Title: Vonoprazan study in patients with erosive esophagitis to evaluate long-term safety: A study to evaluate the safety of long-term administration of vonoprazan in maintenance treatment in patients with erosive esophagitis (EE)

NCT Number: NCT02679508

Statistical analysis plan Approve Date: 01-Feb-2023

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

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

Evaluation of Long-term Safety of Maintenance Treatment with Vonoprazan in Patients with Erosive Esophagitis

(Vonoprazan -4003)

Statistical Analysis Plan

(Ver. 7.0 Date of preparation: 2023/2/1)

Sponsor: Takeda Pharmaceutical Company Limited.

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1. LIST OF TERMS AND ABBREVIATIONS

- TEAE:Treatment-emergent adverse event
- Summary statistics: A general term for the number of subjects, mean, standard deviation, maximum, minimum, and quartiles.
- Treatment groups: Two treatment groups, the vonoprazan group and the lansoprazole group
- Subjects who entered the maintenance phase: Subjects eligible for enrollment in the maintenance phase

2. Handling of TIME WINDOW

For each test/observation/assessment item, evaluable data should be handled in the following manner.

If there are multiple evaluable data at the same evaluation time point, the date of examination/observation/evaluation closest to the reference date will be adopted. If the difference from the reference date is the same, the later data will be adopted.

Endoscopy (evaluation up to the evaluation time point)

Timepoint	Reference date	Acceptable range	
		Days after administration	Days after the end of treatment
At the start of treatment period	Days after administration: 1	-8~1	
Treatment Period Week 4	Days after administration: 29	2~42	<15
Treatment Period Week 8	Days after administration: 57	2~70	<15
Maintenance Period Week 48	Days after administration: 337	2~421	<15
Maintenance Period Week 108	Days after administration: 757	2~841	<15
Maintenance Period Week 156	Days after administration: 1093	2~1177	<15
Maintenance Period Week 204	Days after administration: 1429	2~1513	<15
Maintenance Period Week 260	Days after administration: 1821	2~1905	<15

- For reference date and number of days after administration in the treatment period, the day before administration of study product or the control drug in the treatment period is Day -1 and the day of administration of study product or the control drug in the treatment period is Day 1.

- For reference date and number of days after administration in the maintenance phase, the day of administration of study product or control drug in the maintenance phase is defined as 1 day.
- For the treatment period, 1 day is defined as the number of days after the last dose of study product or the comparator. For the maintenance phase, Day 1 is defined as the day after the end of administration of study product for the maintenance phase or the control drug.
- Data after administration of study product or the comparator in the maintenance phase will be handled as data in the maintenance phase, not as data in the treatment phase, even if the allowable range for Week 4 or 8 of the treatment phase is met.

Endoscopy (evaluation at each time point)

Timepoint	Reference date	Acceptable range	
		Days after administration	Days after the end of treatment
At the start of treatment period	Days after administration: 1	-8~1	
Treatment Period Week 4	Days after administration: 29	15~42	<15
Treatment Period Week 8	Days after administration: 57	43~70	<15
Maintenance Period Week 48	Days after administration: 337	253~421	<15
Maintenance Period Week 108	Days after administration: 757	673~841	<15
Maintenance Period Week 156	Days after administration: 1093	1009~1177	<15
Maintenance Period Week 204	Days after administration: 1429	1345~1513	<15
Maintenance Period Week 260	Days after administration: 1821	1737~1905	<15

- For reference date and number of days after administration in the treatment period, the day before administration of study product or the control drug in the treatment period is Day -1 and the day of administration of study product or the control drug in the treatment period is Day 1.
- For reference date and number of days after administration in the maintenance phase, the day of administration of study product or control drug in the maintenance phase is defined as 1 day.

- For the treatment period, 1 day is defined as the number of days after the last dose of study product or the comparator. For the maintenance phase, Day 1 is defined as the day after the end of administration of study product for the maintenance phase or the control drug.
- Data after administration of study product or the comparator in the maintenance phase will be handled as data in the maintenance phase, not as data in the treatment phase, even if the allowable range for Week 4 or 8 of the treatment phase is met.

Histopathological Examination of Gastric Mucosa and Histological Evaluation of Gastritis (Up to Evaluation Time Points)

Timepoint	Reference date	Acceptable range	
		Days after administration	Days after the end of treatment
At the start of treatment period	Days after administration: 1	-8~1	
Maintenance Period Week 48	Days after administration: 337	2~421	<15
Maintenance Period Week 108	Days after administration: 757	2~841	<15
Maintenance Period Week 156	Days after administration: 1093	2~1177	<15
Maintenance Period Week 204	Days after administration: 1429	2~1513	<15
Maintenance Period Week 260	Days after administration: 1821	2~1905	<15

- For reference date and number of days after administration in the treatment period, the day before administration of study product or the control drug in the treatment period is Day -1 and the day of administration of study product or the control drug in the treatment period is Day 1.
- For reference date and number of days after administration in the maintenance phase, the day of administration of investigational product in the maintenance phase is defined as 1 day.
- In the maintenance phase, 1 day is defined as the number of days after the last dose of study product or the comparator.

Histopathological Examination of Gastric Mucosa and Histological Evaluation of Gastritis at Each Assessment Point

Timepoint	Reference date	Acceptable range	
		Days after administration	Days after the end of

			treatment
At the start of treatment period	Days after administration: 1	-8~1	
Maintenance Period Week 48	Days after administration: 337	253~421	<15
Maintenance Period Week 108	Days after administration: 757	673~841	<15
Maintenance Period Week 156	Days after administration: 1093	1009~1177	<15
Maintenance Period Week 204	Days after administration: 1429	1345~1513	<15
Maintenance Period Week 260	Days after administration: 1821	1737~1905	<15

- For reference date and number of days after administration in the treatment period, the day before administration of study product or the control drug in the treatment period is Day -1 and the day of administration of study product or the control drug in the treatment period is Day 1.
- For reference date and number of days after administration in the maintenance phase, the day of administration of study product or control drug in the maintenance phase is defined as 1 day.
- For the treatment period, 1 day is defined as the number of days after the last dose of study product or the comparator. For the maintenance phase, Day 1 is defined as the day after the end of administration of study product for the maintenance phase or the control drug.

Laboratory test values, vital signs, and serum gastrin level

Timepoint	Reference date	Acceptable range	
		Days after administration	Days after the end of treatment
At the start of treatment period	Days after administration: 1	-8~1	
Treatment Period Week 4	Days after administration: 29	16~43	<15
Treatment Period Week 8	Days after administration: 57	44~71	<15
Maintenance Period Week 12	Days after administration: 85	44~127	<15
Maintenance Period Week	Days after administration:	128~211	<15

24	169		
Maintenance Period Week 36	Days after administration: 253	212~295	<15
Maintenance Period Week 48	Days after administration: 337	296~379	<15
Maintenance Period Week 60	Days after administration: 421	380~463	<15
Maintenance Period Week 72	Days after administration: 505	464~547	<15
Maintenance Period Week 84	Days after administration: 589	548~631	<15
Maintenance Period Week 96	Days after administration: 673	632~715	<15
Maintenance Period Week 108	Days after administration: 757	716~799	<15
Maintenance Period Week 132	Days after administration: 925	884~967	<15
Maintenance Period Week 156	Days after administration: 1093	1052~1135	<15
Maintenance Period Week 180	Days after administration: 1261	1220~1303	<15
Maintenance Period Week 204	Days after administration: 1429	1388~1471	<15
Maintenance Period Week 228	Days after administration: 1597	1556~1639	<15
Maintenance Period Week 260	Days after administration: 1821	1780~1863	<15

- For reference date and number of days after administration in the treatment period, the day before administration of study product or the control drug in the treatment period is Day -1 and the day of administration of study product or the control drug in the treatment period is Day 1.
- For reference date and number of days after administration in the maintenance phase, the day of administration of study product or control drug in the maintenance phase is defined as 1 day.
- For the treatment period, 1 day is defined as the number of days after the last dose of study product or the comparator. For the maintenance phase, Day 1 is defined as the day after the end of administration of study product for the maintenance phase or the control drug.
- Data after administration of study product or the comparator in the maintenance phase will be handled as data in

the maintenance phase, not as data in the treatment phase, even if the allowable range for Week 4 or 8 of the treatment phase is met.

Serum pepsinogen I and II levels, chromogranin A levels

Timepoint	Reference date	Acceptable range	
		Days after administration	Days after the end of treatment
At the start of treatment period	Days after administration: 1	-8~1	
Treatment Period Week 4	Days after administration: 29	16~43	<15
Treatment Period Week 8	Days after administration: 57	44~71	<15
Maintenance Period Week 24	Days after administration: 169	128~211	<15
Maintenance Period Week 48	Days after administration: 337	296~379	<15
Maintenance Period Week 108	Days after administration: 757	716~799	<15
Maintenance Period Week 156	Days after administration: 1093	1052~1135	<15
Maintenance Period Week 204	Days after administration: 1429	1388~1471	<15
Maintenance Period Week 260	Days after administration: 1821	1780~1863	<15

- For reference date and number of days after administration in the treatment period, the day before administration of study product or the control drug in the treatment period is Day -1 and the day of administration of study product or the control drug in the treatment period is Day 1.
- For reference date and number of days after administration in the maintenance phase, the day of administration of study product or control drug in the maintenance phase is defined as 1 day.
- For the treatment period, 1 day is defined as the number of days after the last dose of study product or the comparator. For the maintenance phase, Day 1 is defined as the day after the end of administration of study product for the maintenance phase or the control drug.
- Data after administration of study product or the comparator in the maintenance phase will be handled as data in the maintenance phase, not as data in the treatment phase, even if the allowable range for Week 4 or 8 of the treatment phase is met.

