The exploratory study to investigate the effect of Ramelteon for insomnia patients with major depressive disorder by using actigraphy | |
| Protocol number: Ramelteon-4002 (293/NRP-003) | |
| Clinical study design: Multicenter, open-label study | |
| Objective: To investigate explanatorily the effect of ramelteon 8 mg once daily for 8 weeks in treatment for insomnia patients with depression by using actigraphy. | |
| Study Population: Insomnia patients with major depressive disorder | |
| Planned number of research subjects: 30 | Number of study sites: Approximately 5 medical institutions |
| Dose and method of administration: Ramelteon 8 mg once daily orally at bedtime | Route of administration: Oral |
| Duration of treatment: 8 weeks | Duration of evaluation: 9 weeks (Run-in period for 1 weeks and treatment period for 8 weeks) |
| <p>Main criteria for inclusion:</p> <ol style="list-style-type: none"> 1. Patients with sleep-onset insomnia on ≥ 3 days per week for ≥ 4 consecutive weeks at the time of informed consent 2. Patients with a diagnosis of depression according to the DSM-5 3. Men or women aged ≥ 20 and < 65 years at the time of informed consent 4. Outpatients 5. Patients with the 17-item Hamilton Rating Scale for Depression (HAM-D17) score(s) meeting either of the following at the start of the run-in period and the start of the study treatment period: <ul style="list-style-type: none"> - a score of 2 for the “6: Insomnia Early” item - a score of 1 for the “6: Insomnia Early” item with a subtotal score of ≥ 3 for the “7: Insomnia Middle” and “8: Insomnia Late” items 6. Patients with a total HAM-D17 score of ≤ 16 at the start of the run-in period and the start of the study treatment period 7. Patients on stable antidepressant medication, defined as no change of antidepressant medication (s) and no change in the dosage for at least 4 weeks before the run-in period 8. Patients who maintain a routine sleep schedule in daily life, defined as going to bed between 21:00 and 1:00 on ≥ 4 days a week 9. Patients in whom the run-in period actigraphy shows sleep latency ≥ 30 minutes and total nocturnal | |

sleep time ≤ 6.5 hours on ≥ 3 days

10. Patients who, in the opinion of the principal investigator or investigator, are capable of understanding the contents of the study and complying with study requirements
11. Patients capable of signing and dating the informed consent form in person before any study procedures

Main criteria for exclusion:

1. Patients with a history of hypersensitivity to ramelteon or melatonin
2. Patients with severe liver disorder
3. Patients who took oral ramelteon within 4 weeks before informed consent
4. Patients who took any oral insomnia medications (including investigational drugs and unapproved drugs) within 2 weeks before the study treatment period
5. Shift workers or night workers
6. Patients with concurrent psychiatric or neurological diseases other than depression which may affect sleep status
7. Patients with a score of ≥ 1 for the HAM-D17 "11: Suicide" item at the start of the run-in period or the start of the study treatment period, or with any suicide attempts within 24 weeks before or during the run-in period
8. Pregnant women, nursing mothers, or women who plan to become pregnant or donate eggs before the informed consent, during the study period or within 4 weeks after the end of the study
9. Patients participating in another investigational or post-marketing clinical trial/study
10. Other patients judged by the principal investigator or investigator to be inappropriate for participation in this study

Endpoints:

<Primary endpoint>

Change in actigraphy-measured sleep latency* from baseline (i.e., start of the study treatment period) to the end of the treatment period

*: Mean value from the past 7 days

<Secondary endpoints>

- Change in diary-measured sleep latency* from baseline to the end of the treatment period
- Change in actigraphy-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in actigraphy-measured nocturnal wake time* from baseline to the end of the treatment period
- Change in actigraphy-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured sleep efficiency* from baseline to the end of the treatment

period

- Change in diary-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in diary-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured daytime activity level* from baseline to the end of the treatment period

*: Mean value from the past 7 days

<Additional endpoints>

Efficacy endpoints

- Actigraphy-measured sleep latency, total nocturnal sleep time, nocturnal wake time, number of nocturnal awakenings, sleep efficiency, and daytime activity level
- Diary-measured sleep latency, total nocturnal sleep time, and number of nocturnal awakenings
- PGI
- HAM-D17
- 3DSS

Safety endpoints

- Adverse events
- Body weight

Statistical method:

1. Analysis Sets

The analysis set for this study will be the "Full Analysis Set," which is defined as "all participants given at least one dose of the study drug."

2. Efficacy Analysis

[Primary endpoint]

In the Full Analysis Set, the change in actigraphy-measured sleep latency from baseline to the end of the treatment period will be summarized by calculation of summary statistics (i.e., number of participants, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and a two-sided 95% confidence interval for the mean, and assessed using the one-sample *t*-test.

[Secondary endpoints]

In the Full Analysis Set, the individual secondary endpoints will be summarized by calculation of summary statistics and two-sided 95% confidence intervals for the means, and assessed using the one-sample *t*-test.

Sample Size Justification:

The sample size is set to 30 in light of feasibility of this study to investigate the effect of ramelteon in insomnia patients with depression. This planned sample size is not based on

statistical power calculation.

3.0 ABBREVIATIONS

| | |
|--------|---|
| BZD | Benzodiazepine |
| COI | Conflict of Interest |
| CRO | Contract Research Organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders Fifth Edition |
| HAM-D | Hamilton Rating Scale for Depression |
| PGI | Patient Global Impression |
| 3DSS | 3 Dimensional Sleep Scale |

4.0 INTRODUCTION

4.1 Background

Insomnia is commonly encountered in today's medical practice in Japan, and has been raised as a clinical and social issue.¹⁾ Depression also shows a dramatically increasing trend recently²⁾³⁾, partly because of changes in the working environment, and its social impact is becoming a growing concern. Insomnia and depression are known to be often comorbid⁴⁾, and improvement of insomnia symptoms has been described as a key to successful resolution of depression.⁵⁾ Insomnia is known to be associated with not only aging and lifestyle-related diseases, but also hypervigilance due to tension from excessive expectation about sleep, as well as disturbance of the bodily circadian rhythm due to irregular living schedule with a delayed sleep-wake cycle. Depression, on the other hand, is typically associated with anxiety, but is now known to be linked with negative influence of irregular living schedule as well. Thus, insomnia and depression share some same risk factors, and this can explain the high co-existence rate of these two disorders.⁶⁾⁷⁾

The mainstays in the treatment of insomnia have long been benzodiazepine (BZD)-class hypnotics and nonbenzodiazepine-class hypnotics, both classes of which exert sedative and anxiolytic effects. A novel melatonin receptor agonist, ramelteon (trade name, Rozerem), has been available in Japan since 2010. Ramelteon can improve sleep-onset insomnia by working on the bodily clock mechanism and adjusting the circadian rhythm. Ramelteon's mechanism of action without sedative or anxiolytic properties appears to be of high clinical significance particularly in the treatment of insomnia patients with concurrent depression.

4.2 Rationale for the Proposed Study

Reports have been limited on the efficacy and safety of ramelteon in insomnia patients with depression or other psychiatric diseases⁸⁾⁹⁾, and none used objective measures. The present study is thus designed to use actigraphy to objectively explore the efficacy of ramelteon on insomnia in insomnia patients with depression.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary objective

To investigate exploratorily the effect of ramelteon 8 mg once daily for 8 weeks in treatment for insomnia patients with depression by using actigraphy.

5.1.2 Secondary objective

To investigate exploratorily the safety of ramelteon 8 mg once daily for 8 weeks in insomnia patients with depression.

5.2 Endpoints

5.2.1 Primary endpoint

Change in actigraphy-measured sleep latency* from baseline (i.e., start of the study treatment period) to the end of the treatment period

*: Mean value from the past 7 days

5.2.2 Secondary endpoints

- Change in diary-measured sleep latency* from baseline to the end of the treatment period
- Change in actigraphy-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in actigraphy-measured nocturnal wake time* from baseline to the end of the treatment period
- Change in actigraphy-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured sleep efficiency* from baseline to the end of the treatment period
- Change in diary-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in diary-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured daytime activity level* from baseline to the end of the treatment period

*: Mean value from the past 7 days

5.2.3 Other endpoints

(1) Efficacy

- Actigraphy-measured sleep latency, total nocturnal sleep time, nocturnal wake time, number of nocturnal awakenings, sleep efficiency, and daytime activity level
- Sleep diary-measured sleep latency, total nocturnal sleep time, and number of nocturnal awakenings
- PGI
- HAM-D17
- 3DSS

(2) Safety

- Adverse events
- Body weight

6.0 STUDY DESIGN

6.1 Study Design

(1) Study design

This is a multicenter, open-label study.

(2) Treatment

Participants will take ramelteon 8 mg once daily orally at bedtime for 8 weeks.

(3) Planned sample size

30 patients

(4) Number of study sites

Approximately 5 medical institutions

(5) Duration of evaluation and number of visits in individual participants

The duration of evaluation in this study will be 9 weeks. Participants will make a total 4 visits, i.e., at the start of the run-in period and at the start and Weeks 4 and 8 of the treatment period.

Figure 6.a shows the schematic diagram of the study design. The study schedule is provided in Appendix A.

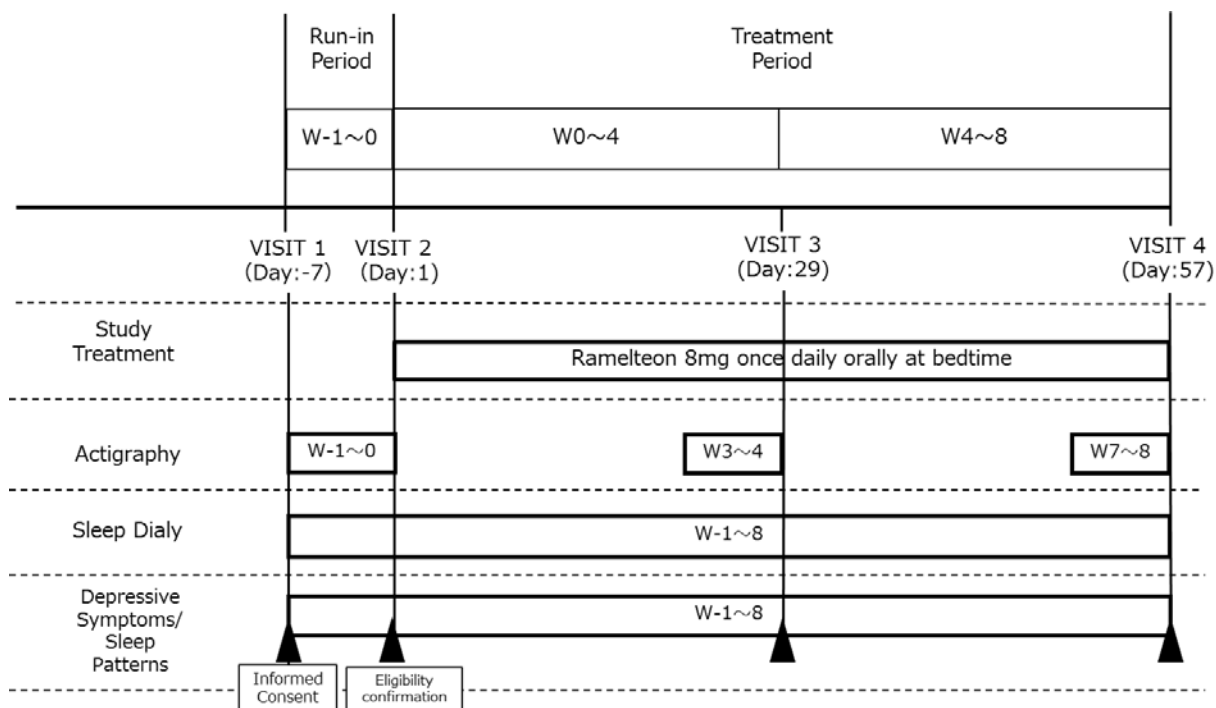


Figure 6.a Schematic of Study Design

6.2 Rationale for the Study Design

<Rationale for the study population>

For ramelteon, a drug approved for "improvement of sleep onset difficulty in insomnia", data have been limited on its efficacy and safety in insomnia patients with psychiatric disease, and construction of the clinical evidence is desired. Among psychiatric diseases, depression is common and often coexists with insomnia symptoms. Thus, the study population is set to insomnia patients with depression.

<Rationale for the study design>

An uncontrolled, open-label design is employed in light of feasibility of this post-marketing clinical research, although the primary objective is to explore the effect of ramelteon in treating insomnia patients with a history of co-morbid depression.

<Rationale for the dosage>

The approved dosage and method of administration for ramelteon are employed.

<Rationale for the endpoints>

The "Guideline for Clinical Evaluation of Hypnotic Agents" (Notification No. 1213-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated December 13, 2011) recommends the use of polysomnography for objective efficacy evaluation in addition to the use of patient-recorded sleep logs for subjective efficacy evaluation. While polysomnography is a complex examination and repeated polysomnography can impose heavy burden on participants, actigraphy has been recognized to provide sleep data highly correlated with those provided by polysomnography and is a simple tool posing less burden to participants. Thus, actigraphy is selected as an objective assessment tool in this study¹⁰⁾. For subjective measures, this study uses a sleep diary, as well as the Patient Global Impression (PGI) as an index of global improvement, and the 3 Dimensional Sleep Scale (3DSS) as a new tool to assess sleep dimensions including sleep phases. The HAM-D17 is selected for evaluation of depressive symptoms, in line with preceding studies.

The safety will be evaluated based on adverse events, body weight.

<Rationale for the treatment duration>

The treatment duration is set to 8 weeks on the basis of the Japanese long-term clinical trial of ramelteon (24-week treatment), which demonstrated gradual

manifestation of the efficacy of ramelteon on sleep latency under repeated dosing over a certain period, and the efficacy peaked around Week 8.

<Rationale for the sample size>

See Section 13.3

6.3 Premature Termination of Entire Clinical Research or Premature Termination of Clinical Research at a Study Site

6.3.1 Premature termination criteria of entire clinical research

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable:

- When new information or other evaluation on the safety or efficacy of the study drug becomes available that shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for research subject participation in the study.
- When there is serious deviation from ethical guidelines that may threaten safety of the research subjects.

6.3.2 Criteria for premature termination of study sites

Termination of involvement of a study site in the study may be requested prematurely at the discretion of the sponsor if the entity (e.g., principal investigator) is found in significant violation of the ethical guidelines, protocol, or contractual agreement, or is unable to ensure proper conduct of the research.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or study at a study site

In the event that the sponsor or a study site committee such as an ethics review committee decides to prematurely suspend or terminate the entire clinical study or clinical study at a study site, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable study sites during the course of clinical study suspension or premature termination.

6.4 Procedures for Protocol Revision

If the protocol needs to be revised, the sponsor shall consider and decide whether to revise the protocol.

The principal investigator of each study site shall be informed of the details of each protocol revision.

