



Title: Vonoprazan Study of Investigating the Effect on Sleep Disturbance Associated with Reflux Esophagitis - Exploratory Evaluation (VISTAEXE)

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Protocol Approve Date: 28-Mar-2017

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

PROTOCOL

Vonoprazan study of investigating the effect on sleep distturbance associated with reflux
esophagitis- exploratory evaluation
(VISTAEXE)

| | |
|------------------------|--|
| Sponsor | Takeda Pharmaceutical Company Limited 12-10, Nihonbashi 2-chome, Chuo-ku, Tokyo |
| Protocol number | Vonoprazan-4006 (MACS-2016-101812) |
| Version Number | 1.0 |
| Study drug: | Vonoprazan fumarate |
| Creation date | March 28, 2017 |

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1.0 STUDY ADMINISTRATIVE INFORMATION AND CLINICAL STUDY PRINCIPLES

1.1 Clinical Study Principles

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this 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.

1.2 Clinical Study Implementation

This study will be conducted in accordance with the requirements of this protocol designed and prepared by the sponsor and also in accordance with the following. Other study administrative structures are shown in the annexes.

Sponsor:

Japan Medical Affairs,
Japan Pharma Business Unit,
Takeda Pharmaceutical Company Limited

The sponsor shall be responsible for matters related to planning/preparation, implementation/operation, and results/reporting in this study. Methods of supervision of the contractor entrusted with the services related to this study will be described in the procedure to be prepared separately.

Expenses* required for the operation of this study will be paid by the sponsor.

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- *: Based on the “Consignment Service Contract,” expenses incurred for the services of Office of Clinical Study, monitoring, registration/allocation center, and statistical processing shall be paid to the contractor entrusted with services related to this study. Expenses agreed by the study site shall be paid to the site based on the “Research Expense Standard.”

Chair of Steering Committee:

PPD



1.3 Contact Information on the Protocol

Study office

PPD



PPD



SIGNATURES

The signature of MACS program head, Medical Director of Japan Medical Affairs and the responsible statistician can be found on the signature page.

PPD

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PPD

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2.0 STUDY SUMMARY

| | |
|---|--|
| Name of Sponsor: Takeda Pharmaceutical Company Limited | Study Drug: Vonoprazan fumarate |
| Title of Protocol: Vonoprazan study of investigating the effect on sleep disturbance associated with reflux esophagitis-exploratory evaluation | |
| Study Number: Vonoprazan-4006 (MACS-2016-101812) | |
| Study Design: <p>This is an interventional, exploratory, multicenter, open-label study to evaluate the effect of the potassium-competitive acid blocker (P-CAB) vonoprazan on sleep disturbance in subjects under maintenance treatment for reflux esophagitis with proton pump inhibitors (PPIs).</p> <p>Subjects who have been diagnosed as reflux esophagitis based on Los Angeles (LA) Classification¹⁾ Grades A to D, undergoing maintenance treatment with a PPI after initial treatment, and with Pittsburgh Sleep Quality Index (PSQI)^{2) 3)} global score ≥ 6.0 at the baseline/start of administration (VISIT 2) will be eligible for study entry and will be administered vonoprazan 20 mg once daily for 8 weeks.</p> <p>Planned number of subjects is 25.</p> <p>The study period is 9 weeks. The number of visits is 6visits.</p> | |
| Objectives: <p>To evaluate the effect of vonoprazan 20 mg on sleep disturbance of patients with reflux esophagitis, who have heartburn and/or regurgitation and ≥ 6.0 in the PSQI global score despite maintenance treatment with PPIs.</p> | |
| Subject Population: Patients with reflux esophagitis | |
| Number of Subjects: 25 subjects | Number of Sites: Approximately 5 sites |
| Dose Level: Vonoprazan 20 mg orally administered once daily | Route of Administration: Oral |
| Duration of Treatment: 8 weeks | Period of Evaluation: 9 weeks |
| Criteria for Inclusion: <p>Subjects fulfilling all of the following criteria shall be included in this study.</p> <ol style="list-style-type: none"> Subjects who completed the initial treatment with PPIs (esomeprazole, omeprazole, rabeprazole or lansoprazole) and have received high dose PPIs (esomeprazole 20 mg, omeprazole 20 mg, | |

- rabeprazole 10 mg or lansoprazole 30 mg) for more than 8 weeks at the time of informed consent as maintenance treatment for LA Classification Grades A to D reflux esophagitis.
2. Subjects who have heartburn and/or regurgitation.
 3. Subjects with reflux esophagitis related sleep disturbance, fulfilling at least one of following in a week before the baseline/start of administration.
 - Difficulty in falling asleep for ≥ 3 nights
 - Nocturnal awaking or early morning awaking for ≥ 3 nights
 4. Subjects whose heartburn and/or regurgitation at the time of informed consent were alleviated from initial treatment.
 5. Subjects with PSQI global score ≥ 6.0
 6. Subjects who, in the opinion of the investigator, are capable of understanding the content of the study and complying with the protocol requirements.
 7. Subjects who can sign and date an informed consent form and information sheet prior to the initiation of the study procedures.
 8. Male or female subjects aged 20 years or older at the time of informed consent
 9. Therapeutic category: Ambulatory

Criteria for Exclusion:

Subjects fulfilling any of the following criteria will be excluded from this study.

1. Subjects with Zollinger-Ellison syndrome.
2. Subjects with diseases that affect sleep (chronic obstructive pulmonary disease, bronchitis asthma, sleep apnea syndrome, mental disorder, etc.)
3. Nightshift workers.
4. Subjects who have a plan to travel beyond three time zones during the study.
5. Subjects with a history of concurrent or suspicious functional dyspepsia or functional heartburn, based on Rome IV criteria.
6. Subjects with history of surgery or treatment affecting gastroesophageal reflux (fundoplication or dilation for esophageal stenosis [except for Schatzki's ring], etc.).
7. Subjects with an esophagus-related complication (eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal stenosis, etc.), a history of radiotherapy or cryotherapy of the esophagus, a caustic or physiochemical trauma (esophageal sclerotherapy, etc.). However, participants with Schatzki's ring (mucosal tissue ring around inferior esophageal sphincter) or Barrett's esophagus are allowed to be included.
8. Subjects with a history of gastrectomy, gastrointestinal resection or vagotomy.
9. Subjects who took antidepressant agents or anti-anxiety agents within 8 weeks before the time of informed consent.
10. Subjects who took H₂ receptor antagonist within 8 weeks before the time of informed consent.

11. Subjects planning to take prohibited concomitant medications during the study period.
12. Subjects who have any of the following abnormal clinical laboratory test values at the screening (VISIT 1):
ALT or AST > ULN
Bilirubin (Total bilirubin) > ULN
13. Subjects with a malignant tumor.
14. Subjects who are pregnant, breast-feeding, possibly pregnant, or planning to become pregnant.
15. Subjects who have serious renal diseases.
16. Subjects with the conditions listed under administration contraindication in the vonoprazan package insert.
17. Subjects participating in other clinical studies.
18. Subjects who have been determined as inappropriate subjects by the investigator.