3. Analysis Sets

- Full Analysis Set of the Treatment Period

  Subjects who were randomized and received study product for the treatment period or the control drug at least once

- Full Analysis Set of the maintenance phase

  Subjects who were randomized and received at least one dose of study product for the maintenance phase or the control drug

- Safety Analysis Set of the Treatment Period

  Subjects who received at least one dose of study product or control drug for the treatment period

- Safety Analysis Set of the maintenance phase

  Subjects who received study product for the maintenance phase or the control drug at least once

4. Analysis Considerations

- confidence coefficient

  The confidence coefficient will be two-sided 95%.

- Number of digits to be displayed

[Mean, confidence interval, and quartiles]

The data will be displayed to the next lower digit by rounding off the number of significant digits.

[Standard deviation]

The data will be displayed to the second decimal place by rounding off the data to the 3rd decimal place.

[Min, Max]

Display up to the significant digit of the data.

[Percentage]

Round the second decimal place and display to the first decimal place.

5. Other Handling

[Handling of study product and control drugs]

- Duration of treatment with study product or control drug in the treatment period

  The day of the last dose in the treatment period − the day of the first dose in the treatment period + 1

- Duration of treatment with study product or control drug in the maintenance phase

  Date of the last dose in the maintenance phase - date of the first dose in the maintenance phase + 1

[Endoscopy]

- Recurrence rate of reflux esophagitis based on endoscopic findings (at each evaluation time point and evaluation up to the evaluation time point)

  (Number of subjects with Grade A to D of the severity classification endoscopically assessed at the relevant

evaluation time point)/(Number of subjects with non-missing data of the severity classification at the relevant evaluation time point)

- Cumulative incidence of endoscopic recurrence of reflux esophagitis

  (1) Reflux oesophagitis recurrent:

  Subjects assessed as Grade A to D in the severity classification by endoscopy in the maintenance phase

  (2) Censored:

  Subjects who discontinued or completed the study without recurrence of reflux esophagitis

  (3) Time to relapse of reflux esophagitis:

  Date of the first endoscopic assessment of reflux esophagitis recurrence − Date of the first dose in the treatment period + 1

  (4) Time to censoring:

  The day of the last dose in the maintenance period − the day of the first dose in the treatment period + 1

- Cure rate of reflux esophagitis at the end of the treatment period

  (Subjects who were endoscopically assessed as Grade O in the severity classification at the relevant evaluation time point)/(subjects with non-missing severity grade at the relevant evaluation point)

- Occurrence of gastric polyps

  If the presence or absence of fundic gland polyps is present or the presence or absence of hyperplastic polyps is present, the presence or absence of gastric polyps is present and the others are absent.

[Handling of histopathological examination of gastric mucosa]

- Incidence of each histopathological finding in the gastric mucosa (evaluation by and up to the evaluation time point)

  (Number of subjects in whom gastric mucosal histopathological examination was judged to be present (1 ~ 4 for endocrine cell proliferation) at the relevant evaluation time point)/(Subjects with histopathological examination of gastric mucosa without missing data at the relevant evaluation time point)

- Cumulative incidence of gastric mucosal histopathological findings

  (1) Occurrence for each finding:

  Subjects with gastric mucosal histopathological positive (1 ~ 4 for endocrine cell proliferation)

  (2) Censored:

  Subjects who discontinued or completed the study without any findings

  (3) Time to onset for each histopathological finding in the gastric mucosa:

  Date of first assessment of each finding in histopathological examination of gastric mucosa − Date of first dose in the treatment period + 1

  (4) Time to censoring *:

  The day of the last dose in the maintenance period − the day of the first dose in the treatment period + 1

  *In the interim analysis, the time to censoring will be “cut-off date - date of first dose in the treatment period + 1.”

[Handling of TEAEs]

- Treatment-Emergent Adverse Events During the Treatment Period:

  TEAEs that occurred between the first dose of study product for the treatment period and the first dose of study product for the maintenance period
- Treatment-Emergent Adverse Events During Maintenance Period:

  Treatment-Emergent Adverse Events Following study product Infusion in the Maintenance Period
- Time of onset of TEAEs during the treatment period

  Date of onset of TEAE in the treatment period - start date of treatment in the treatment period + 1
- Time of onset of TEAEs during the maintenance phase

  Date of onset of TEAE in the maintenance phase - start date of treatment in the maintenance phase + 1
- Time of onset of TEAEs during the study period

  Date of onset of TEAE - start date of treatment in the treatment period + 1

6. Subjects, demographic and other baseline characteristics

6.1. Disposition of Subjects

6.1.1. Clinical research information

Analysis population:	All subjects who gave informed consent
Analysis item:	Date of informed consent, whichever is earlier The day of the last dose of study product or the control drug in the maintenance phase, whichever is later MedDRA Version SAS Version
Analytical methods:	For the above analytical variable, the following analyses should be performed. (1) Display of Analysis Items

6.1.2. Eligibility of Subjects

Analysis population:	All subjects who gave informed consent
Analysis item:	Randomization [Yes, No (and the reason)] Status of transition to the maintenance phase [Yes, No (and the reason)]
Analytical methods:	For the above analytical variable, the following analyses should be performed. (1) Frequency tabulation

6.1.3. Disposition of Subjects

6.1.3.1. End of treatment

Analysis population: All randomized subjects

Analysis item: Status of completion of treatment with study product or control drug for the treatment period [Completed, incomplete (and the reason)]

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group and the pooled treatment group.

(1) Frequency tabulation

6.1.3.2. End of maintenance period

Analysis population: Subjects who completed the treatment period

Analysis item: Status of completion of administration of study product or control drug for the maintenance phase [Completed, incomplete (and the reason)]

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group and the pooled treatment group.

(1) Frequency tabulation

6.1.4. PROTOCOL DEVIATIONS AND DATA SETS TO BE ANALYSED

6.1.4.1. Protocol Deviations

6.1.4.1.1 Protocol deviations during the treatment period

Analysis population: All randomized subjects

Analysis item: Protocol deviations during the treatment period [Significant violation of GCP, violation of inclusion criteria, violation of discontinuation criteria, violation of treatment method/dose, violation of prohibited concomitant drug/therapy, deviation to avoid urgent risk, etc.]

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group and the pooled treatment group.

The number of subjects with protocol deviations during the treatment period will be calculated, and the details of deviations will be presented by classifying them into the above categories. A subject falling into more than one category will be counted as 1 subject in each of the categories (multiple counting).

(1) Frequency tabulation

6.1.4.1.2 Protocol deviations in the maintenance phase

Analysis population: Subjects Enrolled in Maintenance Phase

Analysis item: Protocol deviations in the maintenance phase [Significant violation of GCP, violation of inclusion criteria, violation of discontinuation criteria, violation of treatment method/dose, violation of prohibited concomitant drug/therapy, deviation to avoid urgent risk, etc.]

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group and the pooled treatment group.

The number of subjects with protocol deviations in the maintenance phase will be calculated, and the details of deviations will be presented by classifying the deviations into the above categories. A subject falling into more than one category will be counted as 1 subject in each of the categories (multiple counting).

(1) Frequency tabulation

6.1.4.2. Data Sets Analyzed

6.1.4.2.1 Data sets to be analyzed (treatment period)

Analysis population: All randomized subjects

Analysis item: Subjects in Analysis Sets [Reason for exclusion]

Adoption or rejection of analysis sets

Full Analysis Set of the Treatment Period [Adopted]

Safety Analysis Set of the Treatment Period [Adopted]

Analytical methods: For the above analytical variables, the following analyses should be performed for each treatment group in (1) and for each treatment group and the pooled treatment group in (2).

In (1), a subject falling into more than one category should be counted as 1 subject in each of the categories (multiple counting).

(1) Calculation of frequencies of subjects in each analysis set

(2) Calculation of frequencies of subjects included in each analysis set

6.1.4.2.2 Data sets to be analyzed (maintenance phase)

Analysis population: Subjects Enrolled in Maintenance Phase

Analysis item: Subjects in Analysis Sets [Reason for exclusion]

Adoption or rejection of analysis sets

Full Analysis Set of the maintenance phase [Adopted]

Safety Analysis Set of the maintenance phase [Adopted]

Analytical methods: For the above analytical variables, the following analyses should be performed for each treatment group in (1) and for each treatment group and the pooled treatment group in (2). In (1), a subject falling into more than one category should be counted as 1 subject in each of the categories (multiple counting).

