Title: Drug Use Surveillance of Vonoprazan for "Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis"

NCT Number: NCT03214952

Statistical analysis plan Approve Date: 18-APR-2019

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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.

Statistical Analysis Plan

(Analysis of final results)

Product Name	: Takecab Tablets
Title of Surveillance	: Gastric Ulcer, Duodenal Ulcer, and Reflux Esophagitis
Protocol No.	: Vonoprazan-5001
Sponsor	: Takeda Pharmaceutical Company Limited

PPD Takeda Pharmaceutical Company Limited

PPD

PPD

Version 1: Prepared on April 18, 2019

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List of terms/abbreviations

- The drug: Takecab Tablets
- ADR etc.: Abbreviation of "adverse drug reaction and infection". Adverse events other than those for which the surveillance investigator assessed the causality as "not related". In this statistical analysis plan, the term "ADR/infection" is used in the title, and the term "ADR etc." is used in the text and tables.
- Serious adverse event:
    - An adverse event that the surveillance investigator assessed as "serious". Events included in the MedDRA code list of Takeda Medially Significant AE List are handled as serious even if the surveillance investigator assessed them as "non-serious".
- Causality "related" to this product: Events for which causality with this product is other than "Unrelated" will be handled as "Related," and events for which causality with this product is "Unrelated" will be handled as "Unrelated."
- Summary statistics: An inclusive term for number of patients, mean, standard deviation, maximum value, minimum value, and quartile.
- Treatment days: The day before Takecab Tablets are started is Day -1, and the day when Takecab Tablets are started is Day 1.
- Duration of suffering (days): Date of starting this product - date of diagnosing the target disease + 1
- Duration of use (days): Date of ending this product - date of starting this product + 1
    - For the patients with status recorded as "treatment ongoing at the end of the surveillance" in the surveillance form, the duration of use will be 56 days for gastric ulcer and reflux esophagitis and 42 days for duodenal ulcer. When more than one target disease for this product exists, the duration of use will be handled as 56 days.
- Patients whose surveillance forms have not been collected: Among patients enrolled in the surveillance, patients whose surveillance forms have not been collected.
- Patients whose surveillance forms have been collected: Among patients enrolled in this surveillance, patients whose surveillance forms have been collected.
- BMI (kg/m^2): Calculated as weight (kg) / height (m) ^{2} (rounded to the first decimal place).
- Time of onset of AE (or ADR etc.): When onset date of an AE (or ADR etc.) is unknown, the first date of the month is the onset date. However, when the year and month of the start of Takecab

Tablets and the year and month of AE (or ADR etc.) onset are the same, the time of onset is allocated as the first start date of Takecab Tablets.

Analysis set

In this surveillance, there will be two analysis sets, “safety analysis set” and “efficacy analysis set.” Individual analysis sets are defined as below.

Safety analysis set

In this statistical analysis plan, “safety analysis set” is defined as “patients treated with Takecab Tablets with no significant protocol violation and evaluable for safety”. In the patients whose surveillance forms have been collected, those falling under the following categories are excluded from the safety analysis set.

- Takecab Tablets were not administered
- Administration of Takecab Tablets prior to contract period (revealed post hoc)
- Enrollment in this surveillance 15 days or later after prescription of Takecab Tablets (revealed post hoc)
- It is unknown whether any AE developed or not

Efficacy analysis set

In this statistical analysis plan, “efficacy analysis set” is defined as “patients treated with Takecab Tablets with no significant protocol violation and evaluable for efficacy”. In the safety analysis set, patients falling under the following categories are excluded from the efficacy analysis set.

- Other than the target diseases [revealed post hoc]
- The exclusion criteria are met.
- Patients for whom assessable efficacy data at the time of treatment with this product and post dose are lacking
    - Patients whose data on endoscopy and subjective symptoms were lacking or deviating from the time window at the start of treatment and after treatment

Important identified risks, important potential risks, and important missing information

- Important identified risk: Not applicable
- Important potential risk
    - Hepatic function disorder: An AE falling under SMQ code 20000006 (Drug related hepatic disorders - comprehensive search [SMQ] narrow) is handled as a hepatic function disorder.
    - Gastrointestinal infection with *Clostridium difficile*: An AE falling under SMQ code 20000080 (Pseudomembranous colitis [SMQ] narrow) is handled as a gastrointestinal infection with clostridium difficile.
- Important missing information: Not applicable

Handling of TIME WINDOW

Data of tests/observations/endpoints that are evaluable (i.e., data that are not missing and are considered to be adopted) are handled based on the following details.