Criteria for Evaluation and Analyses:

< Primary endpoint >

- Changes in PSQI global score
[End of study (VISIT 6) – Baseline/Start of Administration (VISIT 2)]

< Secondary endpoints >

Efficacy endpoints:

- Changes in PSQI global score
[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]
- Percentage of subjects with PSQI global score <6.0 at Week 4 (VISIT 4) and the end of study (VISIT 6)
- Changes in 6 component scores of PSQI (Sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Daytime dysfunction)
[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]
[End of study (VISIT 6) – Baseline/Start of Administration (VISIT 2)]
- Changes in number of nocturnal awakenings (assessed by questionnaire)
[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]
[End of study (VISIT 6) – Baseline/Start of Administration (VISIT 2)]
- Changes in actigraph-measured sleep efficiency, sleep latency, and number of nocturnal awakenings
[Week 4 (mean value during 7 days before VISIT 4) – Baseline/Start of Administration (mean value during 7 days before VISIT 2)]
[End of study (mean value during 7 days before VISIT 6) – Baseline/Start of

Administration (mean value during 7 days before VISIT 2)]

Safety endpoints:

- Adverse events

< Additional endpoint >

- Changes in nighttime heartburn and regurgitation (nighttime and daytime)

Statistical Considerations:

Descriptive statistics of primary endpoint and 95% confidence interval of the mean are calculated.

Statistically significance of the change is assessed using paired t-test.

Sample Size Justification :

In the clinical study assessed effect of esomeprazole on sleep disturbance caused by gastroesophageal reflux disease, mean (SD) changes in PSQI global score from baseline at 4 weeks of treatment with esomeprazole 40 mg, 20 mg, and placebo were -3.5 (3.6), -3.8 (3.8), and -2.0 (3.7), respectively⁴⁾. In the similar clinical study with dextlansoprazole, changes in PSQI global score from baseline at 4 weeks of treatment with dextlansoprazole 30 mg, and placebo were -2.70 (3.08), and -1.35 (3.23), respectively⁵⁾. These results suggest that effect sizes during treatment with PPI and placebo are 0.87-1.00 and 0.42-0.54, respectively.

Although subjects for the present study are different from these studies which excluded subjects who received treatment with PPI in a certain period before randomization, we can assume that effect size of the present study will be less than PPI and greater than placebo. So we assumed effect size of changes in PSQI global score from baseline at 8 weeks of treatment will be 0.75.

21 subjects are required as number of subjects for evaluation of primary endpoint to obtain 90% of power using estimated effect size. Considering drop out of certain subject, 25 subjects are required as enrolled subject.

3.0 LIST OF ABBREVIATIONS

| | |
|-------------------|--|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BMI | body mass index |
| COI | conflict of interest |
| CRO | contract study organization |
| EDC | electronic data capture |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonization |
| LA Classification | Los Angeles Classification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NAB | nocturnal acid breakthrough |
| pH4 HTR | pH4 Holding Time Ratio |
| PPI | proton pump inhibitor |
| PSQI | Pittsburgh Sleep Quality Index |
| TEAE | treatment emergent adverse event |

The terms used in this protocol are defined as follows:

Study site:

A corporation, governmental agency and sole proprietor conducting the study, excluding cases where only a part of the services related to storage of samples/information, statistical processing and other studies are entrusted.

Investigators:

Principal investigators and other parties involved in conduct of the study (including operations at institutions involved in collection/distribution of samples/information). Those involved only in providing existing samples/information outside the study sites and those engaged in part of the entrusted operations related to the study are excluded.

Principal Investigator:

An investigator who is engaged in implementation of the study and integrates the operations involved in this study at an affiliated study site.

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Chief executive of the study site:

A representative of a corporation, head of a governmental agency, or a sole proprietor

Subject:

A subject who meets any of the following:

1. Subjects being studied (including those who have been asked to be studied)
2. Subjects from whom existing samples/information to be used in the study have been obtained.

4.0 INTRODUCTION

4.1 Background

Reflux esophagitis is caused by reflux of gastric acid due to relaxation of the inferior esophageal sphincter, reduced esophageal clearance function, impaired esophageal mucosal defense mechanisms and results in the symptoms such as heartburn or regurgitation. Severity of the symptoms caused by reflux esophagitis is correlated with the duration of esophageal exposure to acid and pH of refluxed gastric contents. In the initial treatment of reflux esophagitis, therefore, PPI, which can more strongly suppress gastric acid secretion, is recommended as the first choice⁶⁾.

PPI well suppresses gastric acid secretion during daytime, however, it is known that some patients experience nocturnal acid breakthrough (NAB) under the treatment with PPI⁷⁾.

It is considered that NAB is related to sleep disturbance and the higher prevalence of sleep disturbance among the patients with reflux esophagitis was also reported⁸⁾. Sleep disturbance can cause decreased activity or productivity and affect patients' quality of life. Thus, the efficacy of PPI on sleep disturbance caused by reflux esophagitis has been recently investigated in various ways.

In the study conducted in the US among the patients with moderate-to-severe nighttime heartburn and GERD-related sleep disturbances, 34.3% of the patients treated with esomeprazole 20 mg achieved nighttime heart burn relief and 10.4% of the patients treated with placebo and the difference was statistically significant ($p < 0.0001$).

Furthermore, the percentage of the patients achieved relief of GERD-related sleep disturbance was 71.5% in esomeprazole group and 55.2% in placebo group ($p = 0.006$).

In addition, change in PSQI global score from baseline at 4 weeks of treatment was -2.93 in esomeprazole group and -1.80 in placebo group ($p = 0.0034$)⁹⁾.

In Japan, it has been reported that the sleep disturbance in the patients with reflux esophagitis was improved by PPI administration in some studies¹⁰⁾⁻¹²⁾ and there was a study which showed significant improvement when stratified by the existence of acid reflux symptoms¹³⁾.

On the other hand, it has been also reported that more than 80% of patients taking PPI to treat GERD experience some kind of nocturnal symptoms¹⁴⁾. For the treatment of sleep disturbance related to reflux esophagitis, several therapeutic options such as PPI

administration before dinner, double-dose PPI twice daily, and administration of an additional H₂-receptor antagonist have been investigated. This indicates that the treatment to more strongly suppress gastric acid and alleviate NAB is required in clinical practice⁸⁾.

Vonoprazan is an acid suppressant in a new category that suppresses gastric acid secretion more strongly and more continuously than conventional PPIs by reversibly inhibiting H⁺, K⁺ -ATPase in the final stage of acid secretion in a K⁺ -competitive manner. In Japanese clinical pharmacology study in healthy adult, investigating with crossover design between esomeprazole and vonoprazan, and rabeprazole and vonoprazan, daytime pH4 Holding Time Ratio (pH4 HTR) on 7 days after administration was 77.6% in esomeprazole group and 96.5% in vonoprazan group and night-time pH4 HTR was 44.8% in esomeprazole group and 75.2% in vonoprazan group. In cross-over comparison with rabeprazole, daytime pH4 HTR on Day 7 was 76.1% in rabeprazole group and 98.8% in vonoprazan group and night-time pH4 HTR was 54.1% in rabeprazole group and 88.8% in vonoprazan group¹⁵⁾.

4.2 Rationale for the Proposed Study

It is expected that vonoprazan can improve sleep disturbance caused by NAB better than PPIs due to its strong acid-inhibitory effect, however this has not been investigated so far.

Accordingly, in the present study, the effect of vonoprazan will be evaluated in patients who have sleep disturbance despite the treatment with PPIs for reflux esophagitis.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

To evaluate the effect of vonoprazan 20 mg on sleep disturbance of patients with reflux esophagitis, who have heartburn and/or regurgitation and ≥ 6.0 in the PSQI global score despite maintenance treatment with PPIs.