(1) Calculation of frequencies of subjects in each analysis set

(2) Calculation of frequencies of subjects included in each analysis set

6.2. Demographic and Other Baseline Characteristics

6.2.1. Distribution of Baseline Characteristics

Analysis population: All randomized subjects

Safety Analysis Set of the maintenance phase

Analysis item: Age (years) [Min<= - <65, 65<= - <75, 75<= - <=Max]

Sex [Male, female]

Height (at the start of treatment period) (cm) [Min < = - < 150, 150 < = - < 160,
160<= - <170, 170<= - <=Max]

Body weight (at the start of the treatment period) (kg) [Min<= - <50.0, 50.0<= - <60.0,
60.0<= - <70.0, 70.0<= - <80.0,
80.0<= - <=Max]

BMI (at the start of the treatment period) (kg/m^2) [Min < = - < 18.5, 18.5 < = - < 25.0]
25.0<= - <=Max]

Smoking history [I have never smoked, I am a current smoker,
I used to smoke but now I do not smoke]

Alcohol history [Taking it every day, taking it about 2 or 3 days a week, taking it about 2 or 3 days a month, not taking it at all]

Consumption of caffeine-containing beverages [Yes, No]

Endoscopy (at the start of the treatment period)

Endoscopy (esophagus)

Severity classification [Grade O, Grade A, Grade B,
Grade C, Grade D

CYP2 C 19 genotyping [* 1/* 1, * 1/* 2, * 1/* 3, * 2/* 2, * 2/* 3, * 3/* 3]

Serum gastrin level (at the start of the treatment period) [Min < = - < 200, 200 < = - < = Max]

Serum pepsinogen I/II ratio (at the start of the treatment period)
[Min<= - <=2.0, 2.0< - <=3.0, 3.0< - <=Max]

Analytical methods: For the above analytical variable, the following analyses should be performed for treatment groups combined.

(1) Calculation of frequencies of categorical data and summary statistics of continuous data

6.2.2. Medical history and complications

Analysis population: Safety Analysis Set of the Treatment Period

Analysis item: Medical history

Concomitant conditions

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group.

The analysis items will be coded using MedDRA and summarized by SOC and PT. SOCs should be displayed in alphabetical order and PTs in descending order of frequency.

(1) Calculation of frequencies of previous diseases (by SOC/PT)

(2) Calculation of frequencies of complications (by SOC/PT)

In calculation of frequencies, events should be counted in the following manner.

[Number of cases]

If an event in the same SOC occurs more than once in the same subject, the subject will be counted as 1 subject in the SOC. If an event with the same PT occurs more than once in the same subject, the subject will be counted as 1 subject with the PT.

6.2.3. Prior and concomitant medications

Analysis population: Safety Analysis Set of the Treatment Period

Analysis item: Prior medications

Concomitant Medications

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group. Analysis items will be coded using the World Health Organization (WHO) Drug Dictionary. They should be listed in order of frequency. If the same subject is administered the same drug more than once, the subject will be counted as 1 subject for the drug.

(1) Calculation of frequencies of prior medications

(2) Calculation of frequencies of concomitant medications used during and after the treatment period, starting before administration of study product or the comparator during the treatment period

(3) Calculation of frequencies of concomitant drugs started after administration of study product or control drug in the treatment period

(4) Calculation of frequencies of study product used in the treatment period or the comparator used in the treatment period, or study product used in the maintenance period or the comparator used in the treatment period

6.3. Compliance

6.3.1. Compliance

Analysis population: Safety Analysis Set of the Treatment Period
Safety Analysis Set of the maintenance phase

Analysis item: Compliance [Regular dosing (≥ 90%), regular dosing (≥ 70%), half dosing (≥ 50%), half dosing missed (< 50%)]

Timepoint: [Safety analysis set in the treatment period]
Treatment Period Weeks 4 and 8
[Safety Analysis Set of the maintenance phase]
Maintenance Period Weeks 12, 24, 36, 48, 60, 72, 84, 96, 108, 132, 156, 180, 204, 228 and 260

Analytical methods: For the above analytical variable, the following analyses should be performed at each evaluation time point for treatment groups and treatment groups combined.

(1) Frequency tabulation

6.3.2. Treatment duration

Analysis population: All subjects who received study product or control drug for the treatment period
All subjects who received study product or control drug for the maintenance phase

Analysis item: Duration (days) of treatment with study product or control drug in the treatment period
[1<= - <=28, 29<= - <=56, 57<= - <=Max]
Duration (days) of treatment with study product or control drug in the maintenance phase
[1<= - <=84, 85<= - <=168, 169<= - <=252, 253<= - <=336, 337<= - <=420, 421<= - <=504, 505<= - <=588, 589<= - <=672, 673<= - <=756, 757<= - <=1092, 1093<= - <=1428, 1429<= - <=1820,1821<= - <=Max]

Analytical methods: For the above analytical variable, the following analyses should be performed for treatment groups combined.

(1) Calculation of frequencies of categorical data and summary statistics of continuous data

7. EFFICACY EVALUATION

7.1. Secondary Endpoints and Analytical Methods

7.1.1. Recurrence rate of reflux esophagitis based on endoscopic findings

Analysis population: Full Analysis Set of the maintenance phase

Analysis item: Recurrence rate of reflux esophagitis based on endoscopic findings

Timepoint: Maintenance Period Weeks 48, 108, 156, 204 and 260

Analytical methods: For the above analytical variable, the following analyses should be performed for evaluation at each evaluation time point and evaluation up to the evaluation time point.

(1) Calculation of frequencies, point estimates, and two-sided 95% CIs for the recurrence rate by treatment group

(2) Using the Kaplan-Meier method, the cumulative recurrence rate of reflux esophagitis, standard error according to Greenwood's formula, and two-sided 95% confidence interval will be calculated for each treatment group, and Kaplan-Meier curves will be presented graphically. In addition, the number of patients at risk, cumulative incidence of relapse, and two-sided 95% confidence interval according to Greenwood's formula will be presented for each evaluation time point.

7.1.2. Healing rate of reflux esophagitis during the treatment period

Analysis population: Full Analysis Set of the Treatment Period

Analysis item: Cure rate of reflux esophagitis

Timepoint: Treatment Period Weeks 4 and 8

Analytical methods: For the above analytical variable, the following analyses should be performed for evaluation at each evaluation time point and evaluation up to the evaluation time point.

(1) Calculation of frequencies, point estimates, and two-sided 95% CIs for cure rates by treatment group

7.2. Other Analyses

7.2.1. Barrett's mucosa assessment

Analysis population: Full Analysis Set of the Treatment Period
Full Analysis Set of the maintenance phase

Analysis item: Barrett's mucosa [Present (≥ 3 cm), Present (< 3 cm), Absent, Unknown]

Timepoint: [Full analysis set in the treatment period]
At the start of the treatment period, and Treatment Period Weeks 4 and 8
[Full analysis set in the maintenance phase]

Maintenance Period Weeks 48, 108, 156, 204 and 260

Analytical methods: For the above analytical variable, the following analyses should be performed for each evaluation time point.

(1) Calculation of frequencies by treatment group

7.2.2. Evaluation of esophageal hiatal hernia

Analysis population: Full Analysis Set of the Treatment Period
Full Analysis Set of the maintenance phase

Analysis item: hiatal hernia [Yes (≥ 2 cm), Yes (< 2 cm), None, unknown]

Timepoint: [Full analysis set in the treatment period]
At the start of the treatment period, and Treatment Period Weeks 4 and 8
[Full analysis set in the maintenance phase]
Maintenance Period Weeks 48, 108, 156, 204 and 260

Analytical methods: For the above analytical variable, the following analyses should be performed for each evaluation time point.

(1) Calculation of frequencies by treatment group

8. SAFETY EVALUATION

8.1. Primary Endpoint and Analytical Methods

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: Histopathological examination of gastric mucosa *
Presence or absence of epithelial cell tumorigenesis [Yes, No, Not Evaluable]
Presence or absence of parietal cell elevation/hyperplasia [Yes, No, Not Evaluable]
Presence or absence of crypt epithelial hyperplasia [Yes, No, Not Evaluable]
Endocrine proliferation [Present (1 (atrophic ECM), 2 (hyperplastic ECM), 3 (neoplastic ECM), 4 (typical carcinoid)), absent, not evaluable]
Presence or absence of G cell hyperplasia [Yes, No, Not Evaluable]

*For evaluation up to the evaluation time point, the presence or absence of endocrine cell proliferation should be represented in the order of 4 (typical carcinoid), 3 (neoplastic ECM), 2 (hyperplastic ECM), and 1 (atrophic ECM) as the details of presence. If all tests conducted during TIME WINDOW for each item are “not evaluable, ” the evaluations up to the evaluation time point will be considered“ not evaluable.”

Timepoint: Start of the treatment period, and Weeks 48, 108, 156, 204 and 260 of the maintenance period

Analytical methods: For the above analytical variable, the following analyses should be performed for evaluation at each evaluation time point and evaluation up to the evaluation time point.

(1) Calculation of frequencies and percentages by treatment group

(2) Using the Kaplan-Meier method, the cumulative incidence of each finding in histopathological examination of gastric mucosa, standard error according to Greenwood's formula, and two-sided 95% confidence interval will be calculated for each treatment group, and Kaplan-Meier curves will be illustrated. In addition, the number of patients at risk, the cumulative incidence, and the two-sided 95% confidence interval according to Greenwood's formula will be presented for Weeks 52, 112, 160, 208, and 264 from the start of the treatment period as the starting point.

