



Title: Drug use surveillance of Takecab tablets “Supplement to Helicobacter pylori eradication”

NCT Number: NCT03219723

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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 : Supplement to *Helicobacter pylori* eradication
Protocol No. : Vonoprazan-5002
Sponsor : Takeda Pharmaceutical Company Limited

Japan Development Center, Takeda Pharmaceutical Company Limited
Head of biostatistics unit

_____ Seal

Date:

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List of terms/abbreviations

- The drug: Takecab Tablets
- PPI: Proton pump inhibitor is abbreviated to PPI.
- AMPC: Amoxicillin is abbreviated to AMPC.
- CAM: Clarithromycin is abbreviated to CAM. The dose is presented as a daily dose.
- MTZ: Metronidazole is abbreviated to MTZ.
- Triple therapy: Takecab Tablets, amoxicillin and clarithromycin if it is first-line eradication.
Takecab Tablets, amoxicillin and metronidazole if it is second-line eradication.
- ADR, etc.: Abbreviation of “adverse reaction and infection”. Adverse events other than those 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 which the surveillance investigator assessed as “serious”. Events included in the MedDRA code list of Takeda Medically Significant AE List are handled as serious even if the surveillance investigator assessed as “non-serious”.
- Causality “related” to Takecab Tablets: The causality of an event assessed as “related” to Takecab Tablets or as “unassessable” is handled as “related”, and the causality of an event assessed as “not related” to Takecab Tablets is handled as “not related”.
- Summary statistics: An inclusive term of number of patients, mean, standard deviation, maximum value, minimum value, and quartile.
- Treatment days: The day before Takecab Tablets is started is Day -1, and the day when Takecab Tablets is started is Day 1.
- Post-treatment days: The day after the completion of Takecab Tablets administration is post-treatment Day 1.
- Patients whose survey forms have not been collected: In patients enrolled in the survey, patients whose survey forms have not been collected.
- Patients whose survey forms have been collected: In patients enrolled in this survey, patients whose survey forms have been collected.
- BMI (kg/m²): 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. The classification of time of onset is defined below when AEs (or ADRs, etc.) are counted by time of onset.
 - Duration of triple therapy: From the start day of triple therapy to the completion day of triple therapy.
 - After the completion of triple therapy: On or after the next day of the completion of triple therapy.

Analysis set

In this survey, two analysis sets of “safety analysis set” and “efficacy analysis set” will be set. Individual analysis sets are defined as below. Additionally, a patient enrolled and given both first-line and second-line eradication in this survey will be counted separately.

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 survey forms have been collected, those falling under the following categories are excluded from the safety analysis set.

- Takecab Tablets was not administered
- Administration of Takecab Tablets prior to contract period
- Enrollment in this survey 6 days or later after prescription of triple therapy
- 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.

- Determination of *H. pylori* eradication has not been conducted
- Determination of *H. pylori* eradication less than 28 days after completion or discontinuation of triple therapy
- Treatment was given with a combination of three drugs other than Takecab Tablets + amoxicillin + clarithromycin in patients given first-line eradication
- Treatment was given with a combination of three drugs other than Takecab Tablets + amoxicillin + metronidazole in patients given second-line eradication

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 hepatic function disorder.
 - Gastrointestinal infection with clostridium difficile: An AE falling under SMQ code 20000080 (Pseudomembranous colitis [SMQ] narrow) is handled as gastrointestinal infection with clostridium difficile.
- Important missing information: Not applicable

Handling of TIME WINDOW

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

Data which 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, 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)

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of triple therapy	Post-treatment days: -1	-8 to 1
At the completion of triple therapy	Post-treatment days: 8	2 or more