5.2 Endpoints

5.2.1 Primary Endpoint

- Changes in PSQI global score
[End of Study (VISIT 6) – Baseline/Start of Administration (VISIT 2)]

5.2.2 Secondary Endpoints

Efficacy endpoints:

- Changes in PSQI global score
[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]
- Percentage of subjects with PSQI global score <6.0 at Week 4 (VISIT 4) and the End of Study (VISIT 6)
- Changes in 6 component scores of PSQI (Sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Daytime dysfunction)
[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]
[End of Study (VISIT 6) – Baseline/Start of Administration (VISIT 2)]
- Changes in number of nocturnal awakenings (assessed by questionnaire)
[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]
[End of Study (VISIT 6) – Baseline/Start of Administration (VISIT 2)]
- Changes in actigraph-measured sleep efficiency, sleep latency, and number of nocturnal awakenings
[Week 4 (mean value during 7 days before VISIT 4) – Baseline/Start of Administration (mean value during 7 days before VISIT 2)]
[End of Study (mean value during 7 days before VISIT 6) – Baseline/Start of Administration (mean value during 7 days before VISIT 2)]

Safety endpoints:

- Adverse events

5.2.3 Additional Endpoint

- Changes in nighttime heartburn and regurgitation (daytime and nighttime)

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

<Study design>

This is an interventional, exploratory, multicenter, open-label study to evaluate the effect of the P-CAB vonoprazan on sleep disturbance in subjects under maintenance treatment for reflux esophagitis with PPIs.

Subjects who have been diagnosed as reflux esophagitis based on LA Classification¹⁾ Grades A to D, undergoing maintenance treatment with a PPI after initial treatment, and with PSQI^{2) 3)} global score ≥ 6.0 at the baseline/start of administration (VISIT 2) will be eligible for study entry and will be administered vonoprazan 20 mg once daily for 8 weeks.

Planned number of subjects is 25 subjects.

The study period is 9 weeks. The number of visits is 6visits.

<Treatment>

1. Drugs to be administered

Vonoprazan 20 mg will be administered.

2. Start of study drug administration and dose

After acquisition of informed consent, subjects determined eligible for the study in accordance with the inclusion and exclusion criteria will receive vonoprazan 20 mg orally (once daily). Study drug will be administered at the same time as it was for the previous PPI.

3. Duration of treatment

Vonoprazan 20 mg: 8 weeks

<Planned duration of participation and number of visits for subjects>

The study period is 9 weeks from the screening to the end of study.

The number of visits is 6. Subjects will visit study sites at the time of screening (Week -1), baseline/start of administration (Week 0), Week 2, 4, 6 and the end of study (Week 8).

<Planned number of subjects>

25 subjects

<Number of study sites>

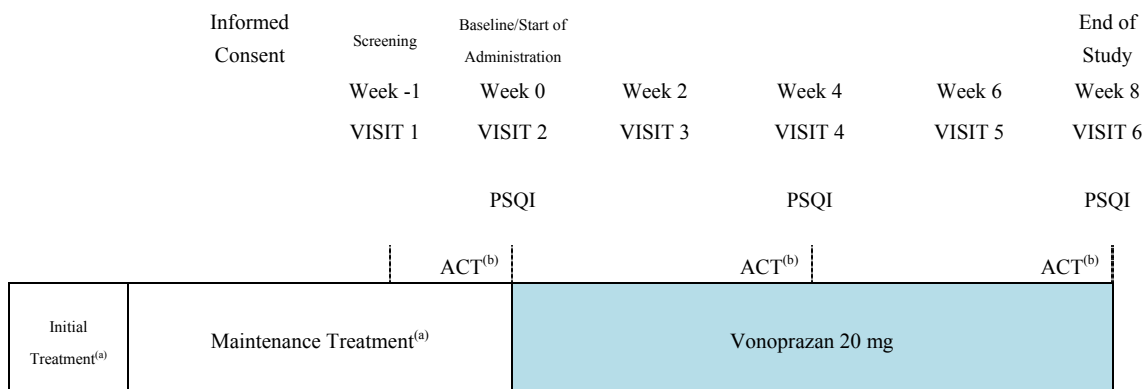
Approximately 5 sites

A schematic of the study design is included as Figure 6 (a). A schedule of assessments is listed in Appendix A.

<Outline of the study design>

Study period: 9 weeks

Number of visits: 6



(a) Treatment of PPIs (in a routine medical practice).

Subjects who have been under maintenance treatment for more than 8 weeks at the time of screening will be included.

(b) ACT: Evaluation of Actigraph

Figure 6.a Schematic of Study Design

6.2 Justification for Study Design

(1) Justification for study design

Since the objective of this study is to evaluate the effect of vonoprazan 20 mg on sleep disturbance of subjects with reflux esophagitis, it is designed as a multicenter, open-label study.

(2) Justification for dose and administration method

Vonoprazan 20 mg will be orally administered once daily to subjects with reflux esophagitis in accordance with the package insert.

(3) Justification for the planned number of subjects

Refer to Section 13.3.

6.3 Premature Termination of Study or Study Site

6.3.1 Criteria for Premature Termination of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises subject safety.

6.3.2 Criteria for Premature Termination of Study Sites

A study site may be terminated prematurely if the site (including the principal investigator) is found in significant violation of the Ethical Guideline for Clinical Research, protocol, or contractual agreement, is unable to ensure adequate performance of the study or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor or a study site committee such as an independent ethics committee (IEC) elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

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. Investigators shall confirm the content of the revision of the protocol and submit an agreement form to the sponsor as evidence of agreement with the protocol revision.

[Protocol revision is required in the following cases:]

1. Change or addition of objectives
2. Change in or addition of efficacy or safety evaluation methods
3. More frequent or additional laboratory tests for which subjects incur additional expenses or changes in laboratory test methods
4. Change in dose
5. Significant change in or addition of inclusion and/or exclusion criteria
6. Change in the planned number of subjects
7. Change in plans or in description of the protocol due to serious adverse events or other reasons
8. Change which is considered as a significant change, as a result of discussion between the sponsor and the chair of the Steering Committee

Upon notification, the principal investigator at each study site shall submit the revised contents to the relevant committees (such as an institutional ethics review committee), for review and approval as necessary according to institutional regulations.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

The investigators shall confirm all the inclusion/exclusion criteria prior to enrollment.

7.1 Inclusion Criteria

Subjects fulfilling all of the following criteria shall be included in this study.

1. Subjects who completed the initial treatment with PPIs (esomeprazole, omeprazole, rabeprazole or lansoprazole) and have received high dose PPI (esomeprazole 20 mg, omeprazole 20 mg, rabeprazole 10 mg, or lansoprazole 30 mg) for more than 8 weeks at the time of informed consent as maintenance treatment for LA Classification Grades A to D reflux esophagitis.
2. Subjects who have heartburn and/or regurgitation.
3. Subjects with reflux esophagitis related sleep disturbance, fulfilling at least one of following in a week before the baseline/start of administration.
 - Difficulty in falling asleep for ≥ 3 nights
 - Nocturnal awaking or early morning awaking for ≥ 3 nights
4. Subjects whose heartburn and/or regurgitation at the time of informed consent were alleviated from initial treatment.
5. Subjects with PSQI global score ≥ 6.0
6. Subjects who, in the opinion of the investigators, are capable of understanding the content of the study and complying with the protocol requirements.
7. Subjects who can sign and date an informed consent form and information sheet prior to the initiation of the study procedures.
8. Male or female subjects aged 20 years or older at the time of informed consent
9. Therapeutic category: Ambulatory

[Justification of inclusion criteria]

- | | |
|---------|---|
| 1-3, 5 | These were set to include the subjects with sleep disturbance caused by heartburn and/or regurgitation even under the maintenance treatment, despite his or her healed mucosal injury by the initial treatment. |
| 4 | This criterion was set to include the subjects who respond to PPI. |
| 6, 7, 9 | These were set as fundamental items for the study. |

8. This was set to evaluate in both genders. The lower age limit was set to 20 years to allow subjects to make a voluntary decision regarding their participation in this study.

7.2 Exclusion Criteria

Subjects fulfilling any of the following criteria will be excluded from this study.