Upon notification, the principal investigator at each study site shall submit the revised contents to committees such as the IEC, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA

7.1 Inclusion Criteria

Participants must fulfill all of the following criteria to be included in this study:

1. Patients with sleep-onset insomnia on ≥ 3 days per week for ≥ 4 consecutive weeks at the time of informed consent
2. Patients with a diagnosis of depression according to the DSM-5
3. Men or women aged ≥ 20 and < 65 years at the time of informed consent
4. Outpatients
5. Patients with the 17-item Hamilton Rating Scale for Depression (HAM-D17) score(s) meeting either of the following at the start of the run-in period and the start of the study treatment period:
 - a score of 2 for the “6: Insomnia Early” item
 - a score of 1 for the “6: Insomnia Early” item with a subtotal score of ≥ 3 for the “7: Insomnia Middle” and “8: Insomnia Late” items
6. Patients with a total HAM-D17 score of ≤ 16 at the start of the run-in period and the start of the study treatment period
7. Patients on stable antidepressant medication, defined as no change of antidepressant medication (s) and no change in the dosage for at least 4 weeks before the run-in period
8. Patients who maintain a routine sleep schedule in daily life, defined as going to bed between 21:00 and 1:00 on ≥ 4 days a week
9. Patients in whom the run-in period actigraphy shows sleep latency ≥ 30 minutes and total nocturnal sleep time ≤ 6.5 hours on ≥ 3 days
10. Patients who, in the opinion of the principal investigator or investigator, are capable of understanding the contents of the study and complying with study requirements
11. Patients capable of signing and dating the informed consent form in person before any study procedures

[Rationale for the inclusion criteria]

- 1: This criterion is set to exclude patients with transient insomnia.
- 2: This criterion is set to specify the target study population and applicable diagnostic criteria.
- 3: This criterion is set because both men and women need to be included for evaluation. The lower age limit of 20 years is set because personal voluntary consent is valid at and above this age. The upper age limit is set for this study to enroll participants who are active during daytime and thus appropriate for evaluation using actigraphy.

4, 6, 7: These criteria are set to determine patients whose depression symptoms have been mild or less and stable.

5, 9: These criteria are set to determine patients with symptoms of sleep-onset insomnia during the run-in period.

8: This criterion was set to ensure appropriate evaluation of the efficacy and safety of the study drug.

10, 11: These criteria are set as essential elements for the study implementation.

7.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from this study:

1. Patients with a history of hypersensitivity to ramelteon or melatonin
2. Patients with severe liver disorder
3. Patients who took oral ramelteon within 4 weeks before informed consent
4. Patients who took any oral insomnia medications (including investigational drugs and unapproved drugs) within 2 weeks before the study treatment period
5. Shift workers or night workers
6. Patients with concurrent psychiatric or neurological diseases other than depression which may affect sleep status
7. Patients with a score of ≥ 1 for the HAM-D17 "11: Suicide" item at the start of the run-in period or the start of the study treatment period, or with any suicide attempts within 24 weeks before or during the run-in period
8. Pregnant women, nursing mothers, or women who plan to become pregnant or donate eggs before the informed consent, during the study period or within 4 weeks after the end of the study
9. Patients participating in another investigational or post-marketing clinical trial/study
10. Other patients judged by the principal investigator or investigator to be inappropriate for participation in this study

[Rationale for the exclusion criteria]

1, 2: These criteria are set in consideration of the safety of the participants.

3 to 6: These criteria are set to ensure appropriate evaluation of the efficacy and safety of the study drug.

7, 8: These criteria are set in consideration of the safety of the participants.

9, 10: These criteria are set as essential elements for the study implementation.

7.3 Prohibited Medications and Therapies

During the study period, the principal investigator or investigator will instruct the participants not to take any other medications than those instructed to be taken, including over-the-counter drugs, without first consulting with the principal investigator or investigator.

[Prohibited medications]

Fluvoxamine maleate will be prohibited from the start of the run-in period. Insomnia medications other than ramelteon (including investigational drug and unapproved drugs) will be prohibited from at least 2 weeks before treatment period to the end of the study period.

1. Fluvoxamine maleate
2. Insomnia medications other than ramelteon (including investigational drug and unapproved drugs)
3. Antidepressant medications other than those used at the time of 4 weeks prior to start of the run-in period

[Rationale for prohibited medications]

1. Fluvoxamine maleate is contraindicated for use with the study drug, ramelteon.
- 2, 3. Medications may prevent appropriate evaluation of the efficacy and safety of the study drug.

7.4 Management of Study Participants

The following should be observed or instructed to the participants by the principal investigator and investigator.

1. Participants should make scheduled visits and undergo physical examination by physician and other specified examinations (Actigraphy, Sleep Diary) . When a scheduled visit cannot be made, the participant should promptly contact the principal investigator or investigator.
2. In the event of any symptomatic worsening or other abnormalities except scheduled visits, the participant should promptly contact the principal investigator or investigator for instructions.

3. Participants should take the study drug as instructed by the principal investigator or investigator. If not, this must be reported to the principal investigator or investigator at the next visit.
4. Participants should not take any other medications than those instructed to be taken, including over-the-counter drugs, without first consulting with the principal investigator or investigator (except for emergency situations).
5. Whenever participants visit another hospital between the informed consent and the end of the study, the participant should tell the physician of the other hospital that he/she is participating in this study.
6. Whenever participants visit another hospital between the informed consent and the end of the study, the participant should report to the principal investigator or investigator about background for the visit and treatment details.
7. Women of childbearing potential whose male partners are not surgically sterile must use appropriate contraception from the time of informed consent to the end of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Research Subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form according to the classification described below. Refer to Section 9.1.12 for research subjects who withdraw from the research before

1. Adverse event

This is selected when an adverse event occurred in a study participant that requires premature termination to avoid an unacceptable risk to the participant's health imposed by continued participation in the study; or the study participant is unwilling to remain in the study because of the adverse event.

2. Major protocol deviation

This is selected when the study participant is found not to fulfill the protocol-specified eligibility criteria after the start of the study treatment, or has failed to adhere to protocol requirements, and thus the participant's continued participation in the study would pose an acceptable risk to his/her health.

3. Lost to follow-up

This is selected when the study participant has not returned to the study site and lost contact. In such instances, all attempts to contact the participant must be recorded in the source document.

4. Voluntary withdrawal

This is selected when the study participant has requested to withdraw his/her participation in the study. The reason for withdrawal, if provided by the participant, will be recorded in the case report form.

5. Discontinuation of the entire study

This is selected when discontinuation of the entire study is decided by the sponsor, institutional review board, regulatory authority, etc. See Section 6.3.1 for details.

6. Pregnancy

This is selected when a female study participant is found to be pregnant.

Note: A participant found to be pregnant must be immediately withdrawn from the study. For the withdrawal procedure, see Section 9.1.11.

7. Lack of efficacy

This is selected when the investigator or subinvestigator has judged that, because of lack of efficacy of study treatment, the participant's continued participation in the study would pose an unacceptable risk to the participant.

8. Sign of suicide

This is selected when the HAM-D17 "11: Suicide" item score became ≥ 1 ; or the principal investigator or investigator judged that the C-SSRS results or other findings indicate a sign of suicide.

9. Remission of depression

This is selected when the participant's depression remitted to no longer require antidepressant medication etc.

10. Other

This is selected when the principal investigator or investigator has decided withdrawal of the participant for any other reason. The reason must be detailed in the case report form.

7.6 Procedures for Discontinuation of Individual Research Subjects

The principal investigator or investigator shall terminate a research subject's research participation when the research subject meets the criteria described in Section 7.5. Individual research subjects may discontinue their research participation without giving a reason at any time during the research. Should a research subject's participation be discontinued, the primary reason for termination shall be recorded on the CRF by the

principal investigator or investigator. In addition, efforts shall be made to perform all tests/observations/evaluations scheduled at the time of discontinuation.

8.0 TREATMENT

8.1 Study Drug

8.1.1 Study drug

Nonproprietary name: Ramelteon [JAN]

Chemical name: N-{2-[(8S)-1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl}
propanamide

Dosage: 8 mg once daily

Method of administration: Orally at bedtime

Duration of treatment: 8 weeks

8.1.2 Overdose

Overdose is defined as intentional or accidental administration of the study drug at a higher dose than that specified in the protocol, either by a health professional or by the research subject.

To consistently collect important safety information about overdose, the principal investigator or investigator(s) shall record all cases of overdose on the "Overdose" page of the CRF, irrespective of the presence or absence of accompanying adverse event. Adverse events associated with overdose shall be recorded on the "Adverse events" page of the CRF, in accordance with the procedures described in Section 10.0, "ADVERSE EVENTS."

In addition, serious adverse events associated with overdose shall be recorded in accordance with the procedures described in Section 10.2.2, "Collection and reporting of SAEs."

In the event of overdose, the principal investigator or investigator shall treat the subject as required based on symptoms

8.2 Prescription of the Study Drug

The principal investigator or investigator will prescribe the study drug according to the protocol, to participants who fulfill all of the inclusion criteria and do not meet any of the exclusion criteria.

8.3 Prescription of Antidepressant Medication

The oral antidepressant medication being used in each participant at the time of 4 weeks prior to start of the run-in period will be continued without any change to the dosage regimen during participation in the study. Addition of antidepressant will not allowed after the time of 4 weeks prior to start of the run-in period.

8.4 Non-pharmacological Insomnia Treatment

During the study period, non-pharmacological insomnia treatment should be added or changed.

9.0 STUDY PLAN

9.1 Study Procedures

The principal investigator or investigator will collect data according to the following procedures. In principle, the same principal investigator or investigator should perform the examinations, observations, and evaluations in the same participant. The study schedule is provided in Appendix A.

9.1.1 Informed consent

Informed consent procedures are described in Section 15.3.

Study procedures may be started only after informed consent is obtained from the participant.

Participants who provided informed consent will be assigned participant identification codes for de-identification. The assigned participant identification codes will be used throughout the study period without changes.

9.1.2 Demographic data, medical history and prior medication

Demographic data will be obtained in terms of date of birth, sex, and history of alcohol consumption, and history of smoking.

Medical history will be obtained in terms of any clinically relevant diseases or symptoms that had disappeared or resolved within 1 year before the informed consent. Ongoing symptoms or diseases should be regarded as concurrent conditions (see Section 9.1.11).

9.1.3 History of insomnia

Regarding current insomnia, the following data will be obtained:

- Date of onset
- Initial/Recurrence
- Any non-pharmacological therapy

9.1.4 History of Depression

Regarding the current depressive episode, the following data will be obtained:

- Date of onset
- Initial/Recurrence
- Any use of psychotherapy

9.1.5 Physical examination

Physical examination will be performed. Findings of physical examination after the start of the treatment period will be compared with those before the treatment period, and assessed for any abnormalities that can be clinically relevant.

9.1.6 Body weight, height and Body Mass Index (BMI)

Body weight and height will be measured. BMI will be calculated by the sponsor, using the following equation:

$$\text{Body Mass Index (BMI)} = \text{Body Weight (kg)} / (\text{Height (m)})^2$$

Height will be measured to the nearest whole number in centimeters. Body weight will be measured to the first decimal place in kilograms. The calculated BMI value will be expressed to the first decimal place.

9.1.7 Actigraphy

At the end of the informed consent, an actigraph will be lent to each participant. After full instructions on actigraphy are provided to the participants, actigraphy recording will be started. Patients meeting the inclusion criteria on the basis of the data in the run-in period will keep the actigraph, and be instructed to wear it until the end of the treatment period.

Participants will be instructed to bring the actigraph at each study visit. For analysis of the data recorded in the actigraph, the actigraph will be connected to a computer with an actigraphy data analysis software installed, and the following data will be transferred to the analysis software: sleep latency, total nocturnal sleep time, nocturnal wake time, the number of nocturnal awakenings, sleep efficiency and daytime activity level (step counts). For each of these parameters, the validity of the measured data will be checked according to the "Procedures for actigraphic sleep assessment" prepared separately, and the data during the run-in period (Weeks -1 to 0) and the treatment period (Weeks 3 to 4 and 7 to 8) will be recorded in the case report form. The actigraph device will be retrieved after completion of the actigraphy recording on the 3 occasions, or when the participant is withdrawn from the study.

9.1.8 Sleep diary

At the end of the informed consent, a sleep diary will be provided to each participant, with instruction on how to keep the diary during the study period. The following diary data during the run-in period (Weeks -1 to 0) and the treatment period (Weeks 3 to 4 and 7 to 8) will be recorded in the case report form: sleep latency, bedtime hour,

awakening hour and number of nocturnal awakenings. Any missing entries, discrepancies, or other potentially dubious entries in the sleep diary will be checked with the participant, and explained in the sleep diary by the participant. Accordingly, necessary additions and corrections will be made to the sleep diary, and recorded in the case report form.

9.1.9 17-item Hamilton Rating Scale for Depression (HAM-D17)

The Hamilton Rating Scale for Depression (HAM-D) is a questionnaire used to rate the severity of depression based on general symptoms of depression, including physical symptoms. The rater will assess individual items on a scale from 0 to 2, 3, or 4 depending on the items, based on an interview with the participant.⁶⁾ The time frame assessed by the HAM-D is one week before each visit. This study will use the 17-item version (HAM-D17), and the scores of individual items and the total score will be assessed and recorded in the case report form.

9.1.10 Patient Global Impression (PGI)

The Patient Global Impression (PGI) is a patient-rated scale to measure the degree of any improvement (or worsening). Participants will rate their own condition compared with the run-in period (before the start of study treatment), and enter the score in the PGI form. The principal investigator or investigator will record the score in the case report form.

9.1.11 3 Dimensional Sleep Scale (3DSS)

The 3 Dimensional Sleep Scale (3DSS) is a patient-administered questionnaire developed in Japan, and used to assess sleep dimensions including sleep phases.⁷⁾ At each visit, participants will assess their own condition within the past month and complete the 3DSS form. The principal investigator or investigator will record the results of 3DSS in the case report form.

9.1.12 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in the individuals during participation in a clinical research.¹³⁾¹⁴⁾ The C-SSRS consists of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The principal investigator or investigator will perform the C-SSRS assessment based on an interview with the participant. Since this is performed to detect any signs of suicide during the study period, the C-SSRS assessment results will not be recorded in the case report form.

9.1.13 Concomitant medications

Concomitant medications are any psychotherapeutic drugs (Drugs for Insomnia, Antidepressant) that are used in addition to the study drug, and include drugs prescribed by doctors or over-the-counter drugs purchased by the participants. At each visit, participants will be interviewed about any psychotherapeutic drugs used other than the study drug from the time of informed consent to the end of the study and specific usage (drug name).

9.1.14 Concurrent conditions

Concurrent conditions are defined as symptoms or diseases that are present at the time of the informed consent. Abnormal findings from physical examination at the start of the run-in period will be regarded as concurrent conditions at the discretion of the principal investigator or investigator.

9.1.15 Pregnancy

If pregnancy of a participant is found during the study, with agreement of the female participant, the principal investigator or investigator will inform her obstetrics/gynecology doctor about the fact of her participation in the clinical study at the onset of the pregnancy, as well as details of the study drug.

All pregnancies reported during the study will be followed up to their outcomes by the principal investigator or investigator, with agreement of the participants with pregnancy. The outcome of pregnancy, including any premature labor, will be reported to the sponsor, using a designated report form. Assessment after childbirth will also be performed.

9.1.16 Documentation of withdrawals before study treatment

For all participants withdrawn before the start of study treatment after signing the consent form, the case report form will be completed.

The following data will be recorded in the case report form:

- Date of informed consent
- Date of birth
- Sex
- Eligibility
- Reason for withdrawal

The main reason for the withdrawal before the start of study treatment will be recorded, using the following classification:

- Not fulfilling all of the inclusion criteria, or meeting any of the exclusion criteria
- Major protocol deviation
- Lost to follow-up
- Voluntary withdrawal (The reason should be specified)
- Discontinuation of the entire study
- Pregnancy
- Other (The reason should be specified)

Participant identification codes assigned to the participants withdrawn before the start of study treatment must not be reused.

9.2 Monitoring of Treatment Compliance in Participants

At each visit, the principal investigator or investigator will assess the participant's compliance with the study drug and antidepressant medication. The compliance status will be classified into 4 categories: nearly all of the prescribed doses were taken ($\geq 90\%$), most of the prescribed doses were taken ($\geq 70\%$), about half of the prescribed doses were taken ($\geq 50\%$), or less than half of the prescribed doses were taken ($< 50\%$).

Throughout the study period, participants will be reinstructed about medication. If poor compliance with the study drug after the previous visit, such as $< 50\%$ of prescribed doses, is found and does not improve, the participant may be withdrawn as appropriate.

