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

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information or company confidential information. This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator’s curriculum vitae).

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)

Sponsor: Takeda Pharmaceutical Company Limited

Authorizer: Takeda Pharmaceutical Company Limited

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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**

<table>
<thead>
<tr>
<th>Assessment time point</th>
<th>Reference Date</th>
<th>Time window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Days after the first administration</td>
</tr>
<tr>
<td>At the start of the treatment</td>
<td>Day 1</td>
<td>Day-14 - Day1</td>
</tr>
<tr>
<td>Week 4</td>
<td>Day 28</td>
<td>Day2 - Day35 &lt;= Day7</td>
</tr>
<tr>
<td>At the end of the study</td>
<td>Day 56</td>
<td>Day2 - Day63 &lt;= Day7</td>
</tr>
</tbody>
</table>

(2) **Laboratory Test**

<table>
<thead>
<tr>
<th>Assessment time point</th>
<th>Reference Date</th>
<th>Time window</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Days after the first administration</td>
</tr>
<tr>
<td>At the screening</td>
<td>Day -7</td>
<td>Day-14 - Day -1</td>
</tr>
<tr>
<td>Week 2</td>
<td>Day 14</td>
<td>Day 1 - Day 21 &lt;= Day 7</td>
</tr>
<tr>
<td>Week 4</td>
<td>Day 28</td>
<td>Day 22 - Day 35 &lt;= Day 7</td>
</tr>
<tr>
<td>Week 6</td>
<td>Day 42</td>
<td>Day 36 - Day 49 &lt;= Day 7</td>
</tr>
<tr>
<td>At the end of the study</td>
<td>Day 56</td>
<td>Day 2 - Day 63 &lt;= Day 7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Ver.</th>
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<td>1.0</td>
<td>12 APR 2017</td>
<td>PPD</td>
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<td>2.0</td>
<td>15 FEB 2018</td>
<td></td>
<td>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.</td>
<td>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.)</td>
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