Data that are evaluable and within the time window will be adopted. If there are multiple evaluable data within the same time window, the nearest date of test/observation/assessment to the standard day will be adopted. If the number of days from the standard day is the same or if there is no provision of the standard day, data of the later date will be adopted. The difference from the standard day is determined based on the post-treatment days.

Laboratory tests (AST, ALT, γ-GTP, ALP, total bilirubin, LDH), endoscopy

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of treatment with this product	Post-treatment days: -1	-8 to 1
At the end of the surveillance	Post-treatment days: -	2 or more

Subjective symptoms

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of treatment with this product	Post-treatment days: -1	-8 to 1
2 Weeks after treatment	Post-treatment days: 15	2 to 22
4 Weeks after treatment	Post-treatment days: 29	23 to 36
6 Weeks after treatment	Post-treatment days: 43	37 to 50
8 Weeks after treatment	Post-treatment days: 57	51 or more
At the end of the surveillance	Post-treatment days: -	2 or more

Handling of other items

- None particularly

1 Number of medical institutions, number of patients enrolled, and patient disposition

1.1 Breakdown of patients (figure of patient disposition)

Analysis population: All patients enrolled in this surveillance (patients enrolled)

Analysis items:
- Patients enrolled
- Number of medical institutions
- Patients whose surveillance forms have not been collected
- Patients whose surveillance forms have been collected
- Patients excluded from safety evaluation*
  - Reason for exclusion (multiple counts) [Takecab Tablets not administered, administration prior to contract period (revealed post hoc), enrollment 15 days or later after prescription of this product (revealed post hoc), unknown whether any AE developed or not]
- Patients targeted for safety evaluation*
- Patients excluded from efficacy evaluation*
  - Reason for exclusion (multiple counts) [Other than the target disease (revealed post hoc), exclusion criteria met, postdose assessable efficacy data lacking]
- Patients targeted for efficacy evaluation*

Analysis method: The following analysis will be conducted for the above analysis items, and a figure of patient disposition will be prepared.

The number of medical institutions will also be calculated concerning patients enrolled in the surveillance. If patients are enrolled in more than one department in one medical institution, the number of the medical institutions is counted as one. The number of patients excluded from safety evaluation and efficacy evaluation are counted by reason for exclusion, and a list will be prepared.

* “Patients targeted for safety evaluation” indicates the “safety analysis set”.
“Patients excluded from safety evaluation” indicates patients excluded from

the “safety analysis set”. “Patients targeted for efficacy evaluation” indicates the “efficacy analysis set”. “Patients excluded from efficacy evaluation” indicates patients excluded from the “efficacy analysis set” in the “safety analysis set”.

(1) Frequency count

2 Patient demographics

2.1 Patient demographics

Analysis population:	Safety analysis set	
Analysis items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target diseases for this product (multiple counts)	[Gastric ulcer, duodenal ulcer, reflux esophagitis]
	Duration of suffering (days)	
	Inpatient/outpatient classification	[Outpatient, Inpatient]
	Existence of a hypersensitivity predisposition	[Absent, Present, Unknown]
	Existence of a complication	[Absent, Present]
	Breakdown of complications (multiple counts)	
	Lifestyle-related disease	[Diabetes mellitus, Hypertension, Dyslipidaemia, Hyperuricaemia]
	Hepatic disease	[Hepatic steatosis, Alcoholic hepatitis, Chronic hepatitis, Hepatic cirrhosis, Viral hepatitis, Autoimmune hepatitis]
	Renal disease	[Nephrotic syndrome, Glomerulonephritis, Chronic renal failure]
	Allergic disease	[Bronchial asthma, Pollinosis, Allergic rhinitis, Allergic dermatitis]
	Malignancies	[Gastric cancer, Lung cancer, Colorectal cancer]
	Others	
	Presence/absence of past medical history of gastric ulcer / duodenal ulcer / reflux esophagitis	[Absent, Present, Unknown]
	Details of past history of illness (multiple counts)	[Gastric ulcer, duodenal ulcer, reflux esophagitis]
	Height (cm)	
	Weight (kg)	

