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

NCT Number: NCT03116841

Statistical analysis plan Approve Date: 15-Feb-2018

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

Vonoprazan study of investigating the effect on sleep disturbance associated with reflux esophagitis- exploratory evaluation

(Protocol number: Vonoprazan-4006)

Statistical Analysis Plan

(Ver.2.0: 15 Feb 2018)

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Contents

1. DEFINITIONS of TERMS

- MedDRA: Medical Dictionary for Regulatory Activities
- PSQI: Pittsburgh Sleep Quality Index
- TEAE: Treatment-emergent adverse event (Adverse event or complication which occurs after the first administration)

2. TIME WINDOW

For each assessment, evaluable data will be selected according to the following table. When there are two or more evaluable data in the same time window, the one with the nearest date to the reference date will be selected, and if the differences from the reference date are the same, the later one will be adopted. For discontinued subjects, data will be evaluated based on days after the first administration and days after the end of treatment.

(1) PSQI, Actigraph, Heartburn and Regurgitation

Assessment time point	Reference Date	Time window	
		Days after the first administration	Days after the end of treatment
At the start of the treatment	Day 1	Day-14 - Day1	
Week 4	Day 28	Day2 - Day35	<= Day7
At the end of the study	Day 56	Day2 - Day63	<= Day7

(2) Laboratory Test

Assessment time point	Reference Date	Time window	
		Days after the first administration	Days after the end of treatment
At the screening	Day -7	Day-14 - Day -1	
Week 2	Day 14	Day 1 - Day 21	<= Day 7
Week 4	Day 28	Day 22 - Day 35	<= Day 7
Week 6	Day 42	Day 36 - Day 49	<= Day 7
At the end of the study	Day 56	Day 2 - Day 63	<= Day 7

For reference date and days after the first administration, the first day of administration will be referred to as Day 1, and the day before the first day of the administration as Day -1.

For days after the end of treatment, the day after the last administration will be referred to as Day 1.

3. ANALYSIS SET

- Full Analysis Set

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

4. CONSIDERATIONS for ANALYSIS

- Confidence coefficient

  95% (two-sided)

- Display digit

  [Mean, Confidence Intervals (CIs), Quartiles]

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

  [Standard Deviation]

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

  [Minimum and Maximum Values]

  Display the data at the significant digits.

  [Proportion, Percentage]

  Round to one decimal place.

5. OTHER DATA HANDLING

[Study Drug]

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

  Date of last dose – date of first dose +1

[PSQI]

- Global PSQI Score, 7 component scores of PSQI

  Scores will be derived from PSQI according to the rule described in the reference 1).

[Change in endpoints]

Changes in endpoints are the differences from the start of the treatment or screening to each time point.

6. SUBJECTS

6.1. Subject Disposition

6.1.1. Study Information

Analysis set: All subjects who are obtained informed consent

Analysis Items: The earliest date of informed consent

The latest date of the last date of administration

Version of MedDRA

Version of SAS

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

(1) The above items will be listed.
If the last date of administration is missing, the last visit date will be substituted.

6.1.2. Eligibility of Subjects

Analysis set: All subjects who are obtained informed consent

Analysis Items: Eligibility to enter the treatment period in the study

[Yes, No (and the reason)]

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

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

6.1.3. Subject Disposition

Analysis set: Full Analysis Set

Analysis Items: Status at the end of study

[Complete, Incomplete (and the reason)]

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

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

6.1.4. Protocol Deviations and Analysis Datasets

6.1.4.1. Protocol Deviations

Analysis set: All subjects who enter the treatment period

Analysis Items: Protocol Deviations

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

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

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

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

6.1.4.2. Datasets Analyzed

Analysis set: All subjects who enter the treatment period

Analysis Items: Full Analysis Set [Inclusion, Exclusion (and the reason)]

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

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

7. GRAPH

7.1. Laboratory Test

Analysis set: Full Analysis Set

Analysis items: Blood serum chemistry (AST, ALT, Total Bilirubin, Creatinine)

Time point: Screening, Week 2, Week 4, Week 6, End of study

Analysis methods: Case plots will be made for observed value and change from screening.

7.2. 7 Components of PSQI

Analysis set: Full Analysis Set

Analysis items: 7 component scores of PSQI

Subjective sleep quality

Sleep latency

Sleep duration

Sleep efficiency

Sleep disturbance

Use of sleep medication

Daytime dysfunction

Time Point: Start of the treatment period, Week 4, End of study

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

(1) For each component score, case plots will be made for observed value and change from the start of the treatment.

(2) For global PSQI score, case plots will be made for observed value and change from the start of the treatment.

7.3. Actigraph

Analysis set: Full Analysis Set

Analysis items: Sleep efficiency, Sleep latency, Number of Nocturnal Awakenings (Actigraph)

Time Point: Start of the treatment period, Week 4, End of study

Analysis Methods: Case plots will be made for observed value and change from the start of the treatment period.

7.4. Heartburn and Regurgitation

Analysis set: Full Analysis Set

Analysis items: Heartburn(daytime), Heartburn(nighttime), Regurgitation(daytime), Regurgitation(nighttime)

Time Point: Start of the treatment period, Week 4, End of study

Analysis Methods: For intensity of the above endpoints, case plots will be made for observed value.

8. LISTING

The following data will be listed for the subjects in Full Analysis Set.

- Demographic data
- Concurrent medical conditions
- Medication history
- Concomitant medications
- Drug compliance
- Discontinued subjects
- PSQI
- Intensity of heartburn and regurgitation
- Actigraph
- Laboratory test
- TEAE

9. CONSIDERATIONS on STATISTICAL ANALYSIS

9.1. Adjustments for Covariates

Adjustments for covariates will not be performed.

9.2. Handling of Dropouts or Missing Data

Any imputation for missing data will not be performed.

9.3. Criteria for Interim Analysis and Early Discontinuation

No interim analyses will be performed.

9.4. Multicenter Studies

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

9.5. Multiple Comparisons/Multiplicity

No statistical adjustments will be made for multiple comparisons.

9.6. Examination of Subgroups

No subgroup analyses will be performed.

10. REFERENCES

Treatment and Practice Guideline for Sleep Disorder. 2nd ed., Edited by Makoto Uchiyama. JIHO. 2012; 246-247

11. REVISION HISTORY

Ver.	Date	Author	Revised Content	Reason for Revision
1.0	12 APR 2017	PPD	-	
2.0	15 FEB 2018		Remove the analysis plans to calculate descriptive statistics such as summary statistics, tabulation by category, 95% CI and statistical test, and add the plans to make graphs and listings.	To amend whole analysis plan because of a deficit of sample size (Although 25 subjects were planned, only 4 subjects were enrolled into the study.)