9.3 Schedule of Examinations and Observations

The schedule for all examinations, observations, and evaluations is shown in Appendix A. The principal investigator or investigator will perform the following examinations, observations, and evaluations as scheduled.

9.3.1 Start of the run-in period (VISIT 1)

After informed consent, the following data will be obtained by physical examination and other examinations. In addition, participants will be instructed to keep a sleep diary and to perform actigraphy recording for 1 week before VISIT 2 (i.e., Week -1 to Week 0). Eligibility of participants will be confirmed against the inclusion and exclusion criteria given in Section 7.0. For documentation of participants withdrawn during the run-in period, the procedures in Section 9.1.13 should be followed.

During the run-in period, the following examinations, observations, and evaluations will be performed:

- Informed consent

- Demographic data, medical history, prior medication, history of insomnia, depressive episodes
- Physical examination
- Height, body weight and BMI
- Concurrent medications
- Concurrent conditions
- HAM-D17
- C-SSRS (baseline)

9.3.2 Start of the study treatment period (VISIT 2)

At the start of administration of the study drug, the following examinations, observations, and evaluations will be performed.

For participants fulfilling all of the inclusion criteria and not meeting any of the exclusion criteria given in Section 7.0, the principal investigator or investigator will instruct to start taking the study drug according to Section 6.1.

- Physical examination
- Body weight
- Concomitant medications
- Concurrent conditions
- HAM-D17
- Assessment of the actigraphy data from Week -1 to Week 0
- Sleep diary
- 3DSS
- C-SSRS (after last assessment)

9.3.3 Treatment period (VISIT 3)

During the treatment period (VISIT 3), the following examinations, observations, and evaluations will be performed.

- Physical examination
- Body weight
- Concomitant medications
- HAM-D17
- Assessment of actigraphy data from Week 3 to Week 4
- Sleep diary

- Adverse events
- 3DSS
- Treatment compliance
- C-SSRS (after last assessment)

9.3.4 At completion (VISIT 4) or withdrawal

Final visit will be made at 8 weeks after the start of study treatment, when the following examinations, observations, and evaluations will be performed. In withdrawn participants, the same examinations, observations, and evaluations will be performed at withdrawal from the study.

- Physical examination
- Body weight
- Concomitant medications
- HAM-D17
- Assessment of actigraphy data from Week 7 to Week 8*
- Sleep diary
- Adverse events
- 3DSS
- Treatment compliance
- C-SSRS(after last assessment)
- PGI

For all participants given the study drug, the study completion/withdrawal status will be recorded in the case report form.

10.0 Pretreatment Event and Adverse Event

10.1 Definitions

10.1.1 Adverse events

An adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product (including a study drug) and which does not necessarily have to have a clear causal relationship with this treatment.

An adverse event can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.1.2 Considerations for Adverse Events

Generally unfavorable findings are described below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of an existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation or a change in the dose of the study drug
- Considered unfavorable by the investigator or the subinvestigator

Diagnosis name and signs/symptoms:

Adverse events shall be recorded by diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms shall not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, the signs or symptoms shall be recorded as the adverse event.

Laboratory test values and ECG findings:

Abnormal laboratory values and ECG findings shall be recorded as adverse events when the principal investigator or investigator judges the results are clinically problematic (in other words, when certain action or medical practice is required, or when the principal investigator or the investigator judges the change has exceeded the normal physiological variation range of the research subject). Retest and/or continued monitoring of an abnormality are not considered medical practice. Also, repeated or additional

conduction of non-invasive tests for verification, evaluation, and monitoring of an abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of a disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the adverse event shall be handled by its diagnosis name.

Pre-existing conditions (at start of treatment period):

A disease or symptoms that had been present since before the start of observation period shall be regarded as a concurrent disease and not an adverse event. When a concurrent medical condition is aggravated, the aggravation shall be determined as an adverse event and the investigator or the subinvestigator shall record on the CRF that the adverse event is an aggravation of the concurrent disease (e.g., "aggravation of hypertension," etc.).

If a research subject has a pre-existing episodic condition (e.g., asthma, epilepsy), each episode shall be recorded as an adverse event if the episodes become more frequent, serious, or severe in nature. If a research subject has a chronic concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition shall be recorded as adverse event if the degree of the worsening exceeds that which would be expected. The principal investigator or investigator shall ensure that the adverse event term to be recorded represents the change in the condition from baseline (e.g. "worsening of...").

Worsening of adverse events:

If a research subject experiences a worsening of the adverse event after a change to the study drug, or secondary signs and symptoms are caused by the adverse event, the worsening or the secondary signs and symptoms shall be recorded as a new adverse event on the CRF. The principal investigator or investigator shall use an adverse event term that explicitly means a change of the condition (e.g., "worsening of...").

Change of severity of adverse events:

If the research subject experiences changes in the severity of an adverse event, the event shall be recorded once, at its peak severity.

Previously planned surgery or treatment:

Preplanned surgeries or interventions that were scheduled before study treatment shall not be considered adverse events. However, when the existing symptom is aggravated to a degree requiring emergency surgery or treatment, the condition or the event shall be considered an adverse event. A concurrent disease that resulted from previously planned surgery shall be reported as an adverse event.

Non-urgent surgery or treatment:

Non-urgent surgery or treatment that does not induce a change in the condition of a research subject (cosmetic surgery, etc.) shall not be considered an adverse event; however, it shall be recorded in the source documents. Concurrent diseases due to a non-urgent surgery shall be reported as an adverse event.

The Insufficient clinical response (lack of efficacy)

Insufficient clinical response, efficacy, or pharmacological action shall not be recorded as an adverse event. The principal investigator or investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

Overdose of the study drug

Overdose of any medication without manifested symptoms shall not be recorded as an adverse event, but the overdose shall be recorded on the "Overdose" page of the CRF. Any manifested symptoms shall also be recorded as adverse events on the "Adverse events" of the CRF.

10.1.3 Serious adverse events

Of all the unfavorable medical events that develop with administration of drugs (irrespective of dose), a serious adverse event is an event that:

1. results in death,
2. is life threatening^{*},
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. leads to a congenital anomaly/birth defect, or
6. other medically significant condition: a medically important event that causes a risk to a research subject even if it is not immediately life-threatening and does not result in death or hospitalization, or requires an action or treatment to prevent the results described in 1 to 5 above. Points described in the Takeda Medically Significant Adverse Event List (Table 10 (a)) are included in this section.

* The term "life threatening" refers to an event in which the research subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

| | |
|--|---|
| Acute respiratory failure/acute respiratory distress syndrome (ARDS) | Hepatic necrosis Acute hepatic failure |
| Torsades de pointes/ ventricular fibrillation/ventricular tachycardia | Anaphylactic shock Acute renal failure |
| Malignant hypertension | Pulmonary hypertension |
| Convulsive seizure (including convulsion and epilepsy) | Pulmonary fibrosis (including interstitial pneumonia) |
| Agranulocytosis | Neuroleptic malignant syndrome/ malignant hyperpyrexia |
| Aplastic anemia | Spontaneous abortion/ stillbirth and fetal death |
| Toxic epidermal necrolysis/ Oculomucocutaneous syndrome (Stevens-Johnson syndrome) | Confirmed or suspected transmission of infection by a medicinal product Confirmed or suspected endotoxin shock |

10.1.4 Severity of adverse events

The severity of adverse events shall be classified and defined as shown below.

| | |
|----------|---|
| Mild | The event is transient and easily tolerated by the subject. |
| Moderate | The event interrupts the subject's usual activities. |
| Severe | The event causes considerable interference with the subject's usual activities. |

10.1.5 Causality of adverse events

The causal relationship of each adverse event to the study drug and control drug shall be classified and defined as shown below.

| | |
|-------------|---|
| Related | An adverse event that follows an apparent temporal sequence (including clinical course after discontinuation). Possibly due to the study drug or control drug, although other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment are also suspected. |
| Not related | An adverse event that does not follow an apparent temporal sequence from administration of the study drug and control drug. Very likely due to other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment. |

10.1.6 Date of onset

The date of onset of adverse events shall be determined according to the following rules:

| | |
|---------------------|---------------|
| Adverse event, etc. | Date of onset |
|---------------------|---------------|

| | |
|---|---|
| Signs, symptoms, diseases (diagnoses) | The date on which the first signs/symptoms were noted by the research subject and/or the principal investigator or investigator. |
| Asymptomatic diseases | The date on which a diagnosis was confirmed through a test(s). The date on which a diagnosis was confirmed, even when the test results indicate an old sign(s) of the disease or an approximate time of its onset. |
| Exacerbation of concurrent diseases | The date on which the first worsening of diseases/symptoms was noted by the research subject and/or the principal investigator or investigator. |
| Onset of a test abnormality after the start of the study drug administration | The date on which a clinically significant laboratory abnormality was detected. |
| Worsening of a baseline test abnormality after initiation of study treatment | The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter. |

10.1.7 Date of resolution

The date of resolution of an adverse event is the date on which the research subject recovered (including resolution with sequelae). If a research subject died due to the adverse event concerned, it shall be the date of death. The adverse event shall be recorded as "ongoing" if the research subject has not yet recovered by the end of the study.

10.1.8 Actions taken for the study drug

Actions taken for the study drug shall be classified or defined as shown below.

| | |
|------------------|---|
| Drug withdrawn | The study drug is discontinued because of an adverse event (including withdrawal by the research subject at his/her own discretion). When the treatment with the study drug is continued after withdrawal from the study, it is defined as "Dose not changed." |
| Dose not changed | The dose was not changed after the onset of the adverse event. The study drug or control drug was discontinued, reduced, or increased because of another adverse event. The study drug was discontinued or reduced for a reason other than the adverse event, e.g., inadvertence of the research subject. |
| Unknown | It has not been possible to determine what action has been taken because the research subject is lost to follow-up. |
| Not Applicable | The administration of the study drug had already been completed or discontinued before the onset of the adverse event. |

| | |
|--------------|--|
| Dose reduced | The dose or control drug was reduced because of the adverse event (including dose reduction by the research subject at his/her own discretion). |
| Washout | The study drug or control drug was suspended (i.e., interrupted) by the research subject at his/her discretion) because of the adverse event (including suspension/interruption, but resumed thereafter. |

10.1.9 Outcome

Outcome of adverse events is classified as follows:

| Category | Criteria |
|-------------------------|--|
| Recovered | Disappearance or recovery of symptoms and findings Laboratory values returned to normal or baseline |
| Improved | The intensity is lowered by one or more stages Symptoms or findings mostly disappeared Laboratory values improved, but have not returned to normal or baseline The research subject died from a cause other than the concerned adverse event while the condition was resolving (recording of the date of death unnecessary) |
| Not recovered | No change in symptoms, findings, or laboratory data The symptoms, findings, or laboratory data on the final day of observable period were aggravated compared with the date of onset Irreversible congenital anomaly The research subject died from another cause before resolution of the concerned adverse event (recording of the date of death unnecessary) |
| Recovered with sequelae | Disability that disturbs daily life |
| Death | Direct relationship between death and the concerned adverse event "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same research subject is not considered as death. The date of death shall be recorded. |
| Unknown | Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc. |

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Adverse event collection period

Adverse events will be collected for the following periods:

- Any adverse events occurring between the start of study drug administration and completion (or discontinuation) of the treatment period

10.2.1.2 Reporting of adverse events

At each study visit, the principal investigator or investigator shall check for the presence of any onset of subjective symptoms. A neutral question, such as "How have you been feeling since your last visit?" may be asked to collect any adverse events that occurred between the previous and present visits.

The principal investigator or investigator shall follow up all research subjects experiencing an adverse event irrespective of the causal relationship with the study drug, until the symptom resolve, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent and irreversible adverse events, etc.). All adverse events shall be entered on the CRF, with the event term, onset date, resolution date, severity, causal relationship with the study drug (i.e. "Unrelated" or "Related"), action taken for the study drug, outcome, causal relationship with any study procedure (with specific procedure if assessed to be causally related), and seriousness.

Follow-up period of adverse events shall be until recovery of the adverse events, or the time when the principal investigator or investigator judges that further follow-up would be unnecessary.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it shall be reported according to the following procedures.

At the time of onset of a serious adverse event or notification of the onset by the research subject, the principal investigator shall report the serious adverse event to the chief executive of the study site immediately, and the sponsor or CRO to whom the sponsor has entrusted responsibility shall notify the principal investigator of the study site.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 day of becoming aware of the event onset. Further, the investigator shall submit a formal report within 10 calendar days to the sponsor.

Furthermore, it shall be mandatory to include the contents below in the report to be submitted to the sponsor within 1 working day, and other items shall be reported as far as possible.

- Brief description of adverse event and the reason for why it was determined as serious

- Research subject ID number
- Name of investigator or the subinvestigator
- Name of the study drug
- Determined causal relationship

10.2.3 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the investigator or the subinvestigator shall confirm the necessary additional information and enter in the EDC system or submit a report within the period specified by the sponsor.

10.3 Follow-up of Serious Adverse Events

When information that was not included in the detailed report was obtained later, the principal investigator or investigator shall state it in the copy of the report on serious adverse events, or create another document and submit it to the contact address shown on the attached sheet. Relevant data collected at the study site (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the IEC upon request.

The investigator or the subinvestigator shall follow-up all serious adverse events, until recovery is confirmed, or the final outcome is determined.

10.3.1 Reporting of serious adverse events to Ethics Review Committee and regulatory authorities

When the chief executive of the study site receives a report of a serious adverse event from the investigator, the chief shall consult the Ethics Review Committee, etc., and notify the study sites that are conducting the clinical research through the sponsor or the CRO consigned by the sponsor.

Serious adverse event reported by the principal investigator is unexpected, the chief executive of the study site shall prepare a written report of the unexpected serious adverse event containing the information reported by the principal investigator plus the information below, and submit the report to the Minister of Health, Labor and Welfare, and notify other clinical study sites. (The chief executive of the study site may report it to the Minister of Health, Labor and Welfare via the sponsor, and notify it to other clinical study sites via the sponsor.)

- Actions taken for serious adverse events (discontinuation of new enrollment, revision of informed consent form, re-consents to other research subjects, etc.)
- Date of review, summary of review, result, necessary action, etc., related to Ethics Review Committee, etc.
- Notification to other study sites

The sponsor shall report, in accordance with regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the investigators, and directors of study sites.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO consigned by the sponsor shall comply with regulatory required time frames for reporting, and make emergency reports concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor shall, in the same way, make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, or continuation of clinical research. The study site shall submit copies of emergency report documents to the Ethics Review Committee, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

The Steering Committee will be established for this study.

11.1.1 Steering Committee

The Steering Committee will comprise of the chair and the sponsor. The Steering Committee will supervise implementation and reporting of the study, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the protocol appropriately. The responsibilities of the committee will be prescribed in the procedures of the Steering Committee.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

CRO shall be in charge of implementing data management operation independently from Medical Affairs department of the sponsor. Adverse events, medical history, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the WHO Drug Dictionary.

12.1 Case Report Form

The principal investigator or investigator shall complete a CRF for each research subject who has signed the informed consent form.

The sponsor or its designee shall provide study sites with access authorization to the electronic CRF. Before use of the electronic CRF system, the sponsor shall provide training to the principal investigator, investigators, and study collaborators. The CRF shall be used to report the information collected during the study period to the sponsor. The CRF shall be made in Japanese. Data shall be directly entered in preparing the CRF.

A change or correction of the CRF shall be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The investigator or its designee shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the case report form. The investigator bears full responsibility for the accuracy and reliability of all the data entered on the CRF.

The following data shall be recorded on the CRF directly.