(3) For endocrine cell proliferation, cross tabulation tables at the start of the treatment period and at each evaluation time point will be prepared. Endocrine proliferation response is considered as none, 1 (atrophic ECM), 2 (hyperplastic ECM), 3 (neoplastic ECM), 4 (typical carcinoid) or not evaluable.

8.2. Secondary Endpoints and Analytical Methods

8.2.1. Incidence of Adverse Events (TEAE)

8.2.1.1. Overview of TEAEs During the Maintenance Period

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: TEAEs Occurring in the Maintenance Period

Category: Relationship to study product or Control Drugs [Related, not related]

Severity [Mild, moderate, severe]

Time of onset [1<= - <=84, 85<= - <=168, 169<= - <=252, 253<= - <=336, 337<= - <=420, 421<= - <=504, 505<= - <=588, 589<= - <=672, 673<= - <=756, 757<= - <=1092, 1093<= - <=1428, 1429<= - <=1820,1821<= - <=Max]

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group.

1) Calculation of frequencies of all TEAEs
2) Calculation of frequencies of TEAEs by causal relationship with study product or control drug
3) Calculation of frequencies of all TEAEs by intensity
4) Calculation of frequencies of TEAEs by severity by causal relationship with study product or control drug
5) Calculation of frequencies of TEAEs leading to study drug discontinuation for

study product or comparator

6) Calculation of frequencies of serious TEAEs
7) Calculation of frequencies of serious TEAEs by causal relationship with study product or the study drug
8) Calculation of frequencies of serious TEAEs leading to treatment discontinuation for study product or comparator
9) Calculation of frequencies of TEAEs with outcome of death
10) Calculation of frequencies of TEAEs by time of onset
11) Calculation of frequencies of serious TEAEs by time of onset
12) Calculation of frequencies of TEAEs related to diarrhea
13) Calculation of frequencies of TEAEs related to intestinal infection
14) Calculation of frequencies of TEAEs related to fracture
15) Calculation of frequencies of TEAEs related to pneumonia

In performing each analysis, events should be counted and incidences should be calculated in the following manner.

[Number of cases]

- When "Calculation of frequencies by severity" is performed

  If a subject experiences TEAEs more than once, the subject will be counted as 1 subject in the severest category. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set in the maintenance phase.

- When "Calculation of frequencies by time of onset" is performed

  If a TEAE occurs more than once in the same subject, each TEAE will be counted as 1 subject in the relevant time of onset category. In the calculation of incidences of TEAEs in each time period, the denominator should be the number of subjects "who received the study product for the maintenance phase or the control drug in and after the time period" or "who experienced the TEAE in and after the time period" in the safety analysis set of the maintenance phase, and the numerator is the number of subjects "who experienced the TEAE in the time period."

- When "Calculation of frequencies by causal relationship" is performed

  A subject who experienced both TEAEs “related ” and“ not related ” to study product or control drug will be counted as 1 subject in the “related ” category.

- When tabulation other than the above is performed

  A subject who experienced a TEAE more than once will be counted as 1 subject. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set in the maintenance phase.

8.2.1.2. Display of TEAEs Occurring in the Maintenance Period

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: TEAEs Occurring in the Maintenance Period

Category: Relationship to study product or Control Drugs [Related, not related]

Severity [Mild, moderate, severe]

Time of onset [1<= - <=84, 85<= - <=168, 169<= - <=252, 253<= - <=336, 337<= - <=420, 421<= - <=504, 505<= - <=588, 589<= - <=672, 673<= - <=756, 757<= - <=1092, 1093<= - <=1428, 1429<= - <=1820,1821<= - <=Max]

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group. TEAEs will be coded using MedDRA and summarized by SOC and PT. When tabulating by SOC/PT, SOCs should be displayed in alphabetical order and PTs in descending order of frequency.

1) Calculation of frequencies of all TEAEs (SOC/PT)
2) Calculation of frequencies of TEAEs by causal relationship with study product or control drug (SOC/PT)
3) Calculation of frequencies of all TEAEs by severity (SOC/PT)
4) Calculation of frequencies of TEAEs by severity for each causal relationship with study product or control drug (SOC/PT)
5) Calculation of frequencies of TEAEs leading to discontinuation of study product or control drug (SOC/PT)
6) Calculation of frequencies of serious TEAEs (SOC/PT)
7) Calculation of frequencies of serious TEAEs by causal relationship to study product or the study drug (SOC/PT)
8) Calculation of frequencies of serious TEAEs leading to discontinuation of study product or control drug (by SOC/PT)
9) Calculation of frequencies of TEAEs with outcome of death (SOC/PT)
10) Calculation of frequencies of TEAEs by time of onset (SOC/PT)
11) Calculation of frequencies of serious TEAEs by time of onset (SOC/PT)
12) Calculation of frequencies of diarrhea-related TEAEs (SOC/PT)
13) Calculation of frequencies of TEAEs related to intestinal infection (SOC/PT)
14) Calculation of frequencies of fracture-related TEAEs (SOC/PT)
15) Calculation of frequencies of pneumonia-related TEAEs (SOC/PT)
16) Calculation of frequencies of non-serious TEAEs with an incidence of > 5%

(SOC/PT)

In performing each analysis, events should be counted and incidences should be calculated in the following manner.

[Number of cases]

- When "frequency tabulation (by SOC/PT)" is performed

  If a subject experiences TEAEs in the same SOC more than once, the subject will be counted as 1 subject in the SOC. If a subject experiences TEAEs with the same PT more than once, the subject will be counted as 1 subject with the PT. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set in the maintenance phase.

- When "Calculation of frequencies by severity (SOC/PT)" is performed

  If a subject experiences TEAEs in the same SOC or with the same PT more than once, the subject will be counted as 1 subject in the severest category of the SOC or PT. In calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set in the maintenance phase.

- When "Calculation of frequencies by time of onset (SOC/PT)" is performed

  A subject who experienced TEAEs in the same SOC or with the same PT more than once will be counted as 1 subject in each of the categories of time of onset. The denominator for the calculation of incidences of TEAEs in each time period is the subjects "who received the study product for the maintenance phase or the control drug in and after the time period" or "who experienced the TEAE in and after the time period" in the safety analysis set of the maintenance phase, and the numerator is the number of subjects "who experienced the TEAE in the time period."

- When "Calculation of frequencies by causal relationship (SOC/PT)" is performed

  A subject who experienced more than one TEAE in the same SOC or TEAE with the same PT and experienced both TEAEs with a causal relationship of “Related ” and“ Not related ” will be counted as 1 subject in the “Related ” category. In calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set in the maintenance phase.

8.2.1.3. Overview of Treatment-Emergent Adverse Events During the Treatment Period

Analysis population:	Safety Analysis Set of the Treatment Period
Analysis item:	Treatment-Emergent Adverse Events During the Treatment Period
Category:	Relationship to study product or Control Drugs [Related, not related]

Severity	[Mild, moderate, severe]
Time of onset	[1<= - <=28, 29<= - <=56, 57<= - <=Max]

Analytical methods: Analyses should be performed in the same manner as in 8.2. 1.1. In performing each analysis, events should be counted and incidences should be calculated in the following manner.

[Number of cases]

- When "Calculation of frequencies by severity" is performed

  If a subject experiences TEAEs more than once, the subject will be counted as 1 subject in the severest category. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.
- When "Calculation of frequencies by time of onset" is performed

  If a TEAE occurs more than once in the same subject, each TEAE will be counted as 1 subject in the relevant time of onset category. In the calculation of incidences of TEAEs in each time period, the denominator should be the number of subjects "who received the study product or the control drug for the treatment period in and after the time period" or "who experienced the TEAE in and after the time period" in the safety analysis set for the treatment period, and the numerator is the number of subjects "who experienced the TEAE in the time period."
- When "Calculation of frequencies by causal relationship" is performed

  A subject who experienced both TEAEs “related ” and“ not related ” to study product or control drug will be counted as 1 subject in the “related ” category.
- When tabulation other than the above is performed

  A subject who experienced a TEAE more than once will be counted as 1 subject. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

8.2.1.4. Display of TEAEs Occurring during the Treatment Period

Analysis population: Safety Analysis Set of the Treatment Period

Analysis item: Treatment-Emergent Adverse Events During the Treatment Period

Category: Relationship to study product or Control Drugs [Related, not related]

Severity [Mild, moderate, severe]

Time of onset [1<= - <=28,
29<= - <=56,
57<= - <=Max]

Analytical methods: Analyses should be performed in the same manner as in 8.2. 1.2. In performing each analysis, events should be counted and incidences should be calculated in the following manner.