	BMI(kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	Presence/absence of *Helicobacter pylori* infection	[Negative, Positive, Unknown]
	Presence/absence of esophageal hiatal hernia	[Absent, Present, Unknown]
	Smoking history	[Non-smoker, Current smoker, Ex-smoker, Unknown]
	Drinking history (consuming alcohol-containing beverages almost daily)	[Yes or No or Unknown]
	Endoscopic findings (gastric ulcer)	[active phase (A1/A2), healing phase (H1/H2)]
	Endoscopic findings (duodenal ulcer)	[active phase (A1/A2), healing phase (H1/H2)]
	Endoscopic findings (reflux esophagitis)	[Grade A, Grade B, Grade C, Grade D]
	Presence/absence of prior treatment	[Absent, Present, Unknown]
	Breakdown of drugs (multiple counts)	[lansoprazole, omeprazole, rabeprazole, esomeprazole, H2 blockers]
	Duration of treatment	[<1 month, ≥1 month - <2 months, ≥2 months]
Analysis method:	The following analysis will be conducted for the above analysis items. (1) Frequency counts of countable data and summary statistics of quantitative data	

3 Treatment details and concomitant drugs

3.1 Treatment details

Analysis population:	Safety analysis set	
Analysis items:	First daily dose	[20 mg, Others]
	Reason for discontinuation of this product	[treatment goal attained, manifestation of AEs, no patient visit due to hospital change etc., pregnancy, lack of effect, others]
Analysis method:	The following analysis will be conducted for the above analysis items. (1) Frequency count	

3.2 Concomitant drug

Analysis population:	Safety analysis set	
Analysis items:	Existence of a concomitant drug	[Absent, Present]
	Type of concomitant drug	
Analysis method:	The following analysis will be conducted for the above analysis items. Concomitant drugs will be coded to terms in the prescription drug term data file, and the data will be summarized by generic name. The drugs will be listed in descending order of frequency. When an identical drug (in generic name) is administered multiple times in a single patient, one patient is counted for the drug (in generic name). When data of a generic name is missing, the product name will be applied. (1) Frequency count	

4 Tabulated analysis of safety results

4.1 Incidences of AEs and ADRs/infections

4.1.1 Incidences of AEs

Analysis population: Safety analysis set

Analysis items: Adverse events

Analysis method: The following analysis will be conducted for the above analysis items.

1) Number of patients with AEs
2) Number of incidences of AEs
3) Proportion of patients with AEs
4) Classification of AEs

The methods to count data for individual analyses are shown below.

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidences of AEs]

- Number of AEs that developed. When an AE develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with AEs]

- To be calculated by the number of patients with AEs/number of patients targeted for safety evaluation x 100.

[Classification of AEs]

- AEs will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with number and proportion of patients with AEs in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with AEs in ascending order of PT codes. When multiple events coded to terms in an identical PT develop in a single patient, one patient will be counted for the PT.

4.1.2 Incidences of ADRs/infections

Analysis population: Safety analysis set

Analysis items: ADRs etc.

Analysis method: The following analysis will be conducted for the above analysis items.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count data for individual analyses are shown below.

[Number of patients with ADRs etc.]

- Number of patients who experienced ADRs etc.

[Number of incidences of ADRs etc.]

- Number of ADRs etc. that developed. When an ADR etc. develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with ADRs etc.]

- To be calculated by the number of patients with ADRs etc./number of patients targeted for safety evaluation x 100.

[Classification of ADRs etc.]

- ADRs etc. will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with the number and proportion of patients with ADR etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC.
- PT will be presented with the number and proportion of patients with ADRs etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT develop in a single patient, one patient will be counted for the PT.