- Severity, degree, the causal relationship with the study drug, control drug, or the study procedures, outcome

When the principal investigator or investigator changes or corrects the content of the CRF after having submitted it to the sponsor, the form for change and correction of a CRF provided by the sponsor (Data Clarification Form) shall be used. The principal investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

The sponsor or the designee shall confirm that the CRF has been made appropriately in conformity with the procedure defined for each research. The sponsor or the designee shall read the medical record or in-hospital record related to the research subject to ensure the accuracy of the CRF. The completed CRF shall be the property of the

sponsor, and the principal investigator or investigator shall not disclose the information to a third party without written permission from the sponsor.

12.2 Storage of Records

The principal investigator or the chief executive of study site shall store the following materials, including those specified in Section 12.1, and study-specific documents to be used by the regulatory authority and the sponsor or its designee for investigation and audit. The documents shall include, but shall not be limited to the research subject ID number list, research subjects' medical records, clinical research work sheet, original signed and dated informed consent forms, {CRFs (copy), change and modification record of the CRF (copy)/ an electronic copy of the electronic CRFs with audit trails, and the drug management records, etc. The principal investigator and the chief executive of the study site shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the research by the principal investigator, or for 3 years from the date of reporting final publication of the study result, whichever date is later. However, when the sponsor requires a longer storage period, the chief executive of the study site shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL METHODS

Statistical analysis will be performed by the responsible biostatistician and his/her designee (i.e., biostatistician of a contract research organization independent of the sponsor). The sponsor is not involved in the analysis of this study.

13.1 Statistical and Analytical Plans

The biostatistician will prepare the initial version of a statistical analysis plan before informed consent of the first participant. The statistical analysis plan will specify detailed definitions of the endpoints and analytical methods to address all study objectives.

13.1.1 Analysis sets

The analysis set for this study will be the "Full Analysis Set," which is defined as all participants given at least one dose of the study drug.

13.1.2 Analysis of demographic and other baseline characteristics

Major demographic and other baseline characteristics in the Full Analysis Set will be summarized.

13.1.3 Efficacy analysis

[Primary endpoint]

Change in actigraphy-measured sleep latency* from baseline (i.e., start of the study treatment period) to the end of the treatment period

*: Mean value from the past 7 days

[Analytical methods]

In the Full Analysis Set, the change in actigraphy-measured sleep latency from baseline to the end of the treatment period will be summarized by calculation of summary statistics (i.e., number of participants, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and a two-sided 95% confidence interval for the mean, and assessed using the one-sample *t*-test.

[Secondary endpoints]

- Change in sleep diary-measured sleep latency* from baseline to the end of the treatment period
- Change in actigraphy-measured total nocturnal sleep time* from baseline to the end of the treatment period

- Change in actigraphy-measured nocturnal wake time* from baseline to the end of the treatment period
- Change in actigraphy-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured sleep efficiency* from baseline to the end of the treatment period
- Change in sleep diary-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in sleep diary-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured daytime activity level* from baseline to the end of the treatment period

*: Mean value from the past 7 days

[Analytical methods]

In the Full Analysis Set, the individual secondary endpoints will be summarized by calculation of summary statistics and two-sided 95% confidence interval for the mean, and assessed using the one sample *t*-test.

[Other endpoints]

- Actigraphy-measured sleep latency, total nocturnal sleep time, nocturnal wake time, number of nocturnal awakenings, sleep efficiency, and daytime activity level
- Diary-measured sleep latency, total nocturnal sleep time, and number of nocturnal awakenings
- PGI
- HAM-D17
- 3DSS

13.1.4 Methods of data conversion and handling of missing data

Details will be specified in the statistical analysis plan prepared separately.

13.1.5 Significance level and confidence coefficient

Significance level: 5% (two-sided testing)

Confidence coefficient: 95% (two-sided estimation)

13.1.6 Safety analysis

[Safety endpoints]

- Adverse events
- Body weight

[Analytical methods]

The safety will be analyzed in the Full Analysis Set as follows:

Treatment-Emergent Adverse Events (TEAEs), defined as adverse events occurring after the start of study drug administration, will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) terms, and summarized by Preferred Term (PT) and System Organ Class (SOC) with frequency tabulation.

Frequency tabulation will be generated for the following:

- All TEAEs
- TEAEs related to the study drug
- All TEAE by severity
- TEAEs related to the study drug by severity
- TEAEs leading to discontinuation of study treatment
- Serious TEAEs

For body weight and vital signs, the measurements at each time point of evaluation will be summarized using frequency tabulation.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The sample size is set to 30 in light of feasibility of this study to investigate the effect of ramelteon in insomnia patients with depression. This planned sample size is not based on statistical power calculation.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the Study Site

The sponsor or its designee shall perform periodic monitoring of study sites during the research to confirm that the research is conducted in accordance with all specifications in the research protocol. In the monitoring, the data recorded on the CRF will be checked by comparing them with those in the source documents. Source documents are the original documents, data and records. The principal investigator and the chief executive of the study site shall ensure that the sponsor or its designee and the Ethics Review Committee, etc., have access to the source documents.

The sponsor or its designee shall access the records, including the list of research subject ID numbers, medical records of the research subjects, and signed and dated original consent forms to confirm that the research is appropriately conducted in compliance with the research protocol. Also, confirm the consistency between CRF and the related source documents. The principal investigator, investigator, and other personnel involved in the research shall spare sufficient time to facilitate monitoring procedures during visits to the study site.

Detailed procedures for monitoring shall be described separately in the quality monitoring plan.

14.2 Deviation from the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Research Protocol.

The principal investigator or investigator shall record all deviations from Ethical Guidelines for Medical and Health Research Involving Human Subjects, and research protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the study site for the clinical research and the sponsor. As necessary, the principal investigator will discuss protocol revisions with the sponsor to reach agreement. For protocol revisions, draft revisions should be submitted as early as possible to the study site for approval of the committee such as the IEC.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site may be research subject to audits by the sponsor or its designee. In such a case, the auditor designated by the sponsor shall contact the study site in advance to determine the date of audit. The auditor may ask to visit the facilities where laboratory specimens are collected and any other facilities used during the clinical research. In addition, this research may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration [FDA], the United

Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified promptly. The principal investigator and the chief executive of the study site shall ensure that the auditor has access to all the research-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL RESEARCH

This research shall be conducted with the highest respect for the individual participants (i.e., research subjects) according to the research protocol, and the ethical principles that have their origin in the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects. Each investigator will conduct the study according to regulatory requirements and in accordance with "Responsibilities of the Investigator" in Appendix B.

15.1 Approval of the Ethical Review Board, etc.

The Ethical Review Board, etc., shall be constituted in accordance with the regulations For implementation or continuation of this study, the principal investigator will provide the head of the medical institution with this protocol, a copy of the informed consent form and other documents required by applicable regulations. The head of the medical institution will then request a review to be done by the institutional review board etc. regarding essential items for proper implementation of the clinical study, including whether the protocol is compliant with the Ethical Guidelines for Medical and Health Researches Involving Human Participants. Documentation of approval of the institutional review board etc. and agreement of the head of the medical institution must be obtained by the principal investigator before implementation or continuation of the study.

The study site shall observe all requirements that the Ethical Review Board, etc. prescribe. The requirements may include notifications to committees such as the IEC, for example, revision of the research protocol, revision of the informed consent form and information sheet, reports on safety in accordance with the regulatory requirements, reports on status of implementation of the research at intervals determined by a study site committee such as the Ethics Review Committee, and submission of the study completion report.

15.2 Conflict of Interests

Prior to the conduction of this clinical research, the investigators involved in this clinical research shall ensure appropriate management of any conflicts (COI) in the conduct of the research in accordance with the rules of the study site.¹⁵⁾⁻¹⁹⁾

The study site shall comply with all requirements specified by a committee such as the Ethics Review Committee, including the COI self-statement form, the research protocol, and the informed consent form and information sheet.

15.3 Informed Consent and Information Sheet, and the Agreement of the Research Subjects

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of research subjects in this clinical research (both in and outside Japan: supply to a third party), and disclosure. The informed consent form and the information sheet will explain in detail the nature of the research, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that research subject is free to withdraw at any time without giving a reason and without any negative effect on the further medical care.

The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and research subject information sheet by the committee such as the IEC. The informed consent form and information sheet must be approved by the committee prior to use.

The informed consent form and information sheet shall be written in language that can be easily understood by the potential research subjects. The principal investigator or investigator shall be responsible for providing detailed explanation of the informed consent form and information sheet to the potential subjects. Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as the IEC.

The principal investigator or investigator shall ensure that the potential research subjects (or the representatives) have (1) an opportunity to inquire about the research and (2) sufficient time to decide on their participation. If a potential research subject (or their representative) decides he or she is willing to participate in the research, then the informed consent form must be signed and dated by the potential research subject (or the representative) prior to entering into the research as a subject. The principal investigator or investigator shall instruct the potential research subject (or representative) to sign using their legal names, not nicknames, using a blue or black ball point ink pen. Also the principal investigator or investigator shall sign and date the informed consent form prior to entering into the research.

Once signed, the original informed consent form shall be retained by the principal investigator or investigator. The principal investigator or investigator shall record the date that the potential research subject signed the informed consent form in the subject's

medical record. A copy of the signed informed consent form shall be given to the research subject.

The principal investigator or investigator shall follow the same procedure as for obtaining the initial consent when newly obtaining re-consent from the concerned research subject (or the representative) when the informed consent form is revised. The date of obtaining new consent shall be recorded in the research subject's medical record, and a copy of the revised consent form shall be provided to the research subject.

15.4 Personal Information of the Research Subjects

The sponsor or the designee shall affirm the principle of the protection of research subjects' private/personal information. Throughout this study, research subject ID numbers shall be used to link the subject's source data to the sponsor's research database and research-related documents. Limited information on research subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of research subjects and confirmation of accuracy of research subject ID number.

For verification of the conduct of the research in compliance with this protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the sponsor shall require the principal investigator to provide the research sponsor's designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to research subjects' original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject's research participation, and autopsy reports.

The principal investigator or investigator shall obtain specific authorization of the research subject as part of the informed consent process for access to research subject's original medical records by research sponsor's designee and representatives of regulatory authorities (see Section 15.3).

When providing a copy of source documents to the sponsor, the principal investigator or investigator shall delete information that may lead to identification of an individual (name and address of research subject, other personal information not recorded on the CRF of the research subject).

15.5 Consultation Windows for the Research Subjects or Persons Related to the Research Concerned

The principal investigator shall establish a contact service to respond to inquiries concerning this clinical research from research subjects or concerned people. Details of the contacts for inquiries will be described in the ICF.

15.6 Financial Burden or Reward to the Research Subjects

Of the expenses for this clinical research, the sponsor shall offer compensation for medical treatment not covered by health insurance as research expenses.

The research subjects shall pay expenses for medical treatment covered by ordinary health insurance.

In addition, the principal investigator shall pay expenses such as transportation expenses for participation in this clinical research to the research subjects at each visit from the research funds. Details of the financial burden on the research subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and Inconveniences to the Research Subjects

15.7.1 Benefits to research subjects

Participation in this study is expected to allow more detailed characterization of the pathological condition of insomnia based on objective measurements, leading to selection of more appropriate treatment in individual patients.

15.7.2 Inconveniences to research subjects

Certain insomnia medications will be restricted during participation in this study.

15.8 Attribution of Research Results and Access Rights

15.8.1 Attribution of research results

The research results and data obtained from this research shall belong to the sponsor. In addition, secondary use (metaanalysis, etc.) of the data obtained in this clinical research may be possible if used in such a way that the data shall not be linked to personal identification information.

15.8.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor.

15.9 Reporting of Results, Publication, Disclosure, and Clinical Research Registration Policy

15.9.1 Reporting of results, publication and disclosure

The principal investigator shall report a written summary of results of the research to the chief executive of the study site and provide the sponsor with all the results and data obtained from the research. Only the sponsor may disclose the research information to other principal investigators, investigators or regulatory authorities during the research period, except when required by laws and regulations. The sponsor shall be responsible for publication of the research protocol and research-related results (including the public web site) except for other cases permitted in the research contract.

During research period and after the end of research, the sponsor or its designee should promptly summarize the results and present it to medical journals and academic conferences, etc. The sponsor may publish any data or information obtained from the research (including data and information provided by the principal investigator) without obtaining agreement of the principal investigator.

The investigator or the subinvestigator should obtain the prior written approval from the sponsor when publishing the information obtained in this research at an academic conference, etc.

15.9.2 Clinical research registration

To ensure that information on clinical research is made accessible to the public in a timely manner and to comply with applicable laws, regulations, and guidelines, Takeda Pharmaceutical Company Limited shall register all clinical research being conducted in patients around the world at public trial registration sites, including at least the website(s) of ClinicalTrials.gov and Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC), before initiation of the clinical research. On such websites, the research location (city, country), subject recruitment status, and contact information for Takeda Pharmaceutical Company Limited are open to the public.

15.9.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited shall post the research results, irrespective of the nature of the results, at the public trial registration sites of Clinical Trials.gov and JAPIC in accordance with applicable laws and regulations.

15.10 Insurance and compensation for injury

The research subjects participating in this research shall be compensated for any injury resulting from participation in the research according to local regulations applicable to the study site. The sponsor or its designee shall buy an insurance policy to compensate for health injury in research subjects

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Protocol

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

| | |
|-----------------------|--|
| Sponsor | Takeda Pharmaceutical Company Limited 12-10 Nihonbashi 2-chome, Chuo-ku, Tokyo 103-8668 |
| Study Number | Ramelteon-4002 |
| Version Number | Version 1.0 |
| Study Drug | Ramelteon |
| Date | March 29, 2016 |

CONFIDENTIAL

Amendment History:

| Date | Amendment Number | Applicable Sites |
|----------------|-------------------------|-------------------------|
| March 29, 2016 | Initial version | All study sites |

CONFIDENTIAL PROPERTY

This document is a confidential communication of Takeda. Acceptance of this document constitutes agreement by the potential recipient of the drug to be administered that no information contained herein will be published or disclosed without written authorization from Takeda except to the extent necessary to obtain informed consent from those research subjects to whom the drug may be administered. Furthermore, the information is only intended for review and compliance by the recipient, his or her staff, and applicable institutional review committee and regulatory agencies to enable conduction of the study.

1.0 STUDY ADMINISTRATIVE INFORMATION AND STUDY PRINCIPLES

1.1 Contact Information and Responsibilities for Study-Related Activities

See the attachment.

1.2 Clinical Study Principals

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Ethical Guideline for Clinical Research (the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare, December 22, 2014).
- All applicable laws and regulations, including, without limitation, data privacy laws and conflict of interest guidelines.