[Number of cases]

- When "frequency tabulation (by SOC/PT)" is performed

  If an event in the same SOC occurs more than once in the same subject, the subject will be counted as 1 subject in the SOC. If an event with the same PT occurs more than once in the same subject, the subject will be counted as 1 subject with the PT. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

- When "Calculation of frequencies by severity (SOC/PT)" is performed

  If an event in the same SOC or with the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in the severest category of the SOC or PT. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

- When "Calculation of frequencies by time of onset (SOC/PT)" is performed

  If an event under the same SOC or with the same PT occurs more than once in the same subject, the subject will be counted as 1 subject in each of the categories of the time of onset. The denominator for the calculation of incidences of TEAEs in each time period is the subjects "who received the study product for the treatment period or the control drug in and after the time period" or "who experienced the TEAE in and after the time period" in the safety analysis set for the treatment period, and the numerator is the number of subjects "who experienced the TEAE in the time period."

- When "Calculation of frequencies by causal relationship (SOC/PT)" is performed

  A subject who experienced more than one TEAE in the same SOC or TEAE with the same PT and experienced both TEAEs with a causal relationship of “Related ” and“ Not related ” will be counted as 1 subject in the “Related ”

category. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

8.2.1.5. Overview of Treatment-Emergent Adverse Events During the Study Period

Analysis population: Safety Analysis Set of the Treatment Period

Analysis item: Treatment-Emergent Adverse Events During the Study Period

Category: Relationship to study product or Control Drugs [Related, not related]

Severity [Mild, moderate, severe]

Time of onset [1<= - <=28, 29<= - <=56, 57<= - <=140, 141<= - <=224, 225<= - <=308, 309<= - <=392, 393<= - <=476, 477<= - <=560, 561<= - <=644, 645<= - <=728, 729<= - <=812, 813<= - <=1148, 1149<= - <=1484, 1485<= - <=1876, 1877<= - <=Max]

Analytical methods: Analyses should be performed in the same manner as in 8.2. 1.1. In performing each analysis, events should be counted and incidences should be calculated in the following manner.

[Number of cases]

- When "Calculation of frequencies by severity" is performed

  If a subject experiences TEAEs more than once, the subject will be counted as 1 subject in the severest category. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

- When "Calculation of frequencies by time of onset" is performed

  If a TEAE occurs more than once in the same subject, each TEAE will be counted as 1 subject in the relevant time of onset category. In the calculation of incidences of TEAEs in each time period, the denominator should be the number of subjects "who received study product or the control drug in and after the time period" or "who experienced the TEAE in and after the time period" in the safety analysis set in the treatment period, and the numerator is the number of subjects "who experienced the TEAE in the time period."

- When "Calculation of frequencies by causal relationship" is performed

  A subject who experienced both TEAEs “related ” and“ not related ” to study product or control drug will be counted as 1 subject in the “related ” category.

- When tabulation other than the above is performed

  A subject who experienced a TEAE more than once will be counted as 1 subject. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

8.2.1.6. Display of TEAEs Occurring during the Study Period

Analysis population: Safety Analysis Set of the Treatment Period

Analysis item: Treatment-Emergent Adverse Events During the Study Period

Category: Relationship to study product or Control Drugs [Related, not related]

Severity [Mild, moderate, severe]

Time of onset [1<= - <=28, 29<= - <=56, 57<= - <=140, 141<= - <=224, 225<= - <=308, 309<= - <=392, 393<= - <=476, 477<= - <=560, 561<= - <=644, 645<= - <=728, 729<= - <=812, 813<= - <=1148, 1149<= - <=1484, 1485<= - <=1876, 1877<= - <=Max]

Analytical methods: Analyses should be performed in the same manner as in 8.2. 1.2. In performing each analysis, events should be counted and incidences should be calculated in the following manner.

[Number of cases]

- When "frequency tabulation (by SOC/PT)" is performed

  If a subject experiences TEAEs in the same SOC more than once, the subject will be counted as 1 subject in the SOC. If a subject experiences TEAEs with the same PT more than once, the subject will be counted as 1 subject with the PT. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

- When "Calculation of frequencies by severity (SOC/PT)" is performed

  If a subject experiences TEAEs in the same SOC or with the same PT more than once, the subject will be counted as 1 subject in the severest category of the SOC or PT. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

- When "Calculation of frequencies by time of onset (SOC/PT)" is performed

  A subject who experienced TEAEs in the same SOC or with the same PT more than once will be counted as 1 subject in each of the categories of time of onset. In the calculation of incidences of TEAEs in each time period, the denominator should be the number of subjects "who received study product or the control drug in and after the time period" or "who experienced the TEAE in and after the time period" in the safety analysis set in the treatment period, and the numerator is the number of subjects "who experienced the TEAE in the time period."

- When "Calculation of frequencies by causal relationship (SOC/PT)" is performed

  A subject who experienced more than one TEAE in the same SOC or TEAE with

the same PT and experienced both TEAEs with a causal relationship of "Related " and" Not related " will be counted as 1 subject in the "Related " category. In the calculation of incidences of TEAEs, the denominator should be the number of subjects in the safety analysis set during the treatment period.

8.2.2. Endoscopic findings, histological evaluation of gastritis according to the Sydney classification

Analysis population: Safety Analysis Set of the maintenance phase
Safety Analysis Set of the treatment period (endoscopic findings only)

Analysis item: Endoscopic findings

fundic gland polyp [Yes, No]
Hyperplastic polyp [Yes, No]
cobblestone mucosa [Yes, No]
Multiple white flat bumps [Yes, No]
black spot lesion [Yes, No]

Histological evaluation of gastritis * (greater curvature of the middle corpus of the stomach, greater curvature of the antrum)

Inflammation (mononuclear cell infiltration) [Present (Mild, moderate, severe), absent, not evaluable]
Active (neutrophil infiltration) [Present (Mild, moderate, severe), absent, not evaluable]
Atrophy [Present (Mild, moderate, severe), absent, not evaluable]
Metaplasia, intestinal [Present (Mild, moderate, severe), absent, not evaluable]
H.pylori [Present (Mild, moderate, severe), absent, not evaluable]

*For assessments made up to the evaluation time point, the details of yes should be represented in order of decreasing severity. If all tests conducted during TIME WINDOW for each item are "not evaluable, " the evaluations up to the evaluation time point will be considered" not evaluable."

Occurrence of gastric polyp [Yes, No]

Timepoint: [Endoscopic findings/Safety analysis set in the treatment period]

At the start of the treatment period, and Treatment Period Weeks 4 and 8

[Endoscopic findings/Safety analysis set in the maintenance phase]

Start of the treatment period, and Weeks 48, 108, 156, 204 and 260 of the maintenance period

[Histological evaluation of gastritis]

Start of the treatment period, and Weeks 48, 108, 156, 204 and 260 of the maintenance period

Analytical methods: For the above analytical variable, the following analyses should be performed for evaluation at each evaluation time point and evaluation up to the evaluation time point by treatment group.

(1) Calculation of frequencies and percentages

(2) For histological evaluation of gastritis, cross tabulation at the start of the treatment period and each evaluation time point will be prepared. The response for histologic assessment of gastritis will be none, mild, moderate, severe, or not evaluable.

8.2.3. Other endpoints and analysis methods

8.2.3.1. Clinical Laboratory Evaluation

Analysis population: Safety Analysis Set of the Treatment Period

Safety Analysis Set of the maintenance phase

Analysis item: Blood tests

AST, ALT, Fe, Mg, Ca, and vitamin B 12

Timepoint: [Safety analysis set in the treatment period]

At the start of the treatment period, and Treatment Period Weeks 4 and 8

[Safety Analysis Set of the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 12 in the maintenance period,

Maintenance Period Weeks 24, 36, 48, and 60

Maintenance Period Weeks 72, 84, 96, and 108

Maintenance Period Weeks 132, 156, 180, and 204

Maintenance Period Week 228, Maintenance Period Week 260

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group in the safety analysis set during the treatment period.

(1) Summary statistics of observed values at each evaluation time and summary statistics of pre- and post-treatment differences (each evaluation time after treatment - at the start of the treatment period) at each evaluation time

(2) Individual Time Profiles

For the above analytical variable, the following analyses will be performed using the safety analysis set in the maintenance phase.

(3) Summary statistics of observed values at each evaluation time and summary statistics of pre- and post-treatment differences (each evaluation time after treatment - at the start of the treatment period) at each evaluation time

(4) Individual Time Profiles

(5) Time-course plots of mean ± SD and box-and-whisker plots will be prepared for each

treatment group at each assessment point during the treatment and maintenance periods. Time-course plots of mean ± SD and box-and-whisker plots will be provided for each treatment group at each assessment point during the study period in the safety analysis set during the treatment period.

8.2.3.2. Serum gastrin, pepsinogen I and II levels, and chromogranin A levels

Analysis population: Safety Analysis Set of the Treatment Period
Safety Analysis Set of the maintenance phase

Analysis item: Serum gastrin level
Serum pepsinogen I level
Serum pepsinogen II level
Serum pepsinogen I/II ratio
Serum chromogranin A level

Timepoint: [Serum gastrin level/safety analysis set during the treatment period]
At the start of the treatment period, and Treatment Period Weeks 4 and 8
[Serum gastrin level/safety analysis set in the maintenance phase]
At the start of the treatment period, and Treatment Period Weeks 4, 8, and 12 in the maintenance period,
Maintenance Period Weeks 24, 36, 48, and 60
Maintenance Period Weeks 72, 84, 96, and 108
Maintenance Period Weeks 132, 156, 180, and 204
Maintenance Period Week 228, Maintenance Period Week 260
[Analysis sets for serum pepsinogen I, pepsinogen II, pepsinogen I/II ratio, and chromogranin A levels/safety data during the treatment period]
At the start of the treatment period, and Treatment Period Weeks 4 and 8
[Serum pepsinogen I, pepsinogen II, pepsinogen I/II ratio, and chromogranin A/safety analysis set in the maintenance phase]
At the start of the treatment period, and Treatment Period Weeks 4, 8, and 24 in the maintenance period,
Maintenance Period Weeks 48, 108, 156, and 204
Maintenance Period Week 260

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group in the safety analysis set during the treatment period.