4.1.3 Incidences of AEs and ADRs/infections falling under the categories of important identified risks, important potential risks, and important missing information

4.1.3.1 Incidences of AEs falling under the categories of important identified risks, important potential risks, and important missing information

Analysis population: Safety analysis set

Analysis items: Adverse events falling under the categories of important identified risks, important potential risks, and important missing information (listed in the list of important identified risks, important potential risks, and important missing information)

Analysis method: The following analysis will be conducted for the above analysis items.

1) Number of patients with AEs
2) Number of incidences of AEs
3) Proportion of patients with AEs
4) Classification of AEs

The methods to count data for individual analyses are shown below.

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidences of AEs]

- Number of AEs that developed. When an AE develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with AEs]

- To be calculated by the number of patients with AEs/number of patients targeted for safety evaluation x 100.

[Classification of AEs]

- AEs will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with number and proportion of patients with AEs in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with AEs in ascending order of PT codes. When multiple events coded to terms in an

identical PT develop in a single patient, one patient will be counted for the PT.

4.1.3.2 Incidences of ADRs/infections falling under the categories of important identified risks, important potential risks, and important missing information

Analysis population: Safety analysis set

Analysis items: ADRs etc. falling under the categories of important identified risks, important potential risks, and important missing information (listed in the list of important identified risks, important potential risks, and important missing information)

Analysis method: The following analysis will be conducted for the above analysis items.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count data for individual analyses are shown below.

[Number of patients with ADRs etc.]

- Number of patients who experienced ADRs etc.

[Number of incidences of ADRs etc.]

- Number of ADRs etc. that developed. When an ADR etc. develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with ADRs etc.]

- To be calculated by the number of patients with ADRs etc./number of patients targeted for safety evaluation x 100.

[Classification of ADRs etc.]

- ADRs etc. will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with the number and proportion of patients with ADR etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC.
- PT will be presented with the number and proportion of patients with ADRs etc. in ascending order of PT codes. When multiple events coded to

terms in an identical PT develop in a single patient, one patient will be counted for the PT.

4.1.3.3 Incidences of ADRs and infections falling in the category of safety considerations (tabulation by type of risk)

Analysis population: Safety analysis set

Analysis items: ADRs etc. falling under the categories of safety considerations (listed as important identified risks, important potential risks, and important missing information)

Subgroup items: Seriousness [Serious, Non-serious]

Analysis method: The following analysis will be conducted for the above analysis items in each subgroup by type of risk. The various risks will be defined as described in the listing of important identified risks, important potential risks, and important missing information.

[Classification of ADRs etc.]

- ADRs etc. will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- For SOC, data on the number and proportion of patients with ADR etc. will be presented in the internationally agreed order of SOC.SOC will be presented with the number and proportion of patients with ADR etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC. However, if the events have different seriousness ratings, one patient will be counted for each serious and non-serious event.
- PT will be presented with the number and proportion of patients with ADRs etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT develop in a single patient, one patient will be counted for the PT. However, if the events have different seriousness ratings, one patient will be counted for each serious and non-serious event.

4.2 Incidences of AEs and ADRs/infections in patients excluded from safety evaluation

4.2.1 Incidences of AEs

Analysis population: Patients excluded from the safety analysis set

Analysis items: Adverse events

Analysis method: The following analysis will be conducted for the above analysis items.

1) Number of patients with AEs
2) Number of incidences of AEs
3) Proportion of patients with AEs
4) Classification of AEs

The methods to count data for individual analyses are shown below.

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidences of AEs]

- Number of AEs that developed. When an AE develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with AEs]

- To be calculated by the number of patients with AEs/number of patients targeted for safety evaluation x 100.

[Classification of AEs]

- AEs will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with number and proportion of patients with AEs in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with AEs in ascending order of PT codes. When multiple events coded to terms in an identical PT develop in a single patient, one patient will be counted for the PT.

4.2.2 Incidences of ADRs/infections

Analysis population: Patients excluded from the safety analysis set

Analysis items: ADRs etc.