Handling of others

- 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 survey (patients enrolled)	
Analysis items:	Patients enrolled	
	Number of medical institutions	
	Patients whose survey forms have not been collected	
	Reason why survey form is not yet collected	[Change of the surveillance investigator, Health reason of the surveillance investigator, Others]
	Patients whose survey forms have been collected	
	Patients excluded from safety evaluation*	
	Reason of exclusion (multiple counts)	[Takecab Tablets not administered, Administration prior to contract period, Enrollment 6 days or later after prescription of triple therapy, Unknown whether any AE developed or not]
	Patients targeted for safety evaluation*	
	Patients excluded from efficacy evaluation*	
	Reason of exclusion (multiple counts)	[Determination of <i>H. pylori</i> eradication not conducted, Determination of eradication within 4 weeks after completion or discontinuation of triple therapy, Treatment with a combination of three drugs other than Takecab Tablets + amoxicillin + clarithromycin in first-line eradication, Treatment with a combination of three drugs other than Takecab Tablets + amoxicillin + metronidazole in second-line eradication]
	Patients targeted for efficacy	

evaluation*

Analysis method: 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 survey. If patients are enrolled in more than one department in one medical institution, the number of the medical institution is counted as one. Number of patients excluded from safety evaluation and efficacy evaluation are counted by reason of exclusion, and a list will be prepared.

* “Patients targeted for safety evaluation” indicates “safety analysis set”.

“Patients excluded from safety evaluation” indicates patients excluded from “safety analysis set”. “Patients targeted for efficacy evaluation” indicates “efficacy analysis set”. “Patients excluded from efficacy evaluation” indicates patients excluded from “efficacy analysis set” in “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 disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
	Inpatient/outpatient classification	[Outpatient, Inpatient]
	Existence of hypersensitivity predisposition	[Yes or No or Unknown]
	Existence of complication	[Yes or No]
	Breakdown of complication (multiple counts)	[Diabetes mellitus, Hypertension, Dyslipidaemia, Hyperuricaemia]
	Lifestyle-related disease	
	Gastrointestinal disease (reflux oesophagitis)	
	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]
	Others	
	Details of previous <i>H. pylori</i> eradication	[PPI + AMPC + CAM 400 mg, PPI + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800

	mg, Unknown]
Height (cm)	
Weight (kg)	
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 (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
<i>H. pylori</i> infection diagnostic method (multiple counts)	[Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> antigen assay]
Treatment details	
First-line eradication	[Takecab Tablets + AMPC + CAM, Takecab Tablets + AMPC + MTZ]
Second-line eradication	
Analysis method:	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 drug

3.1 Treatment details

Analysis Safety analysis set

population:

Analysis items:	Triple therapy	[Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM other doses, Takecab Tablets + AMPC + MTZ]
	Whether triple therapy was discontinued or not	[Yes or No]
	Breakdown of reasons of discontinuation of triple therapy	[Incidence of AE, No patient visit due to reasons such as changing hospital, Pregnancy, Others]
	Method of determination of <i>H. pylori</i> eradication at the completion of triple therapy (multiple counts)	[Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> antigen assay, not yet conducted]

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

(1) Frequency count

3.2 Concomitant drug

Analysis Safety analysis set

population:

Analysis items:	Existence of concomitant drug	[Yes or No]
	Type of concomitant drug	

Analysis method: Following analysis will be conducted for the above analysis items. Concomitant drugs will be coded to terms in 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 one 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 on safety results

4.1 Incidence of AE and ADR/infection

4.1.1 Incidence of AE

Analysis Safety analysis set

population:

Analysis items: Adverse event

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs
- (3) Proportion of patients with AEs
- (4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed in a single patient, one patient will be counted for the PT.

4.1.2 Incidence of ADR/infection

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed in a single patient, one patient will be counted for the PT.

4.1.3 Incidence of AE and ADR/infection falling under the categories of important identified risks, important potential risks, and important missing information

4.1.3.1 Incidence 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

terms/abbreviations)

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs
- (3) Proportion of patients with AEs
- (4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed in a single patient, one patient will be counted for the PT.

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

Analysis Safety analysis set

population:

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

Analysis method: Following analyses will be conducted for the above analysis items by drug

combination (Takecab Tablets + AMPC + CAM and Takecab Tablets + AMPC + MTZ) and pooled data of combinations.

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed in a single patient, one patient will be counted for the PT.

4.2 Incidence of AE and ADR/infection in patients excluded from safety evaluation

4.2.1 Incidence of AE

Analysis Patients excluded from safety analysis set
population:

Analysis items: Adverse event

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs

(3) Proportion of patients with AEs

(4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed in a single patient, one patient will be counted for the PT.

4.2.2 Incidence of ADR/infection

Analysis population: Patients excluded from safety analysis set

Analysis items: ADRs, etc.

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed in a single patient, one patient will be counted for the PT.