(1) Summary statistics of observed values at each evaluation time and summary statistics of pre- and post-treatment differences (each evaluation time after treatment - at the

start of the treatment period) at each evaluation time

(2) Individual Time Profiles

For the above analytical variable, the following analyses will be performed using the safety analysis set in the maintenance phase.

(3) Summary statistics of observed values at each evaluation time and summary statistics of pre- and post-treatment differences (each evaluation time after treatment - at the start of the treatment period) at each evaluation time

(4) Individual Time Profiles

(5) Time-course plots of mean ± SD and box-and-whisker plots will be prepared for each treatment group at each assessment point during the treatment and maintenance periods. Time-course plots of mean ± SD and box-and-whisker plots will be provided for each treatment group at each assessment point during the study period in the safety analysis set during the treatment period.

8.2.3.3. Vital signs

Analysis population: Safety Analysis Set of the Treatment Period
Safety Analysis Set of the maintenance phase

Analysis item: Pulse rate, systolic blood pressure, diastolic blood pressure

Timepoint: [Safety analysis set in the treatment period]

At the start of the treatment period, and Treatment Period Weeks 4 and 8

[Safety Analysis Set of the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 12 in the maintenance period,

Maintenance Period Weeks 24, 36, 48, and 60

Maintenance Period Weeks 72, 84, 96, and 108

Maintenance Period Weeks 132, 156, 180, and 204

Maintenance Period Week 228, Maintenance Period Week 260

Analytical methods: For the above analytical variable, the following analyses should be performed for each treatment group in the safety analysis set during the treatment period.

(1) Summary statistics of observed values at each evaluation time and summary statistics of pre- and post-treatment differences (each evaluation time after treatment - at the start of the treatment period) at each evaluation time

(2) Individual Time Profiles

For the above analytical variable, the following analyses will be performed using the safety analysis set in the maintenance phase.

(3) Summary statistics of observed values at each evaluation time and summary

statistics of pre- and post-treatment differences (each evaluation time after treatment - at the start of the treatment period) at each evaluation time

(4) Individual Time Profiles

9. List

The following list will be prepared for "all randomized subjects."

- Background Information
- Discontinued patients
- Deviation
- Patients excluded from the analysis
- Compliance
- Concomitant conditions
- Prior medications
- Concomitant Medications
- Endoscopic findings
- Histopathological examination of gastric mucosa
- Histological evaluation of gastritis based on the Sydney classification.
- Laboratory Values
- Vital signs
- Adverse events

10. STATISTICAL/ANALYTICAL ISSUES

10.1. Adjustments for Covariates

No adjustment for covariates will be made.

10.2. Handling of Dropouts or Missing Data

Missing values will not be imputed.

10.3. Interim Analysis and Criteria for Early Termination

To evaluate the effects of long-term vonoprazan treatment in the maintenance therapy for recurrent/relapsed reflux esophagitis, the analysis will be performed not only until the last visit but also every year in the maintenance phase. When data from all patients up to the relevant visit [Maintenance Period Weeks 48 (VISIT M 5), 108 (VISIT M 10), 156 (VISIT M 12), and 204 (VISIT M 14)] are obtained, the analysis will be performed using data up to the relevant visit in the relevant patients. This tabulation is not intended to determine whether to continue or discontinue this clinical research.

The following items will be analyzed at the time of interim analysis. The details of the analysis will be determined at the

time of the interim analysis.

- 6. Subjects, demographic and other baseline characteristics
- 8. SAFETY EVALUATION

10.4. Multicenter Studies

No analysis taking into account study sites will be performed.

10.5. Multiple Comparison/Multiplicity

No multiplicity adjustment will be performed.

10.6. Examination of Subgroups

No subgroup analysis will be performed.

11. REVISION HISTORY

Ver.	Date of preparation	Author	Revised Item	Description of Revision
1.0	2016/2/22	[redacted]	Newly created	
2.0	2018/10/1	[redacted]	Cover page (approver) 8.2.1.2. Display of TEAEs Occurring in the Maintenance Period 9.3. Interim Analysis and Criteria for Early Termination	・The principal investigator was added as an approver based on the enforcement of the Clinical Research Act. ・Added frequency tabulation of non-serious TEAEs with an incidence of more than 5% (by SOC/PT) in the tabulation of adverse events by SOC/PT. ・Modified the timing of interim analysis based on the results of discussion at the study steering committee held on 2017/12/2.
3.0	2018/11/13	[redacted]	・Handling of TIME WINDOW ・8.2.1.1. Overview of TEAEs During the Maintenance Period ~ 8.2.1.6. Display of Treatment-Emergent Adverse Events During the Study Period	Since the main objective of the present study was to evaluate the long-term safety of vonoprazan and the results of data review, it was considered desirable to contribute data as much as possible to the analysis. Therefore, the acceptable range of days after administration was modified for endoscopy, histopathological examination of gastric mucosa, histological evaluation of gastritis, laboratory test values, vital signs, serum gastrin levels, pepsinogen I/II levels, and chromogranin A levels. Corrected the description to perform tabulation of "not related" causality, instead of only "related." Added the frequency tabulation of serious TEAEs by time of onset and the frequency tabulation of serious TEAEs by time of onset by SOC/PT to the necessity of tabulation. 8.2.1.5. In the overview of TEAEs that occurred during the study period and 8.2.1.6. Display of TEAEs that occurred during the study period, the category of "309 < = - < = 362" by time of onset was corrected to "309 < = - < = 392"

Ver.	Date of preparation	Author	Revised Item	Description of Revision
				because it was an error.
			・9. LIST	Added since a list needs to be prepared.
			・10.3. Interim Analysis and Criteria for Early Termination	The analysis item at the time of interim analysis was modified from "6.2.1. Distribution of Baseline Characteristics" to "6. Subjects, demographic characteristics and other baseline characteristics."
4.0	2019/3/25	[redacted]	・8.2.3.1. Clinical Laboratory Evaluations 8.2.3.2.Serum gastrin, pepsinogen I and II levels, and chromogranin A levels	Preparation of time-course plots of mean ± SD at each evaluation time point in the treatment and maintenance phases was added for each treatment group. In addition, preparation of time-course plots of mean ± SD at each evaluation time point during the study period was added for each treatment group.
5.0	2020/9/28	[redacted]	・8.1. Primary Endpoint and Analytical Methods ・8.2.2. Endoscopic findings, histological evaluation of gastritis according to the Sydney classification ・8 2 3. Other endpoints and analysis methods	Not Evaluable was added to the evaluation category of each endpoint (Except for endoscopic findings in 8.2.2.). Added that if all tests performed within TIME WINDOW for each item are “not evaluable, ” the assessments up to that evaluation time point will be“ not evaluable.” Treatment Period Weeks 4 and 8 were added to the evaluation time points in the [maintenance phase safety analysis set]. 8.2.3.1.Preparation of box-and-whisker plots was added to Section and 8.2.3.2.
6.0	2022/8/19	[redacted]	3.2 Subgroups 6.3.3. Relation between recurrence of reflux esophagitis and dose increase 6.3.4. Severity classification at the start of the treatment period by presence/absence of dose increase	New addition

Ver.	Date of preparation	Author	Revised Item	Description of Revision
			6.3.5. Severity classification and endoscopic findings before dose increase 7.2.3. Risk factors for recurrence of reflux esophagitis 8.2.3.3. Serum gastrin and chromogranin A levels by the presence or absence of endoscopic findings 8.2.3.4. Correlation between serum gastrin and chromogranin A levels 8.2.3.5. Changes in serum gastrin level during the maintenance phase	Addition of subgroup analysis
			6.2.1. Distribution of Baseline Characteristics 8.1. Primary Endpoint and Analytical Methods	The time points at which the number of patients at risk, cumulative incidence, and two-sided 95% confidence interval according to Greenwood's formula will be presented were modified to Weeks 52, 112, 160, 208, and 264 from the start of the treatment period.
			8.1. Primary Endpoint and Analytical Methods	
7.0*	2023/2/1	[redacted]	3.1 (deletion of section numbers) 3.2 Subgroups 6.3.3. Relation between recurrence of reflux esophagitis and dose increase 6.3.4. Severity classification at the start of the treatment period by presence/absence of dose increase 6.3.5. Severity classification and endoscopic findings before dose increase	Deletion of the item on the left newly added in Ver. 6.0

Ver.	Date of preparation	Author	Revised Item	Description of Revision
			7.2.3. Risk factors for recurrence of reflux esophagitis 8.2.3.3. Serum gastrin and chromogranin A levels by the presence or absence of endoscopic findings 8.2.3.4. Correlation between serum gastrin and chromogranin A levels 8.2.3.5. Changes in serum gastrin level during the maintenance phase 6.2.1. Distribution of Baseline Characteristics 8.1. Primary Endpoint and Analytical Methods	Deletion of subgroup analysis

* Preparation of Ver. 7.0:

It was decided to prepare an additional analysis plan including the items newly added in Ver. 6.0, and Ver. 7.0, which retained only the existing analysis items, was separately prepared for the purpose of document organization.