Analysis method: The following analysis will be conducted for the above analysis items.

1) Number of patients with ADRs etc.

2) Number of incidences of ADRs etc.

3) Proportion of patients with ADRs etc.

4) Classification of ADRs etc.

The methods to count data for individual analyses are shown below.

[Number of patients with ADRs etc.]

- Number of patients who experienced ADRs etc.

[Number of incidences of ADRs etc.]

- Number of ADRs etc. that developed. When an ADR etc. develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with ADRs etc.]

- To be calculated by the number of patients with ADRs etc./number of patients targeted for safety evaluation x 100.

[Classification of ADRs etc.]

- ADRs etc. will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with the number and proportion of patients with ADR etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC.
- PT will be presented with the number and proportion of patients with ADRs etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT develop in a single patient, one patient will be counted for the PT.

4.3 Incidences of AEs and ADRs/infections by seriousness, time of onset, and outcome

4.3.1 Incidences of AEs by seriousness, time of onset, and outcome

Analysis population:	Safety analysis set	
Analysis items:	Adverse events	
Subgroup items:	Seriousness	[Serious, Non-serious]
	Time of onset	[Day 1-14, Day 15-28, Day 29-42, Day 43-56, Day 57 and after, Unknown]

Outcome [Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to this event), Unknown]

Analysis method: The following analysis will be conducted for the above analysis items in each subgroup.

1) Number of patients with AEs
2) Number of incidences of AEs
3) Proportion of patients with AEs
4) Classification of AEs

The methods to count data for individual analyses are shown below.

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidences of AEs]

- Number of AEs that developed. When an AE develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with AEs]

- To be calculated by the number of patients with AEs/number of patients targeted for safety evaluation x 100.

[Classification of AEs]

- AEs will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with number and proportion of patients with AEs in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC. However, in an identical SOC, one event is adopted according to the priority order specified at the foot note.
- PT will be presented with number and proportion of patients with AEs in ascending order of PT codes. When multiple events coded to terms in an identical PT develop in a single patient, one patient will be counted for the PT. However, for an identical PT, one event is adopted according to the following order of priority.

  Seriousness: Serious → Non-serious

  Time of onset: The event that developed earliest after treatment with this product was started

Outcome: Death (due to this event) → Resolved with sequelae → Not resolved → Resolving → Resolved → Unknown

4.3.2 Incidences of ADRs/infections by seriousness, time of onset, and outcome

Analysis population:	Safety analysis set	
Analysis items:	ADRs etc.	
Subgroup items:	Seriousness	[Serious, Non-serious]
	Time of onset	[Day 1-14, Day 15-28, Day 29-42, Day 43-56, Day 57 and after, Unknown]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to this event), Unknown]

Analysis method: The following analysis will be conducted for the above analysis items.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count data for individual analyses are shown below.

[Number of patients with ADRs etc.]

- Number of patients who experienced ADRs etc.

[Number of incidences of ADRs etc.]

- Number of ADRs etc. that developed. When an ADR etc. develops multiple times in a single patient, the total number of events will be counted.

[Proportion of patients with ADRs etc.]

- To be calculated by the number of patients with ADRs etc./number of patients targeted for safety evaluation x 100.

[Classification of ADRs etc.]

- ADRs etc. will be coded to MedDRA/J terms. ADRs will be counted by PT and sorted by SOC. When the SOC is “Investigations”, the event is counted by PT and sorted by HLGT (events will be listed in ascending order of HLGT codes without output).
- SOC will be presented with the number and proportion of patients with ADR etc. in the internationally agreed order of SOC. When multiple events

coded to terms in an identical SOC develop in a single patient, one patient will be counted for the SOC. However, in an identical SOC, one event is adopted according to the priority order specified at the foot note.