1. Subjects with Zollinger-Ellison syndrome.
2. Subjects with diseases that affect sleep (chronic obstructive pulmonary disease, bronchitis asthma, sleep apnea syndrome, mental disorder, etc.)
3. Nightshift workers.
4. Subjects who have a plan to travel beyond three time zones during the study.
5. Subjects with a history of concurrent or suspicious functional dyspepsia or functional heartburn based on Rome IV criteria.
6. Subjects with history of surgery or treatment affecting gastroesophageal reflux (fundoplication or dilation for esophageal stenosis [except for Schatzki's ring], etc.).
7. Subjects with an esophagus-related complication (eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal stenosis, etc.), a history of radiotherapy or cryotherapy of the esophagus, a caustic or physiochemical trauma (esophageal sclerotherapy, etc.). However, participants with Schatzki's ring (mucosal tissue ring around inferior esophageal sphincter) or Barrett's esophagus are allowed to be included.
8. Subjects with a history of gastrectomy, gastrointestinal resection, or vagotomy.
9. Subjects who took antidepressant agents or anti-anxiety agents within 8 weeks before the time of informed consent.
10. Subjects who took H₂ receptor antagonist within 8 weeks before the time of informed consent.
11. Subjects planning to take prohibited concomitant medications during the study period.
12. Subjects who have any of the following abnormal clinical laboratory test values at the screening (VISIT 1):
ALT or AST > ULN.
Bilirubin (Total bilirubin) > ULN

13. Subjects with a malignant tumor.
14. Subjects who are pregnant, breast-feeding, possibly pregnant, or planning to become pregnant.
15. Subjects who have serious renal diseases.
16. Subjects with the conditions listed under administration contraindication in the vonoprazan package insert.
17. Subjects participating in other clinical studies.
18. Subjects who have been determined as inappropriate subjects by the investigator.

[Justification for exclusion criteria]

- | | |
|-------|---|
| 1-11 | These were set because they would affect efficacy evaluation. |
| 12-16 | These were set in consideration of safety of the subjects. |
| 17-18 | These were set as fundamental items for the study. |

7.3 Excluded Medications

The following drugs should not be used concomitantly with the study drug during the study:

1. Drugs with which vonoprazan should not be used concomitantly according to the package insert.
2. PPIs
3. H₂ receptor antagonist
4. Antidepressant agents and anti-anxiety agents

[Justification for excluded medications]

- | | |
|-----|---|
| 1 | These were set in consideration of safety of the subjects. |
| 2-4 | These were set because they would affect efficacy evaluation. |

7.4 Subject Management

The principal investigator and investigators shall instruct subjects to adhere to the following throughout the study period:

1. Adhere to the instructions or restrictions prescribed in the study period (compliance with study treatment, prohibited concomitant drugs, wearing actigraph).

2. Inform the investigator of any planned treatment by another physician. Promptly report any treatment done by another physician.
3. Visit the study site as scheduled to undergo physical examination or other specified tests. Cancel an appointment for study visit in a timely manner if applicable.
4. Avoid excessive eating or drinking, excessive diet change (e.g., change to extremely high-fat diet), and excessive exercise throughout the study period.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (CRF) using the following categories. For subjects who withdraw from the study before administration, refer to Section 9.1.12.

1. Adverse event

The subject has experienced an adverse event (AE) that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.

- Liver Function Test (LFT) Abnormalities.

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status), if the following circumstances occur at any time during study drug treatment:

ALT or AST or bilirubin (total bilirubin) > 2×ULN.

2. Significant protocol deviation

The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

3. Lost to follow-up

The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.

4. Voluntary withdrawal

The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the “voluntary withdrawal” category).

5. Study termination

The sponsor, IEC or regulatory authority terminates the study. Refer to Section 6.3.1 for details.

6. Pregnancy

The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

7. Lack of efficacy

The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.

8. Others

The investigator determined to terminate the study for other reasons.

Note: The specific reasons should be recorded on the CRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subjects

The investigator may discontinue a subject’s study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject’s participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 STUDY TREATMENT

This section indicates the treatment regimen of this study. See the latest package insert for details and handling of the drug.

8.1 Study Drug

Generic name: vonoprazan fumarate

Chemical name: 1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-
N-methylethylmethanamine monofumarate

8.1.1 Dose and Regimen

Vonoprazan 20 mg is to be orally taken once daily for 8 weeks.

Study drug will be administered at the same time as it was for the previous PPI.

8.1.2 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the CRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF according to Section 10.0.

Serious AEs (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of overdose, the subject should be treated symptomatically.

8.2 Prescription of the Study Drug

The investigator will prescribe the study drug to the subject fulfilling all inclusion criteria and not fulfilling any of exclusion criteria in accordance with the study procedure.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.3.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics and Medication History

Demographic information to be obtained will include date of birth (or age at the time of informed consent), sex, smoking status, drinking history, and consumption of caffeine-containing beverage.

Medication history information will be obtained regarding the drug name (trade name or generic name) of following relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 12 weeks prior to the administration of study drug.

- PPIs
- Hypnotics
- Antianxiety agents

9.1.3 Physical Examination Procedure

All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Weight, Height and Body Mass Index

Weight and height will be measured. Body Mass Index (BMI) will be calculated from the following formula by the sponsor.

Metric: $BMI = \text{weight (kg)} / \text{height (m)}^2$

Height is recorded in centimeters without decimal places. Weight is collected in kilograms with 1 decimal place. BMI should be report to 1 decimal place by rounding.

9.1.5 Documentation of Concomitant Drugs

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. At each study visit, subjects will be asked the status of use (drug name, route of administration, treatment period) of any medication other than the study drug (including vitamin compound, over-the-counter medication, and Chinese medicine) used from the time of start of administration of study drug to the end of the study.

9.1.6 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory or physical examination abnormalities noted at baseline examination, according the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.7 Questionnaire About Sleep

The subjects will answer a questionnaire (Appendix C) which consists of PSQI and questions about nocturnal awakenings according to the schedule of study procedures (Appendix A). The investigator will record the answers of subjects in the CRF.

PSQI is a self-rated questionnaire for sleep quality which consists of 18 items and was developed and standardized in the Department of Psychiatry, the University of Pittsburg.

9.1.8 Actigraph

After full instructions are provided an actigraph will be provided to the subject at the time of screening (VISIT 1), and actigraph recording will be started. The subjects will be instructed to wear it until the end of study (VISIT 6).

The subjects will be instructed to bring the actigraph at VISIT 2, 4 and 6. The investigator will collect the actigraph and will provide a new actigraph for the recording during the next 4 weeks.

The value of actigraph parameters will be analyzed by the central analysis organization. The results of analysis will be returned to the investigator, who is responsible for reviewing and filing these results.

The detailed procedures between sending actigraph to the organization and reporting the results of analysis to investigators will be defined in “Procedures for central evaluation for data of actigraph” prepared separately.

The parameters to be observed and evaluated are as follows.

[Parameters]

- 1) Changes in sleep efficiency, sleep latency, and number of nocturnal awakenings
Baseline/Start of Administration (mean value during 7 days* before VISIT 2)
Week 4 (mean value during 7 days* before VISIT 4)
End of Study (mean value during 7 days* before VISIT 6)

*The value of parameters for each sleep during 7 days before each visit will be analyzed and mean values will be calculated.

9.1.9 Heartburn and Regurgitation

Daytime and nighttime heartburn and regurgitation will be recorded respectively as reflux esophagitis related subjective symptoms. Questions for each subjective symptom are shown in Table 9.a.

According to the schedule of study procedures (Appendix A), subjects will answer a questions along with the questionnaire about sleep (Appendix C) during 7 days before each visit based on Table 9.b.