4.3 Incidence of AE and ADR/infection by seriousness, time of onset, and outcome

4.3.1 Incidence of AE by seriousness, time of onset, and outcome

Analysis Safety analysis set

population:

Analysis items: Adverse event

Subgroup items:	Seriousness	[Serious, Non-serious]
	Time of onset	[During triple therapy, After completion of triple therapy]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown]

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs
- (3) Proportion of patients with AEs
- (4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed 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 which developed earliest after triple therapy was started

Outcome: Death → Resolved with sequelae → Not resolved → Resolving → Resolved → Unknown

4.3.2 Incidence of ADR/infection by seriousness, time of onset, and outcome

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Seriousness

[Serious, Non-serious]

Time of onset

[During triple therapy, After completion of triple therapy]

Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown]
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Analysis method: Following analyses will be conducted for the above analysis items in each subgroup by drug combination (Takecab Tablets + AMPC + CAM and Takecab Tablets + AMPC + MTZ) and pooled data of combinations.

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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 sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed 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 ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed 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 which developed earliest after triple therapy was started

Outcome: Death → Resolved with sequelae → Not resolved → Resolving
→ Resolved → Unknown

4.4 Incidence of ADR/infection by factor of patient demographics and treatment details

4.4.1 Incidence of ADR/infection by factor of patient demographics and treatment details

Analysis	Safety analysis set	
population:		
Analysis items:	ADRs, etc.	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
	Existence of complication	[Yes or No]
	Breakdown of complication (multiple counts)	[Lifestyle-related disease, Gastrointestinal disease, Hepatic disease, Renal disease, Allergic disease, Others]
	BMI (kg/ m ²)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	Triple therapy	[Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM other doses, Takecab Tablets + AMPC + MTZ]
	Classification of drugs	[Takecab Tablets + AMPC + CAM, Takecab Tablets + AMPC + MTZ]
	Existence of concomitant drug	[Yes or No]
Analysis method:	Following analysis will be conducted for the above analysis items in each subgroup, and 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 with number of patients with ADRs, etc./number of patients targeted for safety evaluation x 100.

4.4.2 Incidence of ADR/infection by sex

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Sex [Male, Female]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by age subgroup

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Age (year) [Min<= - <65, 65<= - <75, 75<= - <=Max]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by target disease of *H. pylori* eradication

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Target disease (multiple counts) [Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, *H. pylori* gastritis]
[Gastric ulcer or duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma or idiopathic thrombocytopenic purpura or stomach following endoscopic treatment of early gastric cancer or *H. pylori* gastritis]

Analysis method: Following analyses will be conducted for the above analysis items in each subgroup by drug combination (Takecab Tablets + AMPC + CAM and Takecab Tablets + AMPC + MTZ) and pooled data of combinations.

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by presence/absence of complication

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Existence of complication [Yes or No]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by breakdown of complication

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

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by BMI subgroup

Analysis Safety analysis set
population:
Analysis items: ADRs, etc.
Subgroup items: BMI (kg/ m²) [Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by triple therapy

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Triple therapy [Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM other doses, Takecab Tablets + AMPC + MTZ]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by classification of drug

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Classification of drugs [Takecab Tablets + AMPC + CAM, Takecab Tablets + AMPC + MTZ]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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.

4.4.10 Incidence of ADR/infection by presence/absence of concomitant drug

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Existence of concomitant drug [Yes or No]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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.

4.4.11 List of outlines of patients targeted for analysis (Attachment Form 3)

Analysis population: Patients whose survey forms have been collected

Analysis items:

- Patient number
- Name of medical institution (company code)
- Main body of establishment/code
- Prefecture
- Patient initials
- Sex
- Date of birth
- Inpatient/outpatient classification
- Indication (disease code, disease name)
- Baseline severity
- Existence of complication (yes or no, number, term)
- Route of administration
- Maximum dose (daily dose/one dosage)
- Mean dose (daily dose/one dosage)
- Unit
- Daily dose frequency (maximum)
- Treatment period
- Concomitant drug (drug code, name of representative drug, number of drugs)
- Level of effect
- ADR (SOC code, ADR code, ADR term, yes or no, number)
- Outcome
- Survey form No.
- Withdrawal

Analysis method: A list will be prepared for the above analysis items.