- PT will be presented with the number and proportion of patients with ADRs etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT develop in a single patient, one patient will be counted for the PT. However, for an identical PT, one event is adopted according to the following order of priority.
  Seriousness: Serious → Non-serious
  Time of onset: The event that developed earliest after treatment with this product was started
  Outcome: Death (due to this event) → Resolved with sequelae → Not resolved → Resolving → Resolved → Unknown

4.4 Incidences of ADRs/infections by factor of patient demographics and treatment details

4.4.1 Incidences of ADRs/infections by factor of patient demographics and treatment details

Analysis population:	Safety analysis set	
Analysis items:	ADRs etc.	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target diseases for this product (multiple counts)	[Gastric ulcer, duodenal ulcer, reflux esophagitis]
	Existence of a complication	[Absent, Present]
	Breakdown of complications (multiple counts)	[Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Malignancies, Others]
	BMI(kg/ m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	Existence of a hypersensitivity predisposition	[Absent, Present, Unknown]
	Existence of a concomitant drug	[Absent, Present]
Analysis method:	The following analysis will be conducted for the above analysis items in each subgroup, and the chi-square test will be conducted as reference (excluding items falling under the category of multiple counts).	

1) Number of patients with ADRs etc.

2) Proportion of patients with ADRs etc. and its 95% confidence interval (two-sided)

The methods to count data for individual analyses are shown below.

[Number of patients with ADRs etc.]

- Number of patients who experienced ADRs etc.

[Proportion of patients with ADRs etc.]

- To be calculated by the number of patients with ADRs etc./number of patients targeted for safety evaluation x 100.

4.4.2 Incidences of ADRs/infections by sex

Analysis population:	Safety analysis set	
Analysis items:	ADRs etc.	
Subgroup items:	Sex	[Male, Female]

Analysis method: The following analysis will be conducted for the above analysis items in each subgroup.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count individual analysis items are the same as specified in Section 4.2.2.

4.4.3 Incidences of ADRs/infections by age subgroup

Analysis population:	Safety analysis set	
Analysis items:	ADRs etc.	
Subgroup items:	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]

Analysis method: The following analysis will be conducted for the above analysis items in each subgroup.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count individual analysis items are the same as specified in Section 4.2.2.

4.4.4 Incidences of ADRs/infections by target disease for this product

Analysis population:	Safety analysis set	
Analysis items:	ADRs etc.	
Subgroup items:	Target diseases for this product (multiple counts)	[Gastric ulcer, duodenal ulcer, reflux esophagitis]
Analysis method:	The following analysis will be conducted for the above analysis items in each subgroup. 1) Number of patients with ADRs etc. 2) Number of incidences of ADRs etc. 3) Proportion of patients with ADRs etc. 4) Classification of ADRs etc. The methods to count individual analysis items are the same as specified in Section 4.2.2.	

4.4.5 Incidences of ADRs/infections by presence/absence of complication

Analysis population:	Safety analysis set	
Analysis items:	ADRs etc.	
Subgroup items:	Existence of a complication	[Absent, Present]
Analysis method:	The following analysis will be conducted for the above analysis items in each subgroup. 1) Number of patients with ADRs etc. 2) Number of incidences of ADRs etc. 3) Proportion of patients with ADRs etc. 4) Classification of ADRs etc. The methods to count individual analysis items are the same as specified in Section 4.2.2.	

4.4.6 Incidences of ADRs/infections by breakdown of complication

Analysis population:	Safety analysis set	
Analysis items:	ADRs etc.	
Subgroup items:	Breakdown of complications (multiple counts)	[Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Malignancies, Others]

Analysis method: The following analysis will be conducted for the above analysis items in each subgroup.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count individual analysis items are the same as specified in Section 4.2.2.

4.4.7 Incidences of ADRs/infections by BMI subgroup

Analysis population: Safety analysis set

Analysis items: ADRs etc.

Subgroup items: BMI(kg/ m^2) [Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]

Analysis method: The following analysis will be conducted for the above analysis items in each subgroup.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count individual analysis items are the same as specified in Section 4.2.2.

4.4.8 Incidences of ADRs/infections by presence/absence of concomitant drug

Analysis population: Safety analysis set

Analysis items: ADRs etc.

Subgroup items: Existence of a concomitant drug [Absent, Present]

Analysis method: The following analysis will be conducted for the above analysis items in each subgroup.