Evaluation of Long-term Safety of Maintenance Treatment with Vonoprazan in Patients with Erosive Esophagitis

(Vonoprazan -4003)

Statistical Analysis Plan

(additional analysis)

(Ver. 1.0 Date of preparation: 2023/2/1)

Sponsor: Takeda Pharmaceutical Company Limited.

TABLE OF CONTENTS

1. Data handling, etc.

Handling of evaluation time points, matters to be considered in the analysis, and other handling will be in accordance with the analysis plan (Ver. 7.0) for this analysis.

2. Analysis Sets

2.1. Analysis Sets

- Full Analysis Set of the Treatment Period

  Subjects who were randomized and received study product for the treatment period or the control drug at least once
- Full Analysis Set of the maintenance phase

  Subjects who were randomized and received at least one dose of study product for the maintenance phase or the control drug
- Safety Analysis Set of the Treatment Period

  Subjects who received at least one dose of study product or control drug for the treatment period
- Safety Analysis Set of the maintenance phase

Subjects who received study product for the maintenance phase or the control drug at least once

2.2. Subgroup

Based on the mean serum gastrin and chromogranin A levels at Week 12 or later in the maintenance phase, 3 subgroups will be established.

- Serum gastrin level: < 1000 pg/mL, ≥ 1000 pg/mL and < 2000 pg/mL, ≥ 2000 pg/mL
- Serum chromogranin A level: < 500 ng/mL, ≥ 500 to < 1000 ng/mL, ≥ 1000 ng/mL

3. Demographic and Other Baseline Characteristics

3.1. Distribution of Baseline Characteristics

Analysis population: All randomized subjects

Safety Analysis Set of the maintenance phase

Analysis item: Age (years) [Min<= - <65, 65<= - <75, 75<= - <=Max]

Sex [Male, female]

Height (at the start of treatment period) (cm) [Min < = - < 150, 150 < = - < 160,
160<= - <170, 170<= - <=Max]

Body weight (at the start of the treatment period) (kg) [Min<= - <50.0, 50.0<= - <60.0,
60.0<= - <70.0, 70.0<= - <80.0,
80.0<= - <=Max]

BMI (at the start of the treatment period) (kg/m^2) [Min < = - < 18.5, 18.5 < = - < 25.0]
25.0<= - <=Max]

Smoking history [I have never smoked, I am a current smoker,

I used to smoke but now I do not smoke]

Alcohol history [Taking it every day, taking it about 2 or 3 days a week, taking it about 2 or 3 days a month, not taking it at all]

Consumption of caffeine-containing beverages [Yes, No]

Endoscopy (at the start of the treatment period)

Endoscopy (esophagus)

Severity classification [Grade O, Grade A, Grade B, Grade C, Grade D

CYP2 C 19 genotyping [* 1/* 1, * 1/* 2, * 1/* 3, * 2/* 2, * 2/* 3, * 3/* 3]

Serum gastrin level (at the start of the treatment period) [Min < = - < 200, 200 <= - < = Max]

Serum pepsinogen I/II ratio (at the start of the treatment period) [Min<= - <=2.0, 2.0< - <=3.0, 3.0< - <=Max]

Analytical methods: For the subgroups described in 2.2 (Serum gastrin level, serum chromogranin A level), frequency tabulation of discrete data and summary statistics of continuous data will be calculated.

3.2. Compliance

3.2.1. Relation between recurrence of reflux esophagitis and dose increase

Analysis population: Patients with experience of dose increase among all patients who received study product for the maintenance phase or control drug

Analysis item: Presence or absence of recurrence at the last endoscopy before dose increase

Number of days from endoscopic recurrence to dose increase

Analytical methods: A list of analysis items will be prepared.

3.2.2. Severity classification at the start of the treatment period by presence/absence of dose increase

Analysis population: All subjects who received study product or control drug for the maintenance phase

Analysis item: Severity classification at the start of the treatment period by presence/absence of dose increase

Analytical methods: The subjects will be divided into the dose-increasing experienced group and the non-dose-increasing experienced group, and the frequency will be tabulated for each treatment group.

3.2.3. Severity classification and endoscopic findings before dose increase

Analysis population: Patients with experience of dose increase among all patients who received study product for the maintenance phase or control drug

Analysis item: Number of dose escalations

Severity based on the most recent endoscopic finding before dose increase

Presence/absence of recent endoscopic findings before dose increase (Fundus gland polyp, hyperplastic polyp, cobblestone mucosa, multiple white flat protrusions, black spot lesion)

Analytical methods: The following analyses will be performed for subjects with dose escalation experience.

(1) Calculation of the frequency of findings at the latest endoscopy after dose increase

Number of dose escalations will be calculated. The number of events and the rate of dose increase as denominators will be calculated for severity and presence of each finding at the last endoscopy after dose increase.

4. EFFICACY EVALUATION

4.1. Secondary Endpoints and Analytical Methods

4.1.1. Recurrence rate of reflux esophagitis based on endoscopic findings

Analysis population: Full Analysis Set of the maintenance phase

Analysis item: Recurrence rate of reflux esophagitis based on endoscopic findings

Timepoint: Maintenance Period Weeks 48, 108, 156, 204 and 260

Analytical methods: For the above analytical variable, the following analyses should be performed for evaluation at each evaluation time point and evaluation up to the evaluation time point.

(1) Frequency tabulation by treatment group, point estimate of recurrence rate, and two-sided 95% confidence interval will be calculated, and Fisher's exact test will be performed for the difference in recurrence rate between the treatment groups. Mann-Whitney U test will be performed for severity classification.

(2) Using the Kaplan-Meier method, the cumulative recurrence rate of reflux esophagitis, standard error according to Greenwood's formula, and two-sided 95% confidence interval will be calculated for each treatment group, and Kaplan-Meier curves will be presented graphically. In addition, the number of patients at risk, cumulative incidence of relapse, and two-sided 95% confidence interval according to Greenwood's formula will be presented for each evaluation time point. In addition, comparison between groups will be performed by log-rank test.

4.1.2. Healing rate of reflux esophagitis during the treatment period

Analysis population: Full Analysis Set of the Treatment Period

Analysis item: Cure rate of reflux esophagitis

Timepoint: Treatment Period Weeks 4 and 8

Analytical: For evaluation at and by evaluation time points, frequency tabulation by treatment group,

methods:	point estimate of cure rate, and two-sided 95% confidence interval will be calculated. In addition, the difference in the recurrence rate will be compared between the groups by Fisher's exact test.

4.2. Other Analyses

4.2.1. Barrett's mucosa assessment

Analysis population:	Full Analysis Set of the maintenance phase
Analysis item:	Barrett's mucosa [Present (≥ 3 cm), Present (< 3 cm), Absent, Unknown]
Timepoint:	Maintenance Period Weeks 48, 108, 156, 204 and 260
Analytical methods:	For evaluation at each evaluation time point, frequency will be tabulated by treatment group. In addition, the Mann-Whitney U test will be used to compare the treatment groups for the categories other than non-evaluable.

4.2.2. Evaluation of esophageal hiatal hernia

Analysis population:	Full Analysis Set of the maintenance phase
Analysis item:	hiatal hernia [Yes (≥ 2 cm), Yes (< 2 cm), None, unknown]
Timepoint:	Maintenance Period Weeks 48, 108, 156, 204 and 260
Analytical methods:	For evaluation at each evaluation time point, frequency will be tabulated by treatment group. In addition, the Mann-Whitney U test will be used to compare the treatment groups for the categories other than non-evaluable.

4.2.3. Risk factors for recurrence of reflux esophagitis

Analysis population:	Full Analysis Set of the maintenance phase
Analysis item:	Recurrence of reflux esophagitis on endoscopic findings
Analytical methods:	For each treatment group, the following logistic regression analysis will be performed using the presence or absence of recurrence of reflux esophagitis based on endoscopic findings as the dependent variable.