4.4.12 Change of liver function test value

Analysis Safety analysis set

population:

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 of each evaluation period [at the start of triple therapy, at the completion of triple therapy] for the above analysis items. In addition, summary statistics and 95% confidence interval of mean change from the start of triple therapy will be calculated.

5 Tabulated analysis on efficacy results

5.1 Eradication rate of *H. pylori*

5.1.1 Eradication rate of first-line *H. pylori* eradication 4 weeks after completion of first-line eradication

Analysis population: Patients given first-line eradication in the efficacy analysis set

Analysis items: Eradication rate of first-line *H. pylori* eradication 4 weeks after completion of first-line eradication (%)

Analysis method: Frequency will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.

5.1.2 Eradication rate of second-line *H. pylori* eradication 4 weeks after completion of second-line eradication

Analysis population: Patients given second-line eradication in the efficacy analysis set

Analysis items: Eradication rate of second-line *H. pylori* eradication 4 weeks after the completion of the second-line eradication (%)

Analysis method: Frequency will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.

5.2 Factors which may affect efficacy

5.2.1 Eradication rate of *H. pylori* by patient demographic factor (patients of first-line eradication)

Analysis population: Patients given first-line eradication in the efficacy analysis set

Analysis items: Eradication rate of first-line *H. pylori* eradication 4 weeks after completion of first-line eradication (%)

Subgroup items:

Sex	[Male, Female]
Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
Target disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic

	thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
Existence of complication	[Yes or No]
Breakdown of complication (multiple counts)	[Lifestyle-related disease, Gastrointestinal disease, Hepatic disease, Renal disease, Allergic disease, 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 (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
Daily dose of clarithromycin	[400 mg, 800 mg, Others]
Whether triple therapy was discontinued or not	[Yes or No]

Analysis method: Frequency by each subgroup will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.

5.2.2 Eradication rate of *H. pylori* by patient demographic factor (patients of second-line eradication)

Analysis population:	Patients given second-line eradication in the efficacy analysis set	
Analysis items:	Eradication rate of second-line <i>H. pylori</i> eradication 4 weeks after the completion of the second-line eradication (%)	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach

	following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
Existence of complication	[Yes or No]
Breakdown of complication (multiple counts)	[Lifestyle-related disease, Gastrointestinal disease, Hepatic disease, Renal disease, Allergic disease, Others]
Details of previous <i>H. pylori</i> eradication	[PPI + AMPC + CAM 400 mg, PPI + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Unknown]
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 (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
Whether triple therapy was discontinued or not	[Yes or No]
Analysis method: Frequency by each subgroup will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.	

Revision history (version control)

Version	Date	Person who prepared/revised this document	Comment
Version 1	August 18, 2017	PPD [REDACTED]	Preparation of Version 1
Version 2	November 8, 2017	PPD [REDACTED]	Preparation of Version 2

[Attachment 1] Comparison Table of revision of Vonoprazan-5002

Page	Before revision	After revision	Reason of revision
10	<i>H. pylori</i> infection diagnostic method (multiple counts) [Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> <u>antibody</u> assay]	<i>H. pylori</i> infection diagnostic method (multiple counts) [Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> <u>antigen</u> assay]	Correction of the incorrect term.
11	Method of determination of <i>H. pylori</i> eradication at the completion of triple therapy (multiple counts) [Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> <u>antibody</u> assay, not yet conducted]	Method of determination of <i>H. pylori</i> eradication at the completion of triple therapy (multiple counts) [Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> <u>antigen</u> assay, not yet conducted]	Correction of the incorrect term.
11	(New)	When data of a generic name is missing, the product name will be applied.	As there are concomitant drugs of which the drug codes are in three digits and their generic names will become missing data, it was determined to apply product names for these drugs.