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| Sponsor: Takeda Pharmaceutical Company Limited | Study drug: Ramelteon |
| Study title: The exploratory study to investigate the effect of Ramelteon for insomnia patients with major depressive disorder by using actigraphy | |
| Protocol number: Ramelteon-4002 (293/NRP-003) | |
| Clinical study design: Multicenter, open-label study | |
| Objective: To investigate explanatorily the effect of ramelteon 8 mg once daily for 8 weeks in treatment for insomnia patients with depression by using actigraphy. | |
| Study Population: Insomnia patients with major depressive disorder | |
| Planned number of research subjects: 30 | Number of study sites: Approximately 5 medical institutions |
| Dose and method of administration: Ramelteon 8 mg once daily orally at bedtime | Route of administration: Oral |
| Duration of treatment: 8 weeks | Duration of evaluation: 9 weeks (Run-in period for 1 weeks and treatment period for 8 weeks) |
| Main criteria for inclusion: <ol style="list-style-type: none"> 1. Patients with sleep-onset insomnia on ≥ 3 days per week for ≥ 4 consecutive weeks at the time of informed consent 2. Patients with a diagnosis of depression according to the DSM-5 3. Men or women aged ≥ 20 and < 65 years at the time of informed consent 4. Outpatients 5. Patients with the 17-item Hamilton Rating Scale for Depression (HAM-D17) score(s) meeting either of the following at the start of the run-in period and the start of the study treatment period: <ul style="list-style-type: none"> - a score of 2 for the “6: Insomnia Early” item - a score of 1 for the “6: Insomnia Early” item with a subtotal score of ≥ 3 for the “7: Insomnia Middle” and “8: Insomnia Late” items 6. Patients with a total HAM-D17 score of ≤ 16 at the start of the run-in period and the start of the study treatment period 7. Patients on stable antidepressant medication, defined as no change of antidepressant agents for at least 8 weeks before informed consent and no change in the dosage for at least 4 weeks before informed consent 8. Patients who maintain a routine sleep schedule in daily life, defined as going to bed between 21:00 and 1:00 on ≥ 4 days a week | |

9. Patients in whom the run-in period actigraphy shows sleep latency ≥ 30 minutes and total nocturnal sleep time ≤ 6.5 hours on ≥ 3 days
10. Patients who, in the opinion of the principal investigator or investigator, are capable of understanding the contents of the study and complying with study requirements
11. Patients capable of signing and dating the informed consent form in person before any study procedures

Main criteria for exclusion:

1. Patients with a history of hypersensitivity to ramelteon or melatonin
2. Patients with severe liver disorder
3. Patients who took oral ramelteon within 4 weeks before informed consent
4. Patients who took any oral insomnia medications (including investigational drugs and unapproved drugs) within 2 weeks before the study treatment period
5. Shift workers or night workers
6. Patients with current or past history of psychiatric or neurological diseases other than depression
7. Patients with a score of ≥ 1 for the HAM-D17 "11: Suicide" item at the start of the run-in period or the start of the study treatment period, or with any suicide attempts within 24 weeks before or during the run-in period
8. Pregnant women, nursing mothers, or women who plan to become pregnant or donate eggs before the informed consent, during the study period or within 4 weeks after the end of the study
9. Patients participating in another investigational or post-marketing clinical trial/study
10. Other patients judged by the principal investigator or investigator to be inappropriate for participation in this study

Endpoints:

<Primary endpoint>

Change in actigraphy-measured sleep latency* from baseline (i.e., start of the study treatment period) to the end of the treatment period

*: Mean value from the past 7 days

<Secondary endpoints>

- Change in diary-measured sleep latency* from baseline to the end of the treatment period
- Change in actigraphy-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in actigraphy-measured nocturnal wake time* from baseline to the end of the treatment period
- Change in actigraphy-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured sleep efficiency* from baseline to the end of the treatment

period

- Change in diary-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in diary-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured daytime activity level* from baseline to the end of the treatment period

*: Mean value from the past 7 days

<Additional endpoints>

Efficacy endpoints

- Actigraphy-measured sleep latency, total nocturnal sleep time, nocturnal wake time, number of nocturnal awakenings, sleep efficiency, and daytime activity level
- Diary-measured sleep latency, total nocturnal sleep time, and number of nocturnal awakenings
- PGI
- HAM-D17
- 3DSS

Safety endpoints

- Adverse events
- Body weight

Statistical method:

1. Analysis Sets

The analysis set for this study will be the "Full Analysis Set," which is defined as "all participants given at least one dose of the study drug."

2. Efficacy Analysis

[Primary endpoint]

In the Full Analysis Set, the change in actigraphy-measured sleep latency from baseline to the end of the treatment period will be summarized by calculation of summary statistics (i.e., number of participants, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and a two-sided 95% confidence interval for the mean, and assessed using the one-sample *t*-test.

[Secondary endpoints]

In the Full Analysis Set, the individual secondary endpoints will be summarized by calculation of summary statistics and two-sided 95% confidence intervals for the means, and assessed using the one-sample *t*-test.

Sample Size Justification:

The sample size is set to 30 in light of feasibility of this study to investigate the effect of ramelteon in insomnia patients with depression. This planned sample size is not based on

statistical power calculation.

3.0 ABBREVIATIONS

| | |
|--------|---|
| BZD | Benzodiazepine |
| COI | Conflict of Interest |
| CRO | Contract Research Organization |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders Fifth Edition |
| HAM-D | Hamilton Rating Scale for Depression |
| PGI | Patient Global Impression |
| 3DSS | 3 Dimensional Sleep Scale |

4.0 INTRODUCTION

4.1 Background

Insomnia is commonly encountered in today's medical practice in Japan, and has been raised as a clinical and social issue.¹⁾ Depression also shows a dramatically increasing trend recently²⁾³⁾, partly because of changes in the working environment, and its social impact is becoming a growing concern. Insomnia and depression are known to be often comorbid⁴⁾, and improvement of insomnia symptoms has been described as a key to successful resolution of depression.⁵⁾ Insomnia is known to be associated with not only aging and lifestyle-related diseases, but also hypervigilance due to tension from excessive expectation about sleep, as well as disturbance of the bodily circadian rhythm due to irregular living schedule with a delayed sleep-wake cycle. Depression, on the other hand, is typically associated with anxiety, but is now known to be linked with negative influence of irregular living schedule as well. Thus, insomnia and depression share some same risk factors, and this can explain the high co-existence rate of these two disorders.⁶⁾⁷⁾

The mainstays in the treatment of insomnia have long been benzodiazepine (BZD)-class hypnotics and nonbenzodiazepine-class hypnotics, both classes of which exert sedative and anxiolytic effects. A novel melatonin receptor agonist, ramelteon (trade name, Rozerem), has been available in Japan since 2010. Ramelteon can improve sleep-onset insomnia by working on the bodily clock mechanism and adjusting the circadian rhythm. Ramelteon's mechanism of action without sedative or anxiolytic properties appears to be of high clinical significance particularly in the treatment of insomnia patients with concurrent depression.

4.2 Rationale for the Proposed Study

Reports have been limited on the efficacy and safety of ramelteon in insomnia patients with depression or other psychiatric diseases⁸⁾⁹⁾, and none used objective measures. The present study is thus designed to use actigraphy to objectively explore the efficacy of ramelteon on insomnia in insomnia patients with depression.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary objective

To investigate exploratorily the effect of ramelteon 8 mg once daily for 8 weeks in treatment for insomnia patients with depression by using actigraphy.

5.1.2 Secondary objective

To investigate exploratorily the safety of ramelteon 8 mg once daily for 8 weeks in insomnia patients with depression.

5.2 Endpoints

5.2.1 Primary endpoint

Change in actigraphy-measured sleep latency* from baseline (i.e., start of the study treatment period) to the end of the treatment period

*: Mean value from the past 7 days

5.2.2 Secondary endpoints

- Change in diary-measured sleep latency* from baseline to the end of the treatment period
- Change in actigraphy-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in actigraphy-measured nocturnal wake time* from baseline to the end of the treatment period
- Change in actigraphy-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured sleep efficiency* from baseline to the end of the treatment period
- Change in diary-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in diary-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured daytime activity level* from baseline to the end of the treatment period

*: Mean value from the past 7 days

5.2.3 Other endpoints

(1) Efficacy

- Actigraphy-measured sleep latency, total nocturnal sleep time, nocturnal wake time, number of nocturnal awakenings, sleep efficiency, and daytime activity level
- Sleep diary-measured sleep latency, total nocturnal sleep time, and number of nocturnal awakenings
- PGI
- HAM-D17
- 3DSS

(2) Safety

- Adverse events
- Body weight

6.0 STUDY DESIGN

6.1 Study Design

(1) Study design

This is a multicenter, open-label study.

(2) Treatment

Participants will take ramelteon 8 mg once daily orally at bedtime for 8 weeks.

(3) Planned sample size

30 patients

(4) Number of study sites

Approximately 5 medical institutions

(5) Duration of evaluation and number of visits in individual participants

The duration of evaluation in this study will be 9 weeks. Participants will make a total 4 visits, i.e., at the start of the run-in period and at the start and Weeks 4 and 8 of the treatment period.

Figure 6.a shows the schematic diagram of the study design. The study schedule is provided in Appendix A.

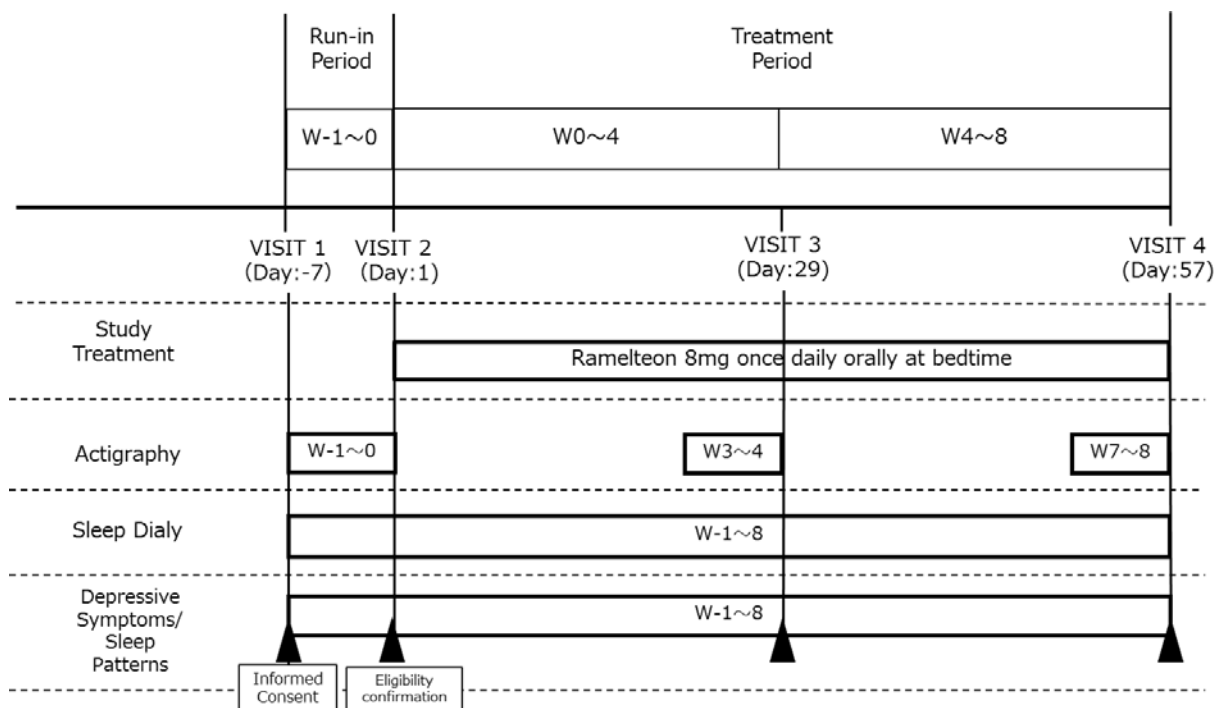


Figure 6.a Schematic of Study Design

6.2 Rationale for the Study Design

<Rationale for the study population>

For ramelteon, a drug approved for "improvement of sleep onset difficulty in insomnia", data have been limited on its efficacy and safety in insomnia patients with psychiatric disease, and construction of the clinical evidence is desired. Among psychiatric diseases, depression is common and often coexists with insomnia symptoms. Thus, the study population is set to insomnia patients with depression.

<Rationale for the study design>

An uncontrolled, open-label design is employed in light of feasibility of this post-marketing clinical research, although the primary objective is to explore the effect of ramelteon in treating insomnia patients with a history of co-morbid depression.

<Rationale for the dosage>

The approved dosage and method of administration for ramelteon are employed.

<Rationale for the endpoints>

The "Guideline for Clinical Evaluation of Hypnotic Agents" (Notification No. 1213-1 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, dated December 13, 2011) recommends the use of polysomnography for objective efficacy evaluation in addition to the use of patient-recorded sleep logs for subjective efficacy evaluation. While polysomnography is a complex examination and repeated polysomnography can impose heavy burden on participants, actigraphy has been recognized to provide sleep data highly correlated with those provided by polysomnography and is a simple tool posing less burden to participants. Thus, actigraphy is selected as an objective assessment tool in this study¹⁰⁾. For subjective measures, this study uses a sleep diary, as well as the Patient Global Impression (PGI) as an index of global improvement, and the 3 Dimensional Sleep Scale (3DSS) as a new tool to assess sleep dimensions including sleep phases. The HAM-D17 is selected for evaluation of depressive symptoms, in line with preceding studies.

The safety will be evaluated based on adverse events, body weight.

<Rationale for the treatment duration>

The treatment duration is set to 8 weeks on the basis of the Japanese long-term clinical trial of ramelteon (24-week treatment), which demonstrated gradual

manifestation of the efficacy of ramelteon on sleep latency under repeated dosing over a certain period, and the efficacy peaked around Week 8.

<Rationale for the sample size>

See Section 13.3

6.3 Premature Termination of Entire Clinical Research or Premature Termination of Clinical Research at a Study Site

6.3.1 Premature termination criteria of entire clinical research

The sponsor should immediately discontinue the study when at least one of the following criteria is applicable:

- When new information or other evaluation on the safety or efficacy of the study drug becomes available that shows a change in the known risk/benefit profile of the concerned compound, and risks/benefits are no longer tolerable for research subject participation in the study.
- When there is serious deviation from ethical guidelines that may threaten safety of the research subjects.

6.3.2 Criteria for premature termination of study sites

Termination of involvement of a study site in the study may be requested prematurely at the discretion of the sponsor if the entity (e.g., principal investigator) is found in significant violation of the ethical guidelines, protocol, or contractual agreement, or is unable to ensure proper conduct of the research.

6.3.3 Procedures of clinical study suspension and premature termination of entire clinical study or study at a study site

In the event that the sponsor or a study site committee such as an ethics review committee decides to prematurely suspend or terminate the entire clinical study or clinical study at a study site, a study-specific procedure shall be provided by the sponsor. The procedure shall be followed by applicable study sites during the course of clinical study suspension or premature termination.

6.4 Procedures for Protocol Revision

If the protocol needs to be revised, the sponsor shall consider and decide whether to revise the protocol.

The principal investigator of each study site shall be informed of the details of each protocol revision.

Upon notification, the principal investigator at each study site shall submit the revised contents to committees such as the IEC, as necessary according to institutional regulations for review, and obtain approval from the director of the entity.

7.0 SELECTION AND WITHDRAWAL CRITERIA

7.1 Inclusion Criteria

Participants must fulfill all of the following criteria to be included in this study:

1. Patients with sleep-onset insomnia on ≥ 3 days per week for ≥ 4 consecutive weeks at the time of informed consent
2. Patients with a diagnosis of depression according to the DSM-5
3. Men or women aged ≥ 20 and < 65 years at the time of informed consent
4. Outpatients
5. Patients with the 17-item Hamilton Rating Scale for Depression (HAM-D17) score(s) meeting either of the following at the start of the run-in period and the start of the study treatment period:
 - a score of 2 for the “6: Insomnia Early” item
 - a score of 1 for the “6: Insomnia Early” item with a subtotal score of ≥ 3 for the “7: Insomnia Middle” and “8: Insomnia Late” items
6. Patients with a total HAM-D17 score of ≤ 16 at the start of the run-in period and the start of the study treatment period
7. Patients on stable antidepressant medication, defined as no change of antidepressant agents for at least 8 weeks before informed consent and no change in the dosage for at least 4 weeks before informed consent
8. Patients who maintain a routine sleep schedule in daily life, defined as going to bed between 21:00 and 1:00 on ≥ 4 days a week
9. Patients in whom the run-in period actigraphy shows sleep latency ≥ 30 minutes and total nocturnal sleep time ≤ 6.5 hours on ≥ 3 days
10. Patients who, in the opinion of the principal investigator or investigator, are capable of understanding the contents of the study and complying with study requirements
11. Patients capable of signing and dating the informed consent form in person before any study procedures

[Rationale for the inclusion criteria]

- 1: This criterion is set to exclude patients with transient insomnia.
- 2: This criterion is set to specify the target study population and applicable diagnostic criteria.
- 3: This criterion is set because both men and women need to be included for evaluation. The lower age limit of 20 years is set because personal voluntary consent is valid at and above this age. The upper age limit is set for this study to enroll participants who are active during daytime and thus appropriate for evaluation using actigraphy.