Table 9.a Question for Reflux Esophagitis Related Subjective Symptoms

| Reflux esophagitis related subjective symptoms | Question |
|--|--|
| Heartburn | Did the subject have heartburn caused by reflux esophagitis? If yes, how bad was it? |
| Regurgitation | Did the subject have acid reflux caused by reflux esophagitis? If yes, how bad it was it? |

Table 9.b Severity Classifications of Reflux Esophagitis Related Symptoms

| Reflux Esophagitis related subjective symptoms | Severity |
|--|------------|
| Heartburn | No symptom |
| Acid reflux | Mild |
| | Moderate |
| | Severe |

9.1.10 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Clinical laboratory tests are listed in Table 9.c.

Table 9.c Clinical Laboratory Tests

| Chemistry |
|-----------------------------|
| AST |
| ALT |
| Bilirubin (total bilirubin) |
| Creatinine |

The central laboratory will perform laboratory tests. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST $> 2 \times \text{ULN}$ or bilirubin (total bilirubin) level $> 2 \times \text{ULN}$, follow-up laboratory tests (at a minimum, serum ALP, ALT, AST, bilirubin (total bilirubin), GGT, and international normalized ratio [INR]) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Refer to Section 7.5 if ALT or AST or bilirubin (total bilirubin) $> 2 \times \text{ULN}$.

In addition, refer to Section 10.2.3 in relation to ALT or AST $> 3 \times \text{ULN}$ in conjunction with bilirubin (total bilirubin) $> 2 \times \text{ULN}$ when a decision is made that these abnormalities in the liver function test cannot reasonably be explained by other factors.

9.1.11 Pregnancy

When a subject or a partner of subject was found to be pregnant during the study period, the investigator should notify the monitoring staff of the sponsor. The investigator

should provide detailed information using the Follow-up Form for Pregnancy separately wherever possible.

9.1.12 Record of Subjects Who Are Withdrawn Before Start of Administration

A CRF shall be created for all subjects who sign the consent form and are then withdrawn before start of administration.

The following items are to be recorded on the CRF:

- Date of consent obtainment
- Date of birth (or the age at the time of informed consent)
- Sex
- Eligibility
- Reason for withdrawal

The primary reason for withdrawal before start of administration shall be recorded on the CRF according to the following classification:

- Did not meet inclusion criteria or did meet exclusion criteria
- Significant protocol deviation
- Lost to follow-up
- Voluntary withdrawal <specify reason>
- Study termination
- Pregnancy
- Others <specify the reason>

Subject identification numbers assigned to subjects withdrawn from the study before start of administration should not be reused.

9.2 Monitoring Subject Treatment Compliance

The investigator will confirm treatment compliance of study drug at every visit.

Treatment compliance will be classified into 4 categories, as follows: “took the drug properly ($\geq 90\%$),” “usually took the drug ($\geq 70\%$),” “took the drug more than half of the time ($\geq 50\%$),” and “took the drug less than half of the time ($< 50\%$).”

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A Schedule of Study Procedures. Assessments should be completed at the designated visit/time points.

9.3.1 Screening [VISIT 1]

After acquisition of informed consent, a physical examination and tests for screening will be performed. Eligibility of subjects will be determined in accordance with the inclusion and exclusion criteria as described in Section 7.0.

Tests and observations to be performed and endpoints to be assessed at the screening (VISIT 1) are shown below.

- Informed consent
- Demographics
- Physical examination
- Weight, height and BMI
- Concurrent medical conditions
- Actigraph (Provide device and instruction how to use)
- Clinical laboratory test

9.3.2 At the Baseline/Start of Administration [VISIT 2]

Tests and observations to be performed and endpoints to be assessed at the baseline/start of administration (VISIT 2) are shown below.

The investigator will explain the administration of study drug according to Section 6.1 toward the subjects fulfilling all inclusion criteria and not fulfilling any of exclusion criteria in Section 7.0

Refer to Section 9.1.12 for the recording of subjects who are withdrawn before the start of administration.

- Medication history
- Physical examination
- Concomitant medications
- Concurrent medical conditions

- Questionnaire about sleep
- Actigraph (mean during 7 days before VISIT 2)
- Heartburn and regurgitation

9.3.3 At Week 2 [VISIT 3]

Tests and observations to be performed and endpoints to be assessed at Week 2 (VISIT 3) are shown below.

- Physical examination
- Concomitant medications
- Clinical laboratory test
- Treatment compliance
- AEs

9.3.4 At Week 4 [VISIT 4]

Tests and observations to be performed and endpoints to be assessed at Week 4 (VISIT 4) are shown below.

- Physical examination
- Concomitant medications
- Questionnaire about sleep
- Actigraph (mean value during 7days before VISIT 4)
- Heartburn and regurgitation
- Clinical laboratory test
- Treatment compliance
- AEs

9.3.5 At Week 6 [VISIT 5]

Tests and observations to be performed and endpoints to be assessed at Week 6 (VISIT 5) are shown below.

- Physical examination
- Concomitant medications

- Clinical laboratory test
- Treatment compliance
- AEs

9.3.6 At the End of Study [VISIT 6] or at the Early Termination

A visit in 8 weeks after start of administration is defined as the last VISIT (VISIT 6). Tests and observations to be performed and endpoints to be assessed at the End of Study (VISIT 6) are shown below. At the Early Termination, following procedures will be performed as well.

- Physical examination
- Concomitant medications
- Questionnaire about sleep
- Actigraph (mean value during 7 days before VISIT 6) and receive of device
- Heartburn and regurgitation
- Clinical laboratory test
- Treatment compliance
- AEs

At the end of the study, the status all subjects administered the study drug will be recorded on the CRF.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product (including the study drug). It does not necessarily have to have a causal relationship with this pharmaceutical product (including the study drug).

An AE can therefore be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a pharmaceutical product (including the study drug) whether or not it is considered related to the pharmaceutical product (including the study drug).

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in the dose of the study drug, or concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnosis vs signs and symptoms:

Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal

value or findings are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions (a disease or symptom that is present at the start of study drug administration):

Pre-existing conditions are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of...").

If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of...").

Worsening of AEs:

If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of...").

Changes in intensity of AEs:

If the subject experiences changes in intensity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgery or interventions):

Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

Cases of overdose with any medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the CRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the CRF.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

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,
6. Is an important medical event that may expose the subject to danger even though the event is not immediately life-threatening or fatal does not result in hospitalization, or requires intervention to prevent items 1 through 5 above. In addition, event or synonym described in the Takeda Medically Significant Adverse Event List (Table 10.a) is included in this section.

* The term "life threatening" refers to an event in which the 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 Adverse Event List

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

10.1.4 Intensity of AEs

The different categories of intensity (severity) are characterized as follows.

| | |
|----------|---|
| 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 AEs

The relationship of each AE to the study drug will be assessed using the following categories.

| | |
|-------------|---|
| Related | An AE that follows a temporal sequence (including clinical course after discontinuation), or an AE in which there is at least a reasonable probability that a causal relationship to the study drug cannot be ruled out, although other factors such as underlying disease, complications, or concomitant drugs/treatment are also suspected. |
| Not related | An AE that does not follow a temporal sequence from administration of the study drug or comparative drug. Very likely due to other factors such as underlying disease, complications, or concomitant drugs/treatment. |

10.1.6 Relationship to Study Procedures

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.7 Start Date

The start date of AEs will be determined using the following criteria.

| AE | Start date |
|---|---|
| Signs, symptoms, diseases (diagnoses) | The date on which the first signs/symptoms were noted by the subject and/or the 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 comorbidities | The date on which the first worsening of diseases/symptoms was noted by the subject and/or the investigator. |
| Onset of a test abnormality after the start of study drug administration | The date on which a clinically significant laboratory abnormality was detected. |
| Worsening of a baseline test abnormality after the start of study drug administration | The date on which a clear increase/decrease in a laboratory parameter was clinically confirmed based on the time profile of the parameter. |

10.1.8 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died. The AE will be recorded as “ongoing” if the subject has not yet recovered by the end of the study.