1) Number of patients with ADRs etc.
2) Number of incidences of ADRs etc.
3) Proportion of patients with ADRs etc.
4) Classification of ADRs etc.

The methods to count individual analysis items are the same as specified in Section 4.2.2.

4.4.9 Change of liver function test value

Analysis population:	Safety analysis set
Analysis items:	AST (IU/L), AL T(IU/L), γ-GTP (IU/L), ALP (IU/L), Total bilirubin (mg/dL), LDH (IU/L)
Analysis method:	Summary statistics will be calculated for the measured values at each evaluation period [at the start of treatment and at the end of the surveillance] for the above analysis items. In addition, summary statistics and the two-sided 95% confidence interval of the mean change from the start of treatment will be calculated.

5 Tabulated analysis of efficacy results

5.1 Endoscopy

Analysis population: Patients in the efficacy analysis set whose target disease for this product is "gastric ulcer"
Patients in the efficacy analysis set whose target disease for this product is "duodenal ulcer"
Patients in the efficacy analysis set whose target disease for this product is "reflux gastritis"

Analysis items: Endoscopic findings

Gastric ulcer	[active phase (A1/A2), healing phase (H1/H2), scarring phase (S1/S2)]
Duodenal ulcer	[active phase (A1/A2), healing phase (H1/H2), scarring phase (S1/S2)]
Reflux esophagitis	[Grade N, Grade M, Grade A, Grade B, Grade C, Grade D]

Analysis method: For each of the above analysis items, frequency in the corresponding analysis set will be counted by evaluation time [at the start of treatment and at the end of the surveillance]. Furthermore, point estimates and the two-sided 95% confidence interval of endoscopic healing rates at the end of the surveillance will be calculated. The endoscopic healing rate is defined as the proportion of the scarring phase (S1/S2) for gastric ulcer and duodenal ulcer and the proportion of Grade N and Grade M for reflux esophagitis with the number of patients in each analysis set, excluding patients with missing endoscopic findings at the end of the surveillance, as the denominator.

5.2 Subjective symptoms

Analysis population: Patients in the efficacy analysis set whose target disease for this product is "gastric ulcer"
Patients in the efficacy analysis set whose target disease for this product is "duodenal ulcer"
Patients in the efficacy analysis set whose target disease for this product is "reflux gastritis"

Analysis items: Subjective symptoms

Heartburns	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Acid reflux	[Asymptomatic, Mild, Moderate, Severe, Unknown]

Postprandial heavy stomach feeling	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Early satiety	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Epigastralgia	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Epigastric burning	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Sensation of abdominal distention	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Nausea/vomiting	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Burping	[Asymptomatic, Mild, Moderate, Severe, Unknown]
Anorexia	[Asymptomatic, Mild, Moderate, Severe, Unknown]

Analysis method: Frequency of each of the above analysis items in each analysis set will be counted by evaluation time [at the start of treatment, Week 2 of treatment, Week 4 of treatment, Week 6 of treatment, Week 8 of treatment, at the end of the surveillance]. Furthermore, for each analysis item, point estimates and the two-sided 95% confidence interval of amelioration rates in subjects with symptoms at the start of treatment will be calculated by evaluation time after the start of treatment. The amelioration rate is defined as the proportion of the number of patients "Ameliorated" dividing by the total number of patients "Ameliorated" and "Not ameliorated"; referring patients achieving an improvement of 1 grade or more from the start of treatment as "Ameliorated" and other than that as "Not ameliorated". Patients with an Unknown rating and patients with missing data at each evaluation time after the start of treatment will be excluded from amelioration rate calculations.