4, 6, 7: These criteria are set to determine patients whose depression symptoms have been mild or less and stable.

5, 9: These criteria are set to determine patients with symptoms of sleep-onset insomnia during the run-in period.

8: This criterion was set to ensure appropriate evaluation of the efficacy and safety of the study drug.

10, 11: These criteria are set as essential elements for the study implementation.

7.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from this study:

1. Patients with a history of hypersensitivity to ramelteon or melatonin
2. Patients with severe liver disorder
3. Patients who took oral ramelteon within 4 weeks before informed consent
4. Patients who took any oral insomnia medications (including investigational drugs and unapproved drugs) within 2 weeks before the study treatment period
5. Shift workers or night workers
6. Patients with current or past history of psychiatric or neurological diseases other than depression
7. Patients with a score of ≥ 1 for the HAM-D17 "11: Suicide" item at the start of the run-in period or the start of the study treatment period, or with any suicide attempts within 24 weeks before or during the run-in period
8. Pregnant women, nursing mothers, or women who plan to become pregnant or donate eggs before the informed consent, during the study period or within 4 weeks after the end of the study
9. Patients participating in another investigational or post-marketing clinical trial/study
10. Other patients judged by the principal investigator or investigator to be inappropriate for participation in this study

[Rationale for the exclusion criteria]

1, 2: These criteria are set in consideration of the safety of the participants.

3 to 6: These criteria are set to ensure appropriate evaluation of the efficacy and safety of the study drug.

7, 8: These criteria are set in consideration of the safety of the participants.

9, 10: These criteria are set as essential elements for the study implementation.

7.3 Prohibited Medications and Therapies

During the study period, the principal investigator or investigator will instruct the participants not to take any other medications than those instructed to be taken, including over-the-counter drugs, without first consulting with the principal investigator or investigator.

[Prohibited medications]

Fluvoxamine maleate will be prohibited from the start of the run-in period. Insomnia medications other than ramelteon (including investigational drug and unapproved drugs) will be prohibited from at least 2 weeks before treatment period to the end of the study period.

1. Fluvoxamine maleate
2. Insomnia medications other than ramelteon (including investigational drug and unapproved drugs)

[Rationale for prohibited medications]

1. Fluvoxamine maleate is contraindicated for use with the study drug, ramelteon.
2. Insomnia medications may prevent appropriate evaluation of the efficacy and safety of the study drug.

7.4 Management of Study Participants

The following should be observed or instructed to the participants by the principal investigator and investigator.

1. Participants should make scheduled visits and undergo physical examination by physician and other specified examinations (Actigraphy, Sleep Diary) . When a scheduled visit cannot be made, the participant should promptly contact the principal investigator or investigator.
2. In the event of any symptomatic worsening or other abnormalities except scheduled visits, the participant should promptly contact the principal investigator or investigator for instructions.
3. Participants should take the study drug as instructed by the principal investigator or investigator. If not, this must be reported to the principal investigator or investigator at the next visit.

4. Participants should not take any other medications than those instructed to be taken, including over-the-counter drugs, without first consulting with the principal investigator or investigator (except for emergency situations).
5. Whenever participants visit another hospital between the informed consent and the end of the study, the participant should tell the physician of the other hospital that he/she is participating in this study.
6. Whenever participants visit another hospital between the informed consent and the end of the study, the participant should report to the principal investigator or investigator about background for the visit and treatment details.
7. Women of childbearing potential whose male partners are not surgically sterile must use appropriate contraception from the time of informed consent to the end of the study.

7.5 Criteria for Discontinuation or Withdrawal of a Research Subject

The principal investigator or investigator shall record the main reason for discontinuation of protocol treatment on the case report form according to the classification described below. Refer to Section 9.1.12 for research subjects who withdraw from the research before

1. Adverse event

This is selected when an adverse event occurred in a study participant that requires premature termination to avoid an unacceptable risk to the participant's health imposed by continued participation in the study; or the study participant is unwilling to remain in the study because of the adverse event.

2. Major protocol deviation

This is selected when the study participant is found not to fulfill the protocol-specified eligibility criteria after the start of the study treatment, or has failed to adhere to protocol requirements, and thus the participant's continued participation in the study would pose an acceptable risk to his/her health.

3. Lost to follow-up

This is selected when the study participant has not returned to the study site and lost contact. In such instances, all attempts to contact the participant must be recorded in the source document.

4. Voluntary withdrawal

This is selected when the study participant has requested to withdraw his/her participation in the study. The reason for withdrawal, if provided by the participant, will be recorded in the case report form.

5. Discontinuation of the entire study

This is selected when discontinuation of the entire study is decided by the sponsor, institutional review board, regulatory authority, etc. See Section 6.3.1 for details.

6. Pregnancy

This is selected when a female study participant is found to be pregnant.

Note: A participant found to be pregnant must be immediately withdrawn from the study. For the withdrawal procedure, see Section 9.1.11.

7. Lack of efficacy

This is selected when the investigator or subinvestigator has judged that, because of lack of efficacy of study treatment, the participant's continued participation in the study would pose an unacceptable risk to the participant.

8. Sign of suicide

This is selected when the HAM-D17 "11: Suicide" item score became ≥ 1 ; or the principal investigator or investigator judged that the C-SSRS results or other findings indicate a sign of suicide.

9. Remission of depression

This is selected when the participant's depression remitted to no longer require antidepressant medication etc.

10. Other

This is selected when the principal investigator or investigator has decided withdrawal of the participant for any other reason. The reason must be detailed in the case report form.

7.6 Procedures for Discontinuation of Individual Research Subjects

The principal investigator or investigator shall terminate a research subject's research participation when the research subject meets the criteria described in Section 7.5. Individual research subjects may discontinue their research participation without giving a reason at any time during the research. Should a research subject's participation be discontinued, the primary reason for termination shall be recorded on the CRF by the principal investigator or investigator. In addition, efforts shall be made to perform all tests/observations/evaluations scheduled at the time of discontinuation.

8.0 TREATMENT

8.1 Study Drug

8.1.1 Study drug

Nonproprietary name: Ramelteon [JAN]

Chemical name: N-{2-[(8S)-1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl]ethyl}
propanamide

Dosage: 8 mg once daily

Method of administration: Orally at bedtime

Duration of treatment: 8 weeks

8.1.2 Overdose

Overdose is defined as intentional or accidental administration of the study drug at a higher dose than that specified in the protocol, either by a health professional or by the research subject.

To consistently collect important safety information about overdose, the principal investigator or investigator(s) shall record all cases of overdose on the "Overdose" page of the CRF, irrespective of the presence or absence of accompanying adverse event. Adverse events associated with overdose shall be recorded on the "Adverse events" page of the CRF, in accordance with the procedures described in Section 10.0, "ADVERSE EVENTS."

In addition, serious adverse events associated with overdose shall be recorded in accordance with the procedures described in Section 10.2.2, "Collection and reporting of SAEs."

In the event of overdose, the principal investigator or investigator shall treat the subject as required based on symptoms

8.2 Prescription of the Study Drug

The principal investigator or investigator will prescribe the study drug according to the protocol, to participants who fulfill all of the inclusion criteria and do not meet any of the exclusion criteria.

8.3 Prescription of Antidepressant Medication

The oral antidepressant medication being used in each participant at the time of informed consent will be continued without any change to the dosage regimen during participation in the study.

8.4 Non-pharmacological Insomnia Treatment

During the study period, non-pharmacological insomnia treatment should be added or changed.

9.0 STUDY PLAN

9.1 Study Procedures

The principal investigator or investigator will collect data according to the following procedures. In principle, the same principal investigator or investigator should perform the examinations, observations, and evaluations in the same participant. The study schedule is provided in Appendix A.

9.1.1 Informed consent

Informed consent procedures are described in Section 15.3.

Study procedures may be started only after informed consent is obtained from the participant.

Participants who provided informed consent will be assigned participant identification codes for de-identification. The assigned participant identification codes will be used throughout the study period without changes.

9.1.2 Demographic data, medical history and prior medication

Demographic data will be obtained in terms of date of birth, sex, and history of alcohol consumption, and history of smoking.

Medical history will be obtained in terms of any clinically relevant diseases or symptoms that had disappeared or resolved within 1 year before the informed consent. Ongoing symptoms or diseases should be regarded as concurrent conditions (see Section 9.1.11).

9.1.3 History of insomnia

Regarding current insomnia, the following data will be obtained:

- Date of onset
- Initial/Recurrence
- Any non-pharmacological therapy

9.1.4 History of Depression

Regarding the current depressive episode, the following data will be obtained:

- Date of onset
- Initial/Recurrence
- Any use of psychotherapy

9.1.5 Physical examination

Physical examination will be performed. Findings of physical examination after the start of the treatment period will be compared with those before the treatment period, and assessed for any abnormalities that can be clinically relevant.

9.1.6 Body weight, height and Body Mass Index (BMI)

Body weight and height will be measured. BMI will be calculated by the sponsor, using the following equation:

$$\text{Body Mass Index (BMI)} = \text{Body Weight (kg)} / (\text{Height (m)})^2$$

Height will be measured to the nearest whole number in centimeters. Body weight will be measured to the first decimal place in kilograms. The calculated BMI value will be expressed to the first decimal place.

9.1.7 Actigraphy

At the end of the informed consent, an actigraph will be lent to each participant. After full instructions on actigraphy are provided to the participants, actigraphy recording will be started. Patients meeting the inclusion criteria on the basis of the data in the run-in period will keep the actigraph, and be instructed to wear it until the end of the treatment period.

Participants will be instructed to bring the actigraph at each study visit. For analysis of the data recorded in the actigraph, the actigraph will be connected to a computer with an actigraphy data analysis software installed, and the following data will be transferred to the analysis software: sleep latency, total nocturnal sleep time, nocturnal wake time, the number of nocturnal awakenings, sleep efficiency and daytime activity level (step counts). For each of these parameters, the validity of the measured data will be checked according to the "Procedures for actigraphic sleep assessment" prepared separately, and the data during the run-in period (Weeks -1 to 0) and the treatment period (Weeks 3 to 4 and 7 to 8) will be recorded in the case report form. The actigraph device will be retrieved after completion of the actigraphy recording on the 3 occasions, or when the participant is withdrawn from the study.

9.1.8 Sleep diary

At the end of the informed consent, a sleep diary will be provided to each participant, with instruction on how to keep the diary during the study period. The following diary data during the run-in period (Weeks -1 to 0) and the treatment period (Weeks 3 to 4 and 7 to 8) will be recorded in the case report form: sleep latency, bedtime hour,

awakening hour and number of nocturnal awakenings. Any missing entries, discrepancies, or other potentially dubious entries in the sleep diary will be checked with the participant, and explained in the sleep diary by the participant. Accordingly, necessary additions and corrections will be made to the sleep diary, and recorded in the case report form.

9.1.9 17-item Hamilton Rating Scale for Depression (HAM-D17)

The Hamilton Rating Scale for Depression (HAM-D) is a questionnaire used to rate the severity of depression based on general symptoms of depression, including physical symptoms. The rater will assess individual items on a scale from 0 to 2, 3, or 4 depending on the items, based on an interview with the participant.⁶⁾ The time frame assessed by the HAM-D is one week before each visit. This study will use the 17-item version (HAM-D17), and the scores of individual items and the total score will be assessed and recorded in the case report form.

9.1.10 Patient Global Impression (PGI)

The Patient Global Impression (PGI) is a patient-rated scale to measure the degree of any improvement (or worsening). Participants will rate their own condition compared with the run-in period (before the start of study treatment), and enter the score in the PGI form. The principal investigator or investigator will record the score in the case report form.

9.1.11 3 Dimensional Sleep Scale (3DSS)

The 3 Dimensional Sleep Scale (3DSS) is a patient-administered questionnaire developed in Japan, and used to assess sleep dimensions including sleep phases.⁷⁾ At each visit, participants will assess their own condition within the past month and complete the 3DSS form. The principal investigator or investigator will record the results of 3DSS in the case report form.

9.1.12 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in the individuals during participation in a clinical research.¹³⁾¹⁴⁾ The C-SSRS consists of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with subquestions assessing the severity. The principal investigator or investigator will perform the C-SSRS assessment based on an interview with the participant. Since this is performed to detect any signs of suicide during the study period, the C-SSRS assessment results will not be recorded in the case report form.

9.1.13 Concomitant medications

Concomitant medications are any psychotherapeutic drugs (Drugs for Insomnia, Antidepressant) that are used in addition to the study drug, and include drugs prescribed by doctors or over-the-counter drugs purchased by the participants. At each visit, participants will be interviewed about any psychotherapeutic drugs used other than the study drug from the time of informed consent to the end of the study and specific usage (drug name).

9.1.14 Concurrent conditions

Concurrent conditions are defined as symptoms or diseases that are present at the time of the informed consent. Abnormal findings from physical examination at the start of the run-in period will be regarded as concurrent conditions at the discretion of the principal investigator or investigator.

9.1.15 Pregnancy

If pregnancy of a participant is found during the study, with agreement of the female participant, the principal investigator or investigator will inform her obstetrics/gynecology doctor about the fact of her participation in the clinical study at the onset of the pregnancy, as well as details of the study drug.

All pregnancies reported during the study will be followed up to their outcomes by the principal investigator or investigator, with agreement of the participants with pregnancy. The outcome of pregnancy, including any premature labor, will be reported to the sponsor, using a designated report form. Assessment after childbirth will also be performed.

9.1.16 Documentation of withdrawals before study treatment

For all participants withdrawn before the start of study treatment after signing the consent form, the case report form will be completed.

The following data will be recorded in the case report form:

- Date of informed consent
- Date of birth
- Sex
- Eligibility
- Reason for withdrawal

The main reason for the withdrawal before the start of study treatment will be recorded, using the following classification:

- Not fulfilling all of the inclusion criteria, or meeting any of the exclusion criteria
- Major protocol deviation
- Lost to follow-up
- Voluntary withdrawal (The reason should be specified)
- Discontinuation of the entire study
- Pregnancy
- Other (The reason should be specified)

Participant identification codes assigned to the participants withdrawn before the start of study treatment must not be reused.

9.2 Monitoring of Treatment Compliance in Participants

At each visit, the principal investigator or investigator will assess the participant's compliance with the study drug and antidepressant medication. The compliance status will be classified into 4 categories: nearly all of the prescribed doses were taken ($\geq 90\%$), most of the prescribed doses were taken ($\geq 70\%$), about half of the prescribed doses were taken ($\geq 50\%$), or less than half of the prescribed doses were taken ($< 50\%$).

Throughout the study period, participants will be reinstructed about medication. If poor compliance with the study drug after the previous visit, such as $< 50\%$ of prescribed doses, is found and does not improve, the participant may be withdrawn as appropriate.

9.3 Schedule of Examinations and Observations

The schedule for all examinations, observations, and evaluations is shown in Appendix A. The principal investigator or investigator will perform the following examinations, observations, and evaluations as scheduled.

9.3.1 Start of the run-in period (VISIT 1)

After informed consent, the following data will be obtained by physical examination and other examinations. In addition, participants will be instructed to keep a sleep diary and to perform actigraphy recording for 1 week before VISIT 2 (i.e., Week -1 to Week 0). Eligibility of participants will be confirmed against the inclusion and exclusion criteria given in Section 7.0. For documentation of participants withdrawn during the run-in period, the procedures in Section 9.1.13 should be followed.

During the run-in period, the following examinations, observations, and evaluations will be performed:

- Informed consent

- Demographic data, medical history, prior medication, history of insomnia, depressive episodes
- Physical examination
- Height, body weight and BMI
- Concurrent medications
- Concurrent conditions
- HAM-D17
- C-SSRS (baseline)

9.3.2 Start of the study treatment period (VISIT 2)

At the start of administration of the study drug, the following examinations, observations, and evaluations will be performed.