10.1.9 Action Concerning Study Drug

Action concerning study drug will be classified or defined as shown below.

| | |
|------------------|---|
| Drug withdrawn | The study drug is discontinued because of an AE (including withdrawal by the subject at his/her discretion). If the study drug is continued after the study termination, the action should be “Dose not changed”. |
| Dose not changed | The dose was not changed after the onset of the AE. The study drug was discontinued, reduced, or increased because of another AE. The study drug was discontinued or reduced for a reason other than the AE, e.g., inadvertence of the subject. |

| | |
|----------------|---|
| Unknown | It has not been possible to determine what action has been taken because the 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 AE. |
| Dose reduced | The dose of the study drug was reduced because of the AE (including dose reduction by the subject at his/her discretion). |
| Washout | The study drug was suspended (i.e., interrupted) because of the AE (including suspension/interruption by the subject at his/her discretion), but resumed later. |

10.1.10 Outcome

Outcome of AEs 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 subject died from a cause other than the concerned AE 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 subject died from another cause before resolution of the concerned AE (recording of the date of death unnecessary) |
| Recovered with sequelae | Disability that disturbs daily life |
| Death | Direct relationship between death and the concerned AE “Direct relationship” means that the concerned AE was the cause of death, or the concerned AE was clearly responsible for death. Outcome of an AE which was not determined (judged, presumed) a direct cause of death observed in the same 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 AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time that the subject is first administered study drug (VISIT 2). Routine collection of AEs will continue until VISIT 6.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?”. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Intensity.
4. Investigator's opinion of the causal relationship between the event and administration of the study drug (related or not related),
5. Investigator's opinion of the causal relationship to study procedures, including the detail of the suspected procedure.
6. Action concerning study drug.
7. Outcome of event.
8. Seriousness.

10.2.2 Collection and Reporting of SAEs

When a SAE occurs through the AE collection period it should be reported according to the following procedure:

At the time of onset of a SAE or notification of the onset by the subject, the principal investigator shall report the SAE to the chief executive of the study site immediately, and the sponsor or the contract study organization (CRO) to whom the sponsor has entrusted responsibility shall notify the principal investigator of the study site.

A SAE should be report by the investigator to the sponsor within 1 business day of the SAE occurrence. The investigator should submit the detailed SAE Form to the sponsor (for contact information, refer 1.3) within 10 calendar days. .

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.

- A short description of the event and the reason for why the event is categorized as serious.
- Study title.
- Subject identification number.
- Study site's name.
- Investigator's name.
- Name of the study drug.
- Causality assessment..

The investigator shall report spontaneously reported SAEs that are collected even after the AE collection period to the sponsor.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST $> 3 \times \text{ULN}$ and bilirubin (total bilirubin) $> 2 \times \text{ULN}$ for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The principal investigator or the investigator must contact the monitoring staff for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.10 must also be performed.

10.2.4 Reporting of Additional Information Concerning AEs

If the sponsor requests provision of additional information concerning AEs for reporting to regulatory authorities, the principal investigator or the investigator shall confirm the

necessary additional information and enter in the electronic data capture (EDC) system or submit a report within the period specified by the sponsor.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form (copy) or provide other written documentation and submit it to the sponsor (for contact information, refer 1.3) within 1 working day. 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 ethics review committee upon request.

All SAEs should be followed up until resolution or permanent outcome of the event.

10.3.1 Reporting of SAEs, etc., to IECs, etc., and Regulatory Authorities

When the chief executive of study site receives a report of a SAE from the principal investigator, the chief executive of study site shall consult the Ethical Review Board, etc., and notify the study sites that are conducting the study through the sponsor or the CRO consigned by the sponsor.

When the principal investigator reported a SAE for which a causal relationship to the study (study drug or comparative drug) cannot be ruled out and is unexpected, the chief executive of the study site shall prepare a written report of the unexpected SAE containing the information reported by the principal investigator plus the information below, and submit the report to the Minister of Health, Labour and Welfare, and notify other study sites conducting the study. (The chief executive of the study site may report it to the Minister of Health, Labour and Welfare via the sponsor, and notify it to other study sites via the sponsor.)

- Actions taken for SAEs
(discontinuation of new enrollment, revision of informed consent form, re-consents from other 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 SAEs that are subject to emergency reporting to regulatory authorities, the investigators, and chief executives 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 risks/benefits of the study drug, continuation of study drug administration, or continuation of study. The study site shall submit copies of emergency report documents to the Ethics Review Committee, etc.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 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 HANDLING AND RECORDKEEPING

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. AEs, medical history, and concurrent conditions shall be coded using MedDRA. Drugs shall be translated using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs

Completed CRFs are required for each subject who signs informed consent.

The sponsor or its designee will provide study sites with access authorization to the EDC system. Before use of the EDC 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 prepared 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 principal investigator or its designee shall ensure the accuracy and completeness of the CRF, and provide an electronic signature on the relevant page of the CRF. The principal investigator bear 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, except for those recorded in the source documents:

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

The following data shall not be recorded on the CRF directly:

- Actigraph
- clinical laboratory test

When the principal investigator or the investigator makes a change or correction in the data entered on the CRF after fixation of clinical data base, a record (Data Clarification Form) of change or correction on the CRF provided by the sponsor 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 study. The sponsor or its designee shall have access to the medical records of the subjects and in-house records to ensure the accuracy of the CRF as necessary. The completed CRF shall be the property of the sponsor, and the investigator shall not disclose the information to a third party without written permission from the sponsor.

12.2 Timing of Data Entry into the EDC System

The sponsor or its designee shall request the principal investigator and investigator to promptly enter data into the EDC system following enrollment of the subject, each visit during study treatment, and completion/discontinuation of the study.

12.3 Storage and Disposal of Specimens, Information, etc.

The principal investigator or the chief executive of the study site shall store human-derived specimens and the following materials (information, etc.), 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 materials related to the information used in the study such as the subject ID number list, subjects' medical records, study work sheet, original signed and dated informed consent forms, an electronic copy of the EDC system with audit trails, and the drug management records. The principal investigator and the chief executive of the study site shall appropriately retain the specimens/information related to this study for at least 5 years from the date of reporting the end of the study 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. When disposing the specimens, information, etc., the chief executive of the study site shall dispose them anonymously.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

The person in charge of analysis shall prepare a statistical analysis plan (SAP) before the acquisition of the informed consent of the earliest subject, and issue the first edition. Detailed definition of endpoints and analysis methods should be specified in the SAP to deal with all the purposes of the study.

13.1.1 Analysis Sets

In this study, “Full Analysis Set” shall be established. The “Full Analysis Set” is defined as “subjects who are given at least one dose of the study drug”.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Using “Full Analysis Set”, major demographic and other baseline characteristics shall be aggregated.

13.1.3 Efficacy Analysis

Using “Full Analysis Set”, efficacy analysis will be performed.

[Primary endpoints]

- Changes in PSQI global score
[End of study(VISIT 6) – Baseline/Start of Administration (VISIT 2)]

[Analytical methods]

For primary endpoints, descriptive statistics, such as summary statistics [sample size, mean, standard deviation (SD), maximum, minimum and quantile] and 95% confidence interval of the mean are calculated. Statistically significance of the changes is assessed using paired t-test.

[Secondary endpoints]

- Changes in PSQI global score
[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]

[Analytical methods]

Descriptive statistics and 95% confidence interval of the mean are calculated.

- Percentage of subjects with PSQI global score <6.0 at Week 4 (VISIT 4) and the end of study (VISIT 6)

[Analytical methods]

Percentage of subjects with PSQI global score <6.0 at Week 4 and the end of study are calculated.