5.3 Factors that may affect efficacy

5.3.1 Endoscopic healing rate by patient demographic factor

Analysis population: Patients in the efficacy analysis set whose target disease for this product is "gastric ulcer"

Patients in the efficacy analysis set whose target disease for this product is "duodenal ulcer"

	Patients in the efficacy analysis set whose target disease for this product is "reflux gastritis"	
Analysis items:	Endoscopic healing rate (at the end of the surveillance) Gastric ulcer Duodenal ulcer Reflux esophagitis	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Existence of a complication	[Absent, Present]
	Breakdown of complications (multiple counts)	[Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Malignancies, Others]
	BMI(kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	Smoking history	[Non-smoker, Current smoker, Ex-smoker, Unknown]
	Drinking history (consuming alcohol-containing beverages almost daily)	[Yes or No or Unknown]
	Existence of a concomitant drug	[Absent, Present]
	Presence/absence of *Helicobacter pylori* infection	[Negative, Positive, Unknown]
	Presence/absence of esophageal hiatal hernia	[Absent, Present, Unknown]
	Presence/absence of prior treatment	[Absent, Present, Unknown]
Analysis method:	For the above analysis items, point estimates and two-sided 95% confidence intervals of endoscopic healing rates at the end of the surveillance will be calculated for each subgroup. Healing rates will be calculated in accordance with the definition described in Section 5.1: Analytical procedures for subjective symptoms.	

5.3.2 Subjective symptom amelioration rate by patient demographic factor

Analysis population:	Patients in the efficacy analysis set whose target disease for this product is "gastric ulcer" Patients in the efficacy analysis set whose target disease for this product is "duodenal ulcer" Patients in the efficacy analysis set whose target disease for this product is "reflux gastritis"

Analysis items:	Subjective symptom amelioration rate (at the end of the surveillance) Heartburns Acid reflux Postprandial heavy stomach feeling Early satiety Epigastralgia Epigastric burning Sensation of abdominal distention Nausea/vomiting Burping Anorexia	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Existence of a complication	[Absent, Present]
	Breakdown of complications (multiple counts)	[Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Malignancies, Others]
	BMI(kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	Smoking history	[Non-smoker, Current smoker, Ex-smoker, Unknown]
	Drinking history (consuming alcohol-containing beverages almost daily)	[Yes or No or Unknown]
	Existence of a concomitant drug	[Absent, Present, Unknown]
	Presence/absence of *Helicobacter pylori* infection	[Negative, Positive, Unknown]
	Presence/absence of esophageal hiatal hernia	[Absent, Present, Unknown]
	Presence/absence of prior treatment	[Absent, Present, Unknown]
Analysis method:	In each analysis set, point estimates and the two-sided 95% confidence interval of amelioration rates at the end of the surveillance will be calculated for the each analysis items in each subgroup. Amelioration rates will be calculated in accordance with the definition described in Section 5.2: Analytical procedures for subjective symptoms.	

6 Incidences of ADRs and infections in the additional pharmacovigilance plan

6.1 Incidences of ADRs and infections in the additional pharmacovigilance plan (Attached Form 12)

Analysis population:	Safety analysis set
Analysis items:	ADRs etc. falling under the categories of safety considerations (listed as important identified risks, important potential risks, and important missing information)
Subgroup items:	Seriousness [Serious, Non-serious]
Analysis method:	The following analysis will be conducted for the above analysis items in each subgroup in accordance with Notes 1 to 4 in Attached Form 12, Yakuseiyakushinhatsu Reexamination Notification No. 1128-2 dated November 28, 2017. 1) Number and proportion of patients with manifested events Risk names and the order of their listing will be in accordance with the list of important identified risks, important potential risks, and important missing information.

7 Case summary in the postmarketing surveillance etc.

7.1 Case summary in the postmarketing surveillance etc. (Attached Form 16)

Analysis population:	Patients whose surveillance forms have been collected
Analysis items:	Patient number Facility name Sex Date of birth Indication (disease code, disease name) Complication (disease code, disease name) Route of administration Maximum dose Mean dose Unit Treatment period Concomitant drug (drug code, name of drug) Level of effect ADR (disease code, disease name, outcome) Survey form No. Withdrawal
Analysis method:	With regard to the above analysis items, a list will be generated in accordance with Notes 1 to 3 in Attached Form 16, Yakuseiyakushinhatsu Reexamination Notification No. 1128-2 dated November 28, 2017.

Revision history (version control)

Version	Date	Person who prepared/revised this document	Comment
Version 1	April 18, 2019	PPD	Preparation of Version 1