For participants fulfilling all of the inclusion criteria and not meeting any of the exclusion criteria given in Section 7.0, the principal investigator or investigator will instruct to start taking the study drug according to Section 6.1.

- Physical examination
- Body weight
- Concomitant medications
- Concurrent conditions
- HAM-D17
- Assessment of the actigraphy data from Week -1 to Week 0
- Sleep diary
- 3DSS
- C-SSRS (after last assessment)

9.3.3 Treatment period (VISIT 3)

During the treatment period (VISIT 3), the following examinations, observations, and evaluations will be performed.

- Physical examination
- Body weight
- Concomitant medications
- HAM-D17
- Assessment of actigraphy data from Week 3 to Week 4
- Sleep diary

- Adverse events
- 3DSS
- Treatment compliance
- C-SSRS (after last assessment)

9.3.4 At completion (VISIT 4) or withdrawal

Final visit will be made at 8 weeks after the start of study treatment, when the following examinations, observations, and evaluations will be performed. In withdrawn participants, the same examinations, observations, and evaluations will be performed at withdrawal from the study.

- Physical examination
- Body weight
- Concomitant medications
- HAM-D17
- Assessment of actigraphy data from Week 7 to Week 8*
- Sleep diary
- Adverse events
- 3DSS
- Treatment compliance
- C-SSRS(after last assessment)
- PGI

For all participants given the study drug, the study completion/withdrawal status will be recorded in the case report form.

10.0 Pretreatment Event and Adverse Event

10.1 Definitions

10.1.1 Adverse events

An adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product (including a study drug) and which does not necessarily have to have a clear causal relationship with this treatment.

An adverse event can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.1.2 Considerations for Adverse Events

Generally unfavorable findings are described below:

- Newly diagnosed disease or unexpected aggravation of existing symptom (intermittent event of an existing symptom is not considered an adverse event)
- Requiring action or medical practice
- Requiring invasive diagnostic treatment
- Requiring discontinuation or a change in the dose of the study drug
- Considered unfavorable by the investigator or the subinvestigator

Diagnosis name and signs/symptoms:

Adverse events shall be recorded by diagnosis name. Accompanying signs (including abnormal laboratory values, abnormal ECG findings) and symptoms shall not be recorded as adverse events. If an adverse event could not be expressed by a diagnosis name, the signs or symptoms shall be recorded as the adverse event.

Laboratory test values and ECG findings:

Abnormal laboratory values and ECG findings shall be recorded as adverse events when the principal investigator or investigator judges the results are clinically problematic (in other words, when certain action or medical practice is required, or when the principal investigator or the investigator judges the change has exceeded the normal physiological variation range of the research subject). Retest and/or continued monitoring of an abnormality are not considered medical practice. Also, repeated or additional

conduction of non-invasive tests for verification, evaluation, and monitoring of an abnormality are not considered medical practice.

However, when abnormal laboratory values and ECG findings are the accompanying symptoms of a disease diagnosed as an adverse event (e.g., increased creatinine due to renal dysfunction, etc.), the adverse event shall be handled by its diagnosis name.

Pre-existing conditions (at start of treatment period):

A disease or symptoms that had been present since before the start of observation period shall be regarded as a concurrent disease and not an adverse event. When a concurrent medical condition is aggravated, the aggravation shall be determined as an adverse event and the investigator or the subinvestigator shall record on the CRF that the adverse event is an aggravation of the concurrent disease (e.g., "aggravation of hypertension," etc.).

If a research subject has a pre-existing episodic condition (e.g., asthma, epilepsy), each episode shall be recorded as an adverse event if the episodes become more frequent, serious, or severe in nature. If a research subject has a chronic concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition shall be recorded as adverse event if the degree of the worsening exceeds that which would be expected. The principal investigator or investigator shall ensure that the adverse event term to be recorded represents the change in the condition from baseline (e.g. "worsening of...").

Worsening of adverse events:

If a research subject experiences a worsening of the adverse event after a change to the study drug, or secondary signs and symptoms are caused by the adverse event, the worsening or the secondary signs and symptoms shall be recorded as a new adverse event on the CRF. The principal investigator or investigator shall use an adverse event term that explicitly means a change of the condition (e.g., "worsening of...").

Change of severity of adverse events:

If the research subject experiences changes in the severity of an adverse event, the event shall be recorded once, at its peak severity.

Previously planned surgery or treatment:

Preplanned surgeries or interventions that were scheduled before study treatment shall not be considered adverse events. However, when the existing symptom is aggravated to a degree requiring emergency surgery or treatment, the condition or the event shall be considered an adverse event. A concurrent disease that resulted from previously planned surgery shall be reported as an adverse event.

Non-urgent surgery or treatment:

Non-urgent surgery or treatment that does not induce a change in the condition of a research subject (cosmetic surgery, etc.) shall not be considered an adverse event; however, it shall be recorded in the source documents. Concurrent diseases due to a non-urgent surgery shall be reported as an adverse event.

The Insufficient clinical response (lack of efficacy)

Insufficient clinical response, efficacy, or pharmacological action shall not be recorded as an adverse event. The principal investigator or investigator shall make the distinction between worsening of a pre-existing condition and lack of therapeutic efficacy.

Overdose of the study drug

Overdose of any medication without manifested symptoms shall not be recorded as an adverse event, but the overdose shall be recorded on the "Overdose" page of the CRF. Any manifested symptoms shall also be recorded as adverse events on the "Adverse events" of the CRF.

10.1.3 Serious adverse events

Of all the unfavorable medical events that develop with administration of drugs (irrespective of dose), a serious adverse event is an event that:

1. results in death,
2. is life threatening^{*},
3. requires inpatient hospitalization or prolongation of existing hospitalization,
4. results in persistent or significant disability/incapacity,
5. leads to a congenital anomaly/birth defect, or
6. other medically significant condition: a medically important event that causes a risk to a research subject even if it is not immediately life-threatening and does not result in death or hospitalization, or requires an action or treatment to prevent the results described in 1 to 5 above. Points described in the Takeda Medically Significant Adverse Event List (Table 10 (a)) are included in this section.

* The term "life threatening" refers to an event in which the research subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Table 10.a Takeda Medically Significant AE List

| | |
|--|---|
| Acute respiratory failure/acute respiratory distress syndrome (ARDS) | Hepatic necrosis Acute hepatic failure |
| Torsades de pointes/ ventricular fibrillation/ventricular tachycardia | Anaphylactic shock Acute renal failure |
| Malignant hypertension | Pulmonary hypertension |
| Convulsive seizure (including convulsion and epilepsy) | Pulmonary fibrosis (including interstitial pneumonia) |
| Agranulocytosis | Neuroleptic malignant syndrome/ malignant hyperpyrexia |
| Aplastic anemia | Spontaneous abortion/ stillbirth and fetal death |
| Toxic epidermal necrolysis/ Oculomucocutaneous syndrome (Stevens-Johnson syndrome) | Confirmed or suspected transmission of infection by a medicinal product Confirmed or suspected endotoxin shock |

10.1.4 Severity of adverse events

The severity of adverse events shall be classified and defined as shown below.

| | |
|----------|---|
| Mild | The event is transient and easily tolerated by the subject. |
| Moderate | The event interrupts the subject's usual activities. |
| Severe | The event causes considerable interference with the subject's usual activities. |

10.1.5 Causality of adverse events

The causal relationship of each adverse event to the study drug and control drug shall be classified and defined as shown below.

| | |
|-------------|---|
| Related | An adverse event that follows an apparent temporal sequence (including clinical course after discontinuation). Possibly due to the study drug or control drug, although other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment are also suspected. |
| Not related | An adverse event that does not follow an apparent temporal sequence from administration of the study drug and control drug. Very likely due to other factors such as underlying disease, concurrent diseases, or concomitant drugs/treatment. |

10.1.6 Date of onset

The date of onset of adverse events shall be determined according to the following rules:

| | |
|---------------------|---------------|
| Adverse event, etc. | Date of onset |
|---------------------|---------------|

| | |
|---|---|
| Signs, symptoms, diseases (diagnoses) | The date on which the first signs/symptoms were noted by the research subject and/or the principal investigator or investigator. |
| Asymptomatic diseases | The date on which a diagnosis was confirmed through a test(s). The date on which a diagnosis was confirmed, even when the test results indicate an old sign(s) of the disease or an approximate time of its onset. |
| Exacerbation of concurrent diseases | The date on which the first worsening of diseases/symptoms was noted by the research subject and/or the principal investigator or investigator. |
| Onset of a test abnormality after the start of the study drug administration | The date on which a clinically significant laboratory abnormality was detected. |
| Worsening of a baseline test abnormality after initiation of study treatment | The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter. |

10.1.7 Date of resolution

The date of resolution of an adverse event is the date on which the research subject recovered (including resolution with sequelae). If a research subject died due to the adverse event concerned, it shall be the date of death. The adverse event shall be recorded as "ongoing" if the research subject has not yet recovered by the end of the study.

10.1.8 Actions taken for the study drug

Actions taken for the study drug shall be classified or defined as shown below.

| | |
|------------------|---|
| Drug withdrawn | The study drug is discontinued because of an adverse event (including withdrawal by the research subject at his/her own discretion). When the treatment with the study drug is continued after withdrawal from the study, it is defined as "Dose not changed." |
| Dose not changed | The dose was not changed after the onset of the adverse event. The study drug or control drug was discontinued, reduced, or increased because of another adverse event. The study drug was discontinued or reduced for a reason other than the adverse event, e.g., inadvertence of the research subject. |
| Unknown | It has not been possible to determine what action has been taken because the research subject is lost to follow-up. |
| Not Applicable | The administration of the study drug had already been completed or discontinued before the onset of the adverse event. |

| | |
|--------------|--|
| Dose reduced | The dose or control drug was reduced because of the adverse event (including dose reduction by the research subject at his/her own discretion). |
| Washout | The study drug or control drug was suspended (i.e., interrupted) by the research subject at his/her discretion) because of the adverse event (including suspension/interruption, but resumed thereafter. |

10.1.9 Outcome

Outcome of adverse events is classified as follows:

| Category | Criteria |
|-------------------------|--|
| Recovered | Disappearance or recovery of symptoms and findings Laboratory values returned to normal or baseline |
| Improved | The intensity is lowered by one or more stages Symptoms or findings mostly disappeared Laboratory values improved, but have not returned to normal or baseline The research subject died from a cause other than the concerned adverse event while the condition was resolving (recording of the date of death unnecessary) |
| Not recovered | No change in symptoms, findings, or laboratory data The symptoms, findings, or laboratory data on the final day of observable period were aggravated compared with the date of onset Irreversible congenital anomaly The research subject died from another cause before resolution of the concerned adverse event (recording of the date of death unnecessary) |
| Recovered with sequelae | Disability that disturbs daily life |
| Death | Direct relationship between death and the concerned adverse event "Direct relationship" means that the concerned adverse event was the cause of death, or the concerned adverse event was clearly responsible for death. Outcome of an adverse event which was not determined (judged, presumed) a direct cause of death observed in the same research subject is not considered as death. The date of death shall be recorded. |
| Unknown | Follow-up specified in the protocol after the date of onset was not possible due to change of hospitals or relocation, etc. |

10.2 Procedures

10.2.1 Collection and reporting of adverse events

10.2.1.1 Adverse event collection period

Adverse events will be collected for the following periods:

- Any adverse events occurring between the start of study drug administration and completion (or discontinuation) of the treatment period

10.2.1.2 Reporting of adverse events

At each study visit, the principal investigator or investigator shall check for the presence of any onset of subjective symptoms. A neutral question, such as "How have you been feeling since your last visit?" may be asked to collect any adverse events that occurred between the previous and present visits.

The principal investigator or investigator shall follow up all research subjects experiencing an adverse event irrespective of the causal relationship with the study drug, until the symptom resolve, or any clinically significant abnormal laboratory values have returned to baseline or there is a satisfactory explanation for the change (permanent and irreversible adverse events, etc.). All adverse events shall be entered on the CRF, with the event term, onset date, resolution date, severity, causal relationship with the study drug (i.e. "Unrelated" or "Related"), action taken for the study drug, outcome, causal relationship with any study procedure (with specific procedure if assessed to be causally related), and seriousness.

Follow-up period of adverse events shall be until recovery of the adverse events, or the time when the principal investigator or investigator judges that further follow-up would be unnecessary.

10.2.2 Collection and reporting of serious adverse events

When a serious adverse event develops during the period of collecting adverse events, it shall be reported according to the following procedures.

At the time of onset of a serious adverse event or notification of the onset by the research subject, the principal investigator shall report the serious adverse event to the chief executive of the study site immediately, and the sponsor or CRO to whom the sponsor has entrusted responsibility shall notify the principal investigator of the study site.

The principal investigator shall then report the serious adverse event to the sponsor (for the contact information, refer to the attachment) within 1 day of becoming aware of the event onset. Further, the investigator shall submit a formal report within 10 calendar days to the sponsor.

Furthermore, it shall be mandatory to include the contents below in the report to be submitted to the sponsor within 1 working day, and other items shall be reported as far as possible.

- Brief description of adverse event and the reason for why it was determined as serious

- Research subject ID number
- Name of investigator or the subinvestigator
- Name of the study drug
- Determined causal relationship

10.2.3 Reporting of additional information concerning adverse events

If the sponsor requests provision of additional information concerning adverse events for reporting to regulatory authorities, the investigator or the subinvestigator shall confirm the necessary additional information and enter in the EDC system or submit a report within the period specified by the sponsor.

10.3 Follow-up of Serious Adverse Events

When information that was not included in the detailed report was obtained later, the principal investigator or investigator shall state it in the copy of the report on serious adverse events, or create another document and submit it to the contact address shown on the attached sheet. Relevant data collected at the study site (e.g., ECG charts, laboratory test values, discharge summary, postmortem results) shall be sent to the sponsor or the committee such as the IEC upon request.

The investigator or the subinvestigator shall follow-up all serious adverse events, until recovery is confirmed, or the final outcome is determined.

10.3.1 Reporting of serious adverse events to Ethics Review Committee and regulatory authorities

When the chief executive of the study site receives a report of a serious adverse event from the investigator, the chief shall consult the Ethics Review Committee, etc., and notify the study sites that are conducting the clinical research through the sponsor or the CRO consigned by the sponsor.

Serious adverse event reported by the principal investigator is unexpected, the chief executive of the study site shall prepare a written report of the unexpected serious adverse event containing the information reported by the principal investigator plus the information below, and submit the report to the Minister of Health, Labor and Welfare, and notify other clinical study sites. (The chief executive of the study site may report it to the Minister of Health, Labor and Welfare via the sponsor, and notify it to other clinical study sites via the sponsor.)

- Actions taken for serious adverse events (discontinuation of new enrollment, revision of informed consent form, re-consents to other research subjects, etc.)
- Date of review, summary of review, result, necessary action, etc., related to Ethics Review Committee, etc.
- Notification to other study sites

The sponsor shall report, in accordance with regulations, unexpected serious adverse drug reactions and other serious adverse events that are subject to emergency reporting to regulatory authorities, the investigators, and directors of study sites.

From the time point of first acknowledging the event or receiving additional information, the sponsor or the CRO consigned by the sponsor shall comply with regulatory required time frames for reporting, and make emergency reports concerning unexpected serious adverse drug reactions and expected serious adverse drug reactions to regulatory authorities. Also, the sponsor shall, in the same way, make an emergency report of other critical safety information that may have a major effect on the study drug risk-benefit, continuation of study drug administration, or continuation of clinical research. The study site shall submit copies of emergency report documents to the Ethics Review Committee, etc.

11.0 COMMITTEES ESTABLISHED FOR THIS STUDY

The Steering Committee will be established for this study.