- Changes in 6 component scores of PSQI (Sleep quality, Sleep latency, Sleep duration, Habitual sleep efficiency, Sleep disturbances, Daytime dysfunction) and number of nocturnal awakenings (assessed by questionnaire)

[Week 4 (VISIT 4) – Baseline/Start of Administration (VISIT 2)]

[End of Study (VISIT 6) – Baseline/Start of Administration (VISIT 2)]

[Analytical methods]

Descriptive statistics and 95% confidence interval of the mean are calculated.

- Changes in actigraph-measured sleep efficiency, sleep latency, and number of nocturnal awakenings

[Week 4 (mean value during 7 days before VISIT 4) – Baseline/Start of Administration (mean value during 7 days before VISIT 2)]

[End of Study (mean value during 7 days before VISIT 6) – Baseline/Start of Administration (mean value during 7 days before VISIT 2)]

[Analytical methods]

Descriptive statistics and 95% confidence interval of the mean are calculated.

13.1.4 Safety Analysis

[Secondary endpoint]

- Incidence of AEs (TEAEs)

[Analytical methods]

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A treatment-emergent AE (TEAE) is defined as any AE occurring after the start of study or control treatment for the healing phase. For TEAEs in the maintenance phase, the analyses listed below shall be performed for each treatment group. TEAEs shall be reported using MedDRA terminology and summarized using the Preferred Term (PT) and System Organ Class (SOC) of the MedDRA.

- Aggregation of frequencies of all TEAEs in the maintenance phase
- Aggregation of frequencies of TEAEs related to the study drug
- Aggregation of frequencies of all TEAEs by severity
- Aggregation of frequencies of TEAEs related to the study drug
- Aggregation of frequencies of TEAEs leading to discontinuation of study treatment
- Aggregation of frequencies of serious TEAEs

13.1.5 Other Analysis

- Changes in heartburn and regurgitation (daytime and nighttime)

[Analytical methods]

Using “Full Analysis Set”, percentage of subjects without each symptom at Week 4 and the end of study among subjects who had symptoms are calculated.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

25 subjects

<Rationale for the number of planned subjects>

In the clinical study assessed effect of esomeprazole on sleep disturbance caused by gastroesophageal reflux disease, mean (SD) changes in PSQI global score from baseline at 4 weeks of treatment with esomeprazole 40 mg, 20 mg, and placebo were -3.5 (3.6), -3.8 (3.8), and -2.0 (3.7), respectively⁴⁾. In the similar clinical study with dexlansoprazole, changes in PSQI global score from baseline at 4 weeks of treatment with dexlansoprazole 30 mg, and placebo were -2.70 (3.08), and -1.35 (3.23), respectively⁵⁾. These results suggest that effect sizes during treatment with PPI and

placebo are 0.87-1.00 and 0.42-0.54, respectively.

Although subjects for the present study is different from these studies which excluded subjects who received treatment with PPI in a certain period before randomization, we can assume that effect size of the present study will be less than PPI and greater than placebo. So we assumed effect size of changes in PSQI global score from baseline at 8 weeks of treatment will be 0.75.

21 subjects are required as number of subjects for evaluation of primary endpoint to obtain 90% of power using estimated effect size. Considering drop out of certain subject, 25 subjects are required as enrolled subject.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

Detailed procedures for monitoring shall be described in a procedure manual prepared separately.

14.2 Deviation from the Ethical Guideline for Clinical Research and the Protocol

The investigator shall record all deviations from the Ethical Guideline for Clinical Research and the protocol.

If any deviation is found, the principal investigator shall promptly notify the chief executive of the study site 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 ethics review committee.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The sponsor or the designee shall perform audit at the study site as necessary. 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 study. In addition, this study 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 study-related source documents.

15.0 ETHICAL ASPECT OF THE STUDY

This study shall be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the Ethical Guideline for Clinical Research. Each investigator will conduct the study according to regulatory requirements and in accordance with “Responsibilities of the Investigator” that are listed in Appendix B.

15.1 IEC Approval

The IEC, etc., shall be constituted in accordance with the regulations.

The sponsor or its designee should obtain the document listing the name and title of each committee member. When a committee member directly participates in this study, the document describing that he/she is not participating in deliberation or voting for the study will be obtained.

The sponsor or the designee shall provide related documents for review and approval of the protocol to the Ethical Review Board, etc. In addition to the protocol, a copy of the informed consent form and information sheet, written materials related to subject recruitment, advertisement, and other documents required by regulations, when necessary, shall be submitted to the central committee or a study site committee such as the Ethics Review Committee to obtain approval. The sponsor or the designee shall obtain records of approval by the Ethical Review Board, etc., for the protocol and the informed consent form and information sheet before the start of the protocol therapy. The records of approval by the Ethical Review Board, etc., shall include the study title, protocol number, preparation / revision date of the protocol, and version number and approval date of other reviewed documents (Example: informed consent and information sheet). The sponsor shall notify the study site and the investigator after confirming the validity of the regulatory documents of the study site. Protocol procedures such as obtainment of consent shall not be started until the study site and investigator receive notification.

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

sponsor or its designee shall obtain written approval from a study site committee such as the Ethics Review Committee related to the above mentioned items and all related materials.

15.2 Conflict of Interests

This study shall be conducted with the support of the sponsor.

Prior to the conduction of this study, the investigators involved in this study shall ensure appropriate management of any conflicts of interest (COI) in the conduct of the study in accordance with the rules of the study site.¹⁶⁾⁻²⁰⁾

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

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

The informed consent and information sheet form shall contain specific requirements of the Declaration of Helsinki, Ethical Guideline for Clinical Research and all applicable laws and regulations. The informed consent form and information sheet shall specify the use of personal information and medical information of subjects in this study (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 study, its objectives, and potential risks and benefits. The informed consent form will detail the requirements of the participant and the fact that 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 subject information sheet by the committee such as ethics review committee. 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 subjects. The 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 ethics review committee.

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

Once signed, the original informed consent form shall be retained by the investigator. The investigator shall record the date that the potential 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 subject.

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

15.4 Personal Information of Subjects

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

For verification of the conduct of the study in compliance with this protocol and the Ethical Guideline for Clinical Research, the sponsor shall require the principal investigator to provide the study sponsor's designee, representatives of regulatory authorities, designated auditors, and committees such as the Ethical Review Board direct access to subjects' original medical records (source data or documents), including laboratory test results, ECG results, admission and discharge records during a subject's study participation, and autopsy reports. The investigator shall obtain specific authorization of the subject as part of the informed consent process for access to subject's original medical records by study sponsor's designee and representatives of regulatory authorities (see Section 15.3).

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

15.5 Consultation for Subjects or Persons Related to the Study

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

15.6 Financial Burden or Reward to Subjects

Of the expenses for this study, the sponsor shall pay for medical treatment not covered by health insurance and examinations necessary for the study as study expenses. The 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 study to the subjects at each visit from the study funds. Details of the financial burden on the subjects and rewards shall be described in the informed consent form and information sheet.

15.7 Benefits and Inconveniences to Subjects

15.7.1 Benefits to Subjects

The subjects will obtain detailed information on the status of his or her EE through participation in this study.

15.7.2 Inconveniences to Subjects

Participation in this study may increase burden on the subjects due to increased frequencies of visits and examinations, as compared with routine medical practice.

15.8 Attribution of Study Results and Access Rights

15.8.1 Attribution of Study Results

The study results and data obtained from this study shall belong to the sponsor. In addition, secondary use (meta-analysis, etc.) of the data obtained in this study 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 Study Registration Policy

15.9.1 Reporting of Results, Publication and Disclosure

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

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

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

The sponsor shall report to the chief executive of the study site when final publication of the study results has been made.

15.9.2 Clinical Study Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC) before start of study. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing.