(1) Univariate analysis with patient background factors (Age, sex, BMI, smoking history, drinking history, intake of caffeine-containing beverages, LA classification at the start of the treatment period, and CYP2C 19 genotyping), endoscopic findings at the start of the treatment period (Fundus gland polyp, hyperplastic polyp, cobblestone mucosa, multiple white flat protrusions, black spot lesion), and histological evaluation of

gastritis (Inflammation (mononuclear cell infiltration), activity (neutrophil infiltration), atrophy, intestinal metaplasia, H. pylori) (greater curvature of the middle corpus of the stomach, greater curvature of the antrum) as independent variables

(2) Multivariate analysis using factors suggested in the univariate analysis and medically important factors as independent variables

5. SAFETY EVALUATION

5.1. Primary Endpoint and Analytical Methods

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: Histopathological examination of gastric mucosa *

Presence or absence of epithelial cell tumorigenesis [Yes, No, Not Evaluable]

Presence or absence of parietal cell elevation/hyperplasia [Yes, No, Not Evaluable]

Presence or absence of crypt epithelial hyperplasia [Yes, No, Not Evaluable]

Endocrine proliferation [Present (1 (atrophic ECM), 2 (hyperplastic ECM), 3 (neoplastic ECM), 4 (typical carcinoid)), absent, not evaluable]

Presence or absence of G cell hyperplasia [Yes, No, Not Evaluable]

*For evaluation up to the evaluation time point, the presence or absence of endocrine cell proliferation should be represented in the order of 4 (typical carcinoid), 3 (neoplastic ECM), 2 (hyperplastic ECM), and 1 (atrophic ECM) as the details of presence. If all tests conducted during TIME WINDOW for each item are “not evaluable, ” the evaluations up to the evaluation time point will be considered“ not evaluable.”

Timepoint: Start of the treatment period, and Weeks 48, 108, 156, 204 and 260 of the maintenance period

Analytical methods: For the above analytical variable, the following analyses should be performed for evaluation at each evaluation time point and evaluation up to the evaluation time point.

(1) For the safety analysis set in the maintenance phase, between-group comparison by Fisher's exact test will be performed for the proportion of "Present" for each finding.

(2) The frequencies in the safety analysis set in the maintenance phase and the subgroups described in 2.2 (Serum gastrin level, serum chromogranin A level) will be presented by treatment group.

(3) Using the Kaplan-Meier method, the cumulative incidence of each finding in histopathological examination of gastric mucosa, standard error according to Greenwood's formula, and two-sided 95% confidence interval will be calculated for each treatment group, and Kaplan-Meier curves will be illustrated. In addition, the number of patients at risk, the cumulative incidence, and the two-sided 95% confidence interval according to Greenwood's formula will be presented for Weeks 52,

112, 160, 208, and 264 from the start of the treatment period as the starting point. In addition, comparison between groups will be performed by log-rank test.

5.2. Secondary Endpoints and Analytical Methods

5.2.1. Endoscopic findings, histological evaluation of gastritis according to the Sydney classification

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: Endoscopic findings

fundic gland polyp [Yes, No]

Hyperplastic polyp [Yes, No]

cobblestone mucosa [Yes, No]

Multiple white flat bumps [Yes, No]

black spot lesion [Yes, No]

Histological evaluation of gastritis * (greater curvature of the middle corpus of the stomach, greater curvature of the antrum)

Inflammation (mononuclear cell infiltration) [Present (Mild, moderate, severe), absent, not evaluable]

Active (neutrophil infiltration) [Present (Mild, moderate, severe), absent, not evaluable]

Atrophy [Present (Mild, moderate, severe), absent, not evaluable]

Metaplasia, intestinal [Present (Mild, moderate, severe), absent, not evaluable]

H.pylori [Present (Mild, moderate, severe), absent, not evaluable]

*For assessments made up to the evaluation time point, the details of yes should be represented in order of decreasing severity. If all tests conducted during TIME WINDOW for each item are “not evaluable, ” the evaluations up to the evaluation time point will be considered“ not evaluable.”

Occurrence of gastric polyp [Yes, No]

Timepoint: Start of the treatment period, and Weeks 48, 108, 156, 204 and 260 of the maintenance period

[Histological evaluation of gastritis]

Start of the treatment period, and Weeks 48, 108, 156, 204 and 260 of the maintenance period

Analytical methods: For the analysis items, frequency of evaluation at each evaluation time point and evaluation up to the evaluation time point will be tabulated by treatment group, and the proportion of “present ” for each finding will be compared between groups by Fisher's exact test.

5.2.2. Other endpoints and analysis methods

5.2.2.1. Clinical Laboratory Evaluation

Analysis population: Safety Analysis Set of the Treatment Period

Safety Analysis Set of the maintenance phase

Analysis item: Blood tests

AST, ALT, Fe, Mg, Ca, and vitamin B 12

Timepoint: [Safety analysis set in the treatment period]

At the start of the treatment period, and Treatment Period Weeks 4 and 8

[Safety Analysis Set of the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 12 in the maintenance period,

Maintenance Period Weeks 24, 36, 48, and 60

Maintenance Period Weeks 72, 84, 96, and 108

Maintenance Period Weeks 132, 156, 180, and 204

Maintenance Period Week 228, Maintenance Period Week 260

Analytical methods: For the analysis items, summary statistics of values at each evaluation time point and summary statistics of pre- and post-treatment differences (value at each evaluation time point after treatment - value at the start of the treatment period) at each evaluation time point will be calculated, and group comparisons of mean pre- and post-treatment differences will be performed using the Mann-Whitney U test.

5.2.2.2. Serum gastrin, pepsinogen I and II levels, and chromogranin A levels

Analysis population: Safety Analysis Set of the Treatment Period

Safety Analysis Set of the maintenance phase

Analysis item: Serum gastrin level

Serum pepsinogen I level

Serum pepsinogen II level

Serum pepsinogen I/II ratio

Serum chromogranin A level

Timepoint: [Serum gastrin level/safety analysis set during the treatment period]

At the start of the treatment period, and Treatment Period Weeks 4 and 8

[Serum gastrin level/safety analysis set in the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 12 in the

maintenance period,

Maintenance Period Weeks 24, 36, 48, and 60

Maintenance Period Weeks 72, 84, 96, and 108

Maintenance Period Weeks 132, 156, 180, and 204

Maintenance Period Week 228, Maintenance Period Week 260

[Analysis sets for serum pepsinogen I, pepsinogen II, pepsinogen I/II ratio, and chromogranin A levels/safety data during the treatment period]

At the start of the treatment period, and Treatment Period Weeks 4 and 8

[Serum pepsinogen I, pepsinogen II, pepsinogen I/II ratio, and chromogranin A/safety analysis set in the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 24 in the maintenance period,

Maintenance Period Weeks 48, 108, 156, and 204

Maintenance Period Week 260

Analytical methods: For the analysis items during the treatment period, summary statistics of values at each evaluation time point and summary statistics of pre- and post-treatment differences (value at each evaluation time point after treatment - value at the start of the treatment period) at each evaluation time point will be calculated, and the mean pre- and post-treatment differences will be compared between the groups using the Mann-Whitney U test.

5.2.2.3. Serum gastrin and chromogranin A levels by the presence or absence of endoscopic findings

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: Serum gastrin level, chromogranin A level

Timepoint: [Serum gastrin level/safety analysis set in the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 12 in the maintenance period,

Maintenance Period Weeks 24, 36, 48, and 60

Maintenance Period Weeks 72, 84, 96, and 108

Maintenance Period Weeks 132, 156, 180, and 204

Maintenance Period Week 228, Maintenance Period Week 260

[Serum chromogranin A level/safety analysis set in the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 24 in the maintenance period,

Maintenance Period Weeks 48, 108, 156, and 204

Maintenance Period Week 260

Analytical methods: Endoscopic findings (Fundus gland polyp, hyperplastic polyp, cobblestone mucosa, multiple white flat protrusions, black spot lesion) will be analyzed by presence/absence at the start of the treatment period and further divided into 4 groups: subjects without findings at the start of the treatment period who developed them during the study period and subjects without findings throughout the study period. The following analyses will be performed.

(1) Summary statistics

5.2.2.4. Correlation between serum gastrin and chromogranin A levels

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: Correlation between serum gastrin and chromogranin A levels

Timepoint: [Safety Analysis Set of the maintenance phase]

At the start of the treatment period, and Treatment Period Weeks 4, 8, and 24 in the maintenance period,

Maintenance Period Weeks 48, 108, 156, and 204

Maintenance Period Week 260

Analytical methods: For the safety analysis set in the maintenance phase, a scatter plot of serum gastrin level on the abscissa and chromogranin A level on the ordinate will be prepared for each time point. Scatter plots will be prepared by treatment group and overlaid with both groups.

5.2.2.5. Changes in serum gastrin level during the maintenance phase

Analysis population: Safety Analysis Set of the maintenance phase

Analysis item: Serum gastrin level

Timepoint: [Serum gastrin level/safety analysis set in the maintenance phase]

At the start of the treatment period, Week 12 of the maintenance period,

Maintenance Period Weeks 24, 36, 48, and 60

Maintenance Period Weeks 72, 84, 96, and 108

Maintenance Period Weeks 132, 156, 180, and 204

Maintenance Period Week 228, Maintenance Period Week 260

Analytical methods: Line charts depicting the proportions of patients with serum gastrin levels < 500 pg/mL, ≥ 500 pg/mL and < 1000 pg/mL, and ≥ 1000 pg/mL are shown. The denominator will be the safety analysis set in the maintenance phase.

6. STATISTICAL/ANALYTICAL ISSUES

6.1. Multiple Comparison/Multiplicity

No multiplicity adjustment will be performed.

7. REVISION HISTORY

Ver.	Date of preparation	Author	Revised Item	Description of Revision
1.0	2023/2/1	[redacted]	Newly created	