11.1.1 Steering Committee

The Steering Committee will comprise of the chair and the sponsor. The Steering Committee will supervise implementation and reporting of the study, secure medical guidance of a high degree of professionalism and a high-level scientific quality, and revise the protocol appropriately. The responsibilities of the committee will be prescribed in the procedures of the Steering Committee.

12.0 DATA MANAGEMENT AND STORAGE OF RECORDS

Data Management department of the sponsor shall be in charge of implementing data management operation according to the standard operating procedures, independently from Medical Affairs department. Adverse events, medical history, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the WHO Drug Dictionary.

12.1 Case Report Form

The principal investigator or investigator shall complete a CRF for each research subject who has signed the informed consent form.

The sponsor or its designee shall provide study sites with access authorization to the electronic CRF. Before use of the electronic CRF system, the sponsor shall provide training to the principal investigator, investigators, and study collaborators. The CRF shall be used to report the information collected during the study period to the sponsor. The CRF shall be made in Japanese. Data shall be directly entered in preparing the CRF.

A change or correction of the CRF shall be recorded as an audit trail that records the information before and after the change or correction, the person who made the change or correction, date of change or correction, and its reason.

The investigator or its designee shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the case report form. The investigator bears full responsibility for the accuracy and reliability of all the data entered on the CRF.

The following data shall be recorded on the CRF directly.

- Severity, degree, the causal relationship with the study drug, control drug, or the study procedures, outcome

When the principal investigator or investigator changes or corrects the content of the CRF after having submitted it to the sponsor, the form for change and correction of a CRF provided by the sponsor (Data Clarification Form) shall be used. The principal investigator shall confirm that the record of change or correction on the CRF is accurate and complete, and sign or write name/ affix a seal, and date it.

The sponsor or the designee shall confirm that the CRF has been made appropriately in conformity with the procedure defined for each research. The sponsor or the designee shall read the medical record or in-hospital record related to the research subject to ensure the accuracy of the CRF. The completed CRF shall be the property of the

sponsor, and the principal investigator or investigator shall not disclose the information to a third party without written permission from the sponsor.

12.2 Storage of Records

The principal investigator or the chief executive of study site shall store the following materials, including those specified in Section 12.1, and study-specific documents to be used by the regulatory authority and the sponsor or its designee for investigation and audit. The documents shall include, but shall not be limited to the research subject ID number list, research subjects' medical records, clinical research work sheet, original signed and dated informed consent forms, {CRFs (copy), change and modification record of the CRF (copy)/ an electronic copy of the electronic CRFs with audit trails, and the drug management records, etc. The principal investigator and the chief executive of the study site shall appropriately retain the material/information related to this study for at least 5 years from the date of reporting the end of the research by the principal investigator, or for 3 years from the date of reporting final publication of the study result, whichever date is later. However, when the sponsor requires a longer storage period, the chief executive of the study site shall discuss the period and methods of storage with the sponsor.

13.0 STATISTICAL METHODS

Statistical analysis will be performed by the responsible biostatistician and his/her designee (i.e., biostatistician of a contract research organization independent of the sponsor). The sponsor is not involved in the analysis of this study.

13.1 Statistical and Analytical Plans

The biostatistician will prepare the initial version of a statistical analysis plan before informed consent of the first participant. The statistical analysis plan will specify detailed definitions of the endpoints and analytical methods to address all study objectives.

13.1.1 Analysis sets

The analysis set for this study will be the "Full Analysis Set," which is defined as all participants given at least one dose of the study drug.

13.1.2 Analysis of demographic and other baseline characteristics

Major demographic and other baseline characteristics in the Full Analysis Set will be summarized.

13.1.3 Efficacy analysis

[Primary endpoint]

Change in actigraphy-measured sleep latency* from baseline (i.e., start of the study treatment period) to the end of the treatment period

*: Mean value from the past 7 days

[Analytical methods]

In the Full Analysis Set, the change in actigraphy-measured sleep latency from baseline to the end of the treatment period will be summarized by calculation of summary statistics (i.e., number of participants, mean, standard deviation, maximum, minimum, and quartiles; hereinafter the same) and a two-sided 95% confidence interval for the mean, and assessed using the one-sample *t*-test.

[Secondary endpoints]

- Change in sleep diary-measured sleep latency* from baseline to the end of the treatment period
- Change in actigraphy-measured total nocturnal sleep time* from baseline to the end of the treatment period

- Change in actigraphy-measured nocturnal wake time* from baseline to the end of the treatment period
- Change in actigraphy-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured sleep efficiency* from baseline to the end of the treatment period
- Change in sleep diary-measured total nocturnal sleep time* from baseline to the end of the treatment period
- Change in sleep diary-measured number of nocturnal awakenings* from baseline to the end of the treatment period
- Change in actigraphy-measured daytime activity level* from baseline to the end of the treatment period

*: Mean value from the past 7 days

[Analytical methods]

In the Full Analysis Set, the individual secondary endpoints will be summarized by calculation of summary statistics and two-sided 95% confidence interval for the mean, and assessed using the one sample *t*-test.

[Other endpoints]

- Actigraphy-measured sleep latency, total nocturnal sleep time, nocturnal wake time, number of nocturnal awakenings, sleep efficiency, and daytime activity level
- Diary-measured sleep latency, total nocturnal sleep time, and number of nocturnal awakenings
- PGI
- HAM-D17
- 3DSS

13.1.4 Methods of data conversion and handling of missing data

Details will be specified in the statistical analysis plan prepared separately.

13.1.5 Significance level and confidence coefficient

Significance level: 5% (two-sided testing)

Confidence coefficient: 95% (two-sided estimation)

13.1.6 Safety analysis

[Safety endpoints]

- Adverse events
- Body weight

[Analytical methods]

The safety will be analyzed in the Full Analysis Set as follows:

Treatment-Emergent Adverse Events (TEAEs), defined as adverse events occurring after the start of study drug administration, will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) terms, and summarized by Preferred Term (PT) and System Organ Class (SOC) with frequency tabulation.

Frequency tabulation will be generated for the following:

- All TEAEs
- TEAEs related to the study drug
- All TEAE by severity
- TEAEs related to the study drug by severity
- TEAEs leading to discontinuation of study treatment
- Serious TEAEs

For body weight and vital signs, the measurements at each time point of evaluation will be summarized using frequency tabulation.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The sample size is set to 30 in light of feasibility of this study to investigate the effect of ramelteon in insomnia patients with depression. This planned sample size is not based on statistical power calculation.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Monitoring of the Study Site

The sponsor or its designee shall perform periodic monitoring of study sites during the research to confirm that the research is conducted in accordance with all specifications in the research protocol. In the monitoring, the data recorded on the CRF will be checked by comparing them with those in the source documents. Source documents are the original documents, data and records. The principal investigator and the chief executive of the study site shall ensure that the sponsor or its designee and the Ethics Review Committee, etc., have access to the source documents.

The sponsor or its designee shall access the records, including the list of research subject ID numbers, medical records of the research subjects, and signed and dated original consent forms to confirm that the research is appropriately conducted in compliance with the research protocol. Also, confirm the consistency between CRF and the related source documents. The principal investigator, investigator, and other personnel involved in the research shall spare sufficient time to facilitate monitoring procedures during visits to the study site.

Detailed procedures for monitoring shall be described separately in the quality monitoring plan.

14.2 Deviation from the Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Research Protocol.

The principal investigator or investigator shall record all deviations from Ethical Guidelines for Medical and Health Research Involving Human Subjects, and research protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the study site for the clinical research and the sponsor. As necessary, the principal investigator will discuss protocol revisions with the sponsor to reach agreement. For protocol revisions, draft revisions should be submitted as early as possible to the study site for approval of the committee such as the IEC.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site may be research subject to audits by the sponsor or its designee. In such a case, the auditor designated by the sponsor shall contact the study site in advance to determine the date of audit. The auditor may ask to visit the facilities where laboratory specimens are collected and any other facilities used during the clinical research. In addition, this research may be inspected by regulatory agencies, including those of foreign governments (e.g., the Food and Drug Administration [FDA], the United

Kingdom Medicines and Healthcare products Regulatory Agency [MHRA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified promptly. The principal investigator and the chief executive of the study site shall ensure that the auditor has access to all the research-related source documents.

15.0 ETHICAL CONDUCT OF CLINICAL RESEARCH

This research shall be conducted with the highest respect for the individual participants (i.e., research subjects) according to the research protocol, and the ethical principles that have their origin in the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects. Each investigator will conduct the study according to regulatory requirements and in accordance with "Responsibilities of the Investigator" in Appendix B.

15.1 Approval of the Ethical Review Board, etc.

The Ethical Review Board, etc., shall be constituted in accordance with the regulations For implementation or continuation of this study, the principal investigator will provide the head of the medical institution with this protocol, a copy of the informed consent form and other documents required by applicable regulations. The head of the medical institution will then request a review to be done by the institutional review board etc. regarding essential items for proper implementation of the clinical study, including whether the protocol is compliant with the Ethical Guidelines for Medical and Health Researches Involving Human Participants. Documentation of approval of the institutional review board etc. and agreement of the head of the medical institution must be obtained by the principal investigator before implementation or continuation of the study.

The study site shall observe all requirements that the Ethical Review Board, etc. prescribe. The requirements may include notifications to committees such as the IEC, for example, revision of the research protocol, revision of the informed consent form and information sheet, reports on safety in accordance with the regulatory requirements, reports on status of implementation of the research at intervals determined by a study site committee such as the Ethics Review Committee, and submission of the study completion report.

15.2 Conflict of Interests

Prior to the conduction of this clinical research, the investigators involved in this clinical research shall ensure appropriate management of any conflicts (COI) in the conduct of the research in accordance with the rules of the study site.¹⁵⁾⁻¹⁹⁾

The study site shall comply with all requirements specified by a committee such as the Ethics Review Committee, including the COI self-statement form, the research protocol, and the informed consent form and information sheet.

15.3 Informed Consent and Information Sheet, and the Agreement of the Research Subjects

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guidelines for Medical and Health Research Involving Human Subjects and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of research subjects in this clinical research (both in and outside Japan: supply to a third party), and disclosure. The informed consent form and the information sheet will explain in detail the nature of the research, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that research subject is free to withdraw at any time without giving a reason and without any negative effect on the further medical care.

The principal investigator is responsible for the preparation, contents, and approval of the informed consent form and research subject information sheet by the committee such as the IEC. The informed consent form and information sheet must be approved by the committee prior to use.

The informed consent form and information sheet shall be written in language that can be easily understood by the potential research subjects. The principal investigator or investigator shall be responsible for providing detailed explanation of the informed consent form and information sheet to the potential subjects. Information should be given in both oral and written form whenever possible and in manner deemed appropriate by the committee such as the IEC.

The principal investigator or investigator shall ensure that the potential research subjects (or the representatives) have (1) an opportunity to inquire about the research and (2) sufficient time to decide on their participation. If a potential research subject (or their representative) decides he or she is willing to participate in the research, then the informed consent form must be signed and dated by the potential research subject (or the representative) prior to entering into the research as a subject. The principal investigator or investigator shall instruct the potential research subject (or representative) to sign using their legal names, not nicknames, using a blue or black ball point ink pen. Also the principal investigator or investigator shall sign and date the informed consent form prior to entering into the research.

Once signed, the original informed consent form shall be retained by the principal investigator or investigator. The principal investigator or investigator shall record the date that the potential research subject signed the informed consent form in the subject's

medical record. A copy of the signed informed consent form shall be given to the research subject.

The principal investigator or investigator shall follow the same procedure as for obtaining the initial consent when newly obtaining re-consent from the concerned research subject (or the representative) when the informed consent form is revised. The date of obtaining new consent shall be recorded in the research subject's medical record, and a copy of the revised consent form shall be provided to the research subject.

15.4 Personal Information of the Research Subjects

The sponsor or the designee shall affirm the principle of the protection of research subjects' private/personal information. Throughout this study, research subject ID numbers shall be used to link the subject's source data to the sponsor's research database and research-related documents. Limited information on research subjects such as gender, age, and date of birth may be used within the scope of all applicable laws and regulations for identification of research subjects and confirmation of accuracy of research subject ID number.

For verification of the conduct of the research in compliance with this protocol and the Ethical Guidelines for Medical and Health Research Involving Human Subjects, the sponsor shall require the principal investigator to provide the research sponsor's designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to research subjects' original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject's research participation, and autopsy reports.

The principal investigator or investigator shall obtain specific authorization of the research subject as part of the informed consent process for access to research subject's original medical records by research sponsor's designee and representatives of regulatory authorities (see Section 15.3).

When providing a copy of source documents to the sponsor, the principal investigator or investigator shall delete information that may lead to identification of an individual (name and address of research subject, other personal information not recorded on the CRF of the research subject).

15.5 Consultation Windows for the Research Subjects or Persons Related to the Research Concerned

The principal investigator shall establish a contact service to respond to inquiries concerning this clinical research from research subjects or concerned people. Details of the contacts for inquiries will be described in the ICF.

15.6 Financial Burden or Reward to the Research Subjects

Of the expenses for this clinical research, the sponsor shall offer compensation for medical treatment not covered by health insurance as research expenses.

The research subjects shall pay expenses for medical treatment covered by ordinary health insurance.

In addition, the principal investigator shall pay expenses such as transportation expenses for participation in this clinical research to the research subjects at each visit from the research funds. Details of the financial burden on the research subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and Inconveniences to the Research Subjects

15.7.1 Benefits to research subjects

Participation in this study is expected to allow more detailed characterization of the pathological condition of insomnia based on objective measurements, leading to selection of more appropriate treatment in individual patients.

15.7.2 Inconveniences to research subjects

Certain insomnia medications will be restricted during participation in this study.

15.8 Attribution of Research Results and Access Rights

15.8.1 Attribution of research results

The research results and data obtained from this research shall belong to the sponsor. In addition, secondary use (metaanalysis, etc.) of the data obtained in this clinical research may be possible if used in such a way that the data shall not be linked to personal identification information.

15.8.2 Data access rights

Access rights for all data and information generated from this study will be given to personnel approved by the sponsor.

15.9 Reporting of Results, Publication, Disclosure, and Clinical Research Registration Policy

15.9.1 Reporting of results, publication and disclosure

The principal investigator shall report a written summary of results of the research to the chief executive of the study site and provide the sponsor with all the results and data obtained from the research. Only the sponsor may disclose the research information to other principal investigators, investigators or regulatory authorities during the research period, except when required by laws and regulations. The sponsor shall be responsible for publication of the research protocol and research-related results (including the public web site) except for other cases permitted in the research contract.

During research period and after the end of research, the sponsor or its designee should promptly summarize the results and present it to medical journals and academic conferences, etc. The sponsor may publish any data or information obtained from the research (including data and information provided by the principal investigator) without obtaining agreement of the principal investigator.

The investigator or the subinvestigator should obtain the prior written approval from the sponsor when publishing the information obtained in this research at an academic conference, etc.

15.9.2 Clinical research registration

To ensure that information on clinical research is made accessible to the public in a timely manner and to comply with applicable laws, regulations, and guidelines, Takeda Pharmaceutical Company Limited shall register all clinical research being conducted in patients around the world at public trial registration sites, including at least the website(s) of ClinicalTrials.gov and Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC), before initiation of the clinical research. On such websites, the research location (city, country), subject recruitment status, and contact information for Takeda Pharmaceutical Company Limited are open to the public.

15.9.3 Clinical trial results disclosure

Takeda Pharmaceutical Company Limited shall post the research results, irrespective of the nature of the results, at the public trial registration sites of ClinicalTrials.gov and JAPIC in accordance with applicable laws and regulations.

15.10 Insurance and compensation for injury

The research subjects participating in this research shall be compensated for any injury resulting from participation in the research according to local regulations applicable to the study site. The sponsor or its designee shall buy an insurance policy to compensate for health injury in research subjects

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