15.9.3 Clinical Study Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and JAPIC, as required by applicable laws and/or regulations.

15.10 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

| | Screening | Baseline/Start of Administration | Week 2 | Week 4 | Week 6 | End of Study |
|---|-----------|----------------------------------|---------|---------|---------|----------------------------------|
| Visit timing | -1W | 0W | 2W | 4W | 6W | 8W/ Withdrawal ^(d) |
| Allowable range (Day) ^(a) | -14~7 | 1 | 11~17 | 25~31 | 39~45 | 53~59 |
| VISIT Number | VISIT 1 | VISIT 2 | VISIT 3 | VISIT 4 | VISIT 5 | VISIT 6 |
| Informed consent procedure ^(b) | × | | | | | |
| Inclusion/Exclusion criteria | × | × | | | | |
| Demographics | × | | | | | |
| Medication history | | × | | | | |
| Physical examination | × | × | × | × | × | × |
| Weight, height and BMI | × | | | | | |
| Concomitant drugs | | × | × | × | × | × |
| Concurrent medical conditions | × | × | | | | |
| Questionnaire about sleep | | × | | × | | × |
| Actigraph | | × ^(c) | | × | | × |
| Heartburn/ regurgitation | | × | | × | | × |
| Clinical laboratory test | × | | × | × | × | × |
| Prescription of study drug | | × | × | × | × | |
| Treatment compliance | | | × | × | × | × |
| AE monitoring | | | × | × | × | × |

- (a) The starting day of study treatment (day of the first dose) will be designated as Day 1.
- (b) Informed consent will be obtained, prior to all study procedures.
- (c) An actigraph will be lent to the subject and the subject will be instructed on how to wear and evaluate an actigraph on at the screening (VISIT 1).
- (d) At 8 weeks after the start of treatment with study drug, which is the final visit, tests/observations/evaluations, will be performed. When subjects are withdrawn from the clinical study, all tests/observations/evaluations will be performed within 7 days after the day of the last administration of study drug as possible (the next day after last administration will be designated as first day).

Appendix B Responsibilities of the principal investigator

1. To appropriately conduct the study in compliance with this protocol and the Ethical Guideline for Clinical Research and with the highest respect for human rights, safety, and welfare of subjects.
2. To prepare a list of any other investigators and/or study collaborators when certain important study-related activities are divided by investigators and/or study collaborators, and submit the list to the sponsor as required.
3. To prepare the informed consent form and revise it as necessary.
4. To check the contents of the study contract.
5. To provide sufficient information on the protocol, drug and duties of each personnel to investigators and study collaborators, and give guidance and supervision.
6. To select subjects who satisfy the inclusion criteria, give explanation using written information, and obtain consent in writing.
7. To be responsible for all medical judgments related to the study.
8. Corresponding to request from the chief executive of the study site, to report the latest progress status at least once a year to the chief executive of the study site.
9. To ensure that the most updated status is confirmed and comprehended regarding the COI of the investigators participating in the study according to the procedure defined by the study site.
10. To ensure, together with the chief executive of the study site, that sufficient medical care is provided to subjects for all study-related clinically problematic AEs throughout the period of subjects' study participation and thereafter.
11. When a subject is treated at another medical institution or department, to inform the acting physician at the medical institution or department in writing of the subject's study participation and study completion/discontinuation after obtaining the subject's consent, and prepare a record.
12. When emergency reporting of SAEs, etc., is required, to immediately report it in writing to the chief executive of the study site and the sponsor.
13. To ensure that the CRFs are accurate and complete, electronically sign, and submit them to the sponsor.
14. To verify any entries on the CRFs made by the investigator or transcribed by the collaborator from source documents, electronically sign, and submit them to the sponsor.

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15. To discuss a revision of the protocol, etc., when proposed by the sponsor.
16. To report the study completion in writing to the chief executive of the study site.
17. To receive continuing education and training for conducting the study properly including Ethical Guideline for Clinical Research and GCP during the study period (at least once a year is recommended).

Appendix C Questionnaire about sleep and symptoms

Instructions:

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

Please answer all questions.

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

USUAL BED TIME

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

NUMBER OF MINUTES

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

USUAL GETTING UP TIME

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

HOURS OF SLEEP PER NIGHT

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

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

- (a) Cannot get to sleep within 30 minutes

Not during the
past month

Less than once
a week

Once or twice
a week

Three or more
times a week

- (b) Wake up in the middle of the night or early morning

Not during the
past month

Less than once
a week

Once or twice
a week

Three or more
times a week

- (c) Have to get up to use the bathroom

Not during the
past month

Less than once
a week

Once or twice
a week

Three or more
times a week

- (d) Cannot breathe comfortably

Not during the
past month

Less than once
a week

Once or twice
a week

Three or more
times a week

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(e) Cough or snore loudly

| Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|------------------------------|--------------------------|-------------------------|-------------------------------|
| _____ | _____ | _____ | _____ |

(f) Feel too cold

| Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|------------------------------|--------------------------|-------------------------|-------------------------------|
| _____ | _____ | _____ | _____ |

(g) Feel too hot

| Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|------------------------------|--------------------------|-------------------------|-------------------------------|
| _____ | _____ | _____ | _____ |

(h) Had bad dreams

| Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|------------------------------|--------------------------|-------------------------|-------------------------------|
| _____ | _____ | _____ | _____ |

(i) Have pain

| Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|------------------------------|--------------------------|-------------------------|-------------------------------|
| _____ | _____ | _____ | _____ |

(j) Other reason(s), please describe

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

| Not during the past month | Less than once a week | Once or twice a week | Three or more times a week |
|------------------------------|--------------------------|-------------------------|-------------------------------|
| _____ | _____ | _____ | _____ |

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

| | |
|-------------|-------|
| Very good | _____ |
| Fairly good | _____ |
| Fairly bad | _____ |
| Very bad | _____ |

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

| | | | |
|----------------|----------------|---------------|---------------|
| Not during the | Less than once | Once or twice | Three or more |
| past month | a week | a week | times a week |
| _____ | _____ | _____ | _____ |

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

| | | | |
|----------------|----------------|---------------|---------------|
| Not during the | Less than once | Once or twice | Three or more |
| past month | a week | a week | times a week |
| _____ | _____ | _____ | _____ |

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

| | |
|----------------------------|-------|
| No problem at all | _____ |
| Only a very slight problem | _____ |
| Somewhat of a problem | _____ |
| A very big problem | _____ |

Instructions:

The following questions ask you condition of your sleep during the past week.

10. During the past week, did you wake up in the middle of the night?

| | |
|-----------------|----------------|
| No | Yes |
| (this is end of | (please answer |
| this question) | next question) |
| _____ | _____ |

11. During the past week, how many times did you wake up in the middle of the night in the most frequent night?

_____ times

Instructions:

The following questions ask you condition of symptoms during the past week.

12. During the past week, did you have heartburn caused by reflux esophagitis during daytime? If yes, how bad was it?

| | |
|-----------|-------|
| No | _____ |
| Yes: Mild | _____ |
| Moderate | _____ |
| Severe | _____ |

13. During the past week, did you have regurgitation caused by reflux esophagitis during daytime? If yes, how bad was it?

| | |
|-----------|-------|
| No | _____ |
| Yes: Mild | _____ |
| Moderate | _____ |
| Severe | _____ |

14. During the past week, did you have heartburn caused by reflux esophagitis during nighttime? If yes, how bad was it?

| | |
|-----------|-------|
| No | _____ |
| Yes: Mild | _____ |
| Moderate | _____ |
| Severe | _____ |

15. During the past week, did you have regurgitation caused by reflux esophagitis during nighttime? If yes, how bad was it?

| | |
|-----------|-------|
| No | _____ |
| Yes: Mild | _____ |
| Moderate | _____ |
| Severe | _____ |