Statistical Analysis Plan

(Analysis of final results)

Product Name : Takecab Tablets
Title of Surveillance : Supplement to *Helicobacter pylori* eradication
Protocol No. : Vonoprazan-5002
Sponsor : Takeda Pharmaceutical Company Limited

Japan Development Center, Takeda Pharmaceutical Company Limited
Head of biostatistics unit

_____ Seal

Date:

Version 1: Prepared on August 18, 2017

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List of terms/abbreviations

- The drug: Takecab Tablets
- PPI: Proton pump inhibitor is abbreviated to PPI.
- AMPC: Amoxicillin is abbreviated to AMPC.
- CAM: Clarithromycin is abbreviated to CAM. The dose is presented as a daily dose.
- MTZ: Metronidazole is abbreviated to MTZ.
- Triple therapy: Takecab Tablets, amoxicillin and clarithromycin if it is first-line eradication.
Takecab Tablets, amoxicillin and metronidazole if it is second-line eradication.
- ADR, etc.: Abbreviation of “adverse reaction and infection”. Adverse events other than those 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 which the surveillance investigator assessed as “serious”. Events included in the MedDRA code list of Takeda Medically Significant AE List are handled as serious even if the surveillance investigator assessed as “non-serious”.
- Causality “related” to Takecab Tablets: The causality of an event assessed as “related” to Takecab Tablets or as “unassessable” is handled as “related”, and the causality of an event assessed as “not related” to Takecab Tablets is handled as “not related”.
- Summary statistics: An inclusive term of number of patients, mean, standard deviation, maximum value, minimum value, and quartile.
- Treatment days: The day before Takecab Tablets is started is Day -1, and the day when Takecab Tablets is started is Day 1.
- Post-treatment days: The day after the completion of Takecab Tablets administration is post-treatment Day 1.
- Patients whose survey forms have not been collected: In patients enrolled in the survey, patients whose survey forms have not been collected.
- Patients whose survey forms have been collected: In patients enrolled in this survey, patients whose survey forms have been collected.
- BMI (kg/m²): 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. The classification of time of onset is defined below when AEs (or ADRs, etc.) are counted by time of onset.
 - Duration of triple therapy: From the start day of triple therapy to the completion day of triple therapy.
 - After the completion of triple therapy: On or after the next day of the completion of triple therapy.

Analysis set

In this survey, two analysis sets of “safety analysis set” and “efficacy analysis set” will be set. Individual analysis sets are defined as below. Additionally, a patient enrolled and given both first-line and second-line eradication in this survey will be counted separately.

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 survey forms have been collected, those falling under the following categories are excluded from the safety analysis set.

- Takecab Tablets was not administered
- Administration of Takecab Tablets prior to contract period
- Enrollment in this survey 6 days or later after prescription of triple therapy
- 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.

- Determination of *H. pylori* eradication has not been conducted
- Determination of *H. pylori* eradication less than 28 days after completion or discontinuation of triple therapy
- Treatment was given with a combination of three drugs other than Takecab Tablets + amoxicillin + clarithromycin in patients given first-line eradication
- Treatment was given with a combination of three drugs other than Takecab Tablets + amoxicillin + metronidazole in patients given second-line eradication

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 hepatic function disorder.
 - Gastrointestinal infection with clostridium difficile: An AE falling under SMQ code 20000080 (Pseudomembranous colitis [SMQ] narrow) is handled as gastrointestinal infection with clostridium difficile.
- Important missing information: Not applicable

Handling of TIME WINDOW

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

Data which 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, 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)

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of triple therapy	Post-treatment days: -1	-8 to 1
At the completion of triple therapy	Post-treatment days: 8	2 or more

Handling of others

- 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 survey (patients enrolled)	
Analysis items:	Patients enrolled	
	Number of medical institutions	
	Patients whose survey forms have not been collected	
	Reason why survey form is not yet collected	[Change of the surveillance investigator, Health reason of the surveillance investigator, Others]
	Patients whose survey forms have been collected	
	Patients excluded from safety evaluation*	
	Reason of exclusion (multiple counts)	[Takecab Tablets not administered, Administration prior to contract period, Enrollment 6 days or later after prescription of triple therapy, Unknown whether any AE developed or not]
	Patients targeted for safety evaluation*	
	Patients excluded from efficacy evaluation*	
	Reason of exclusion (multiple counts)	[Determination of <i>H. pylori</i> eradication not conducted, Determination of eradication within 4 weeks after completion or discontinuation of triple therapy, Treatment with a combination of three drugs other than Takecab Tablets + amoxicillin + clarithromycin in first-line eradication, Treatment with a combination of three drugs other than Takecab Tablets + amoxicillin + metronidazole in second-line eradication]
	Patients targeted for efficacy	

evaluation*

Analysis method: 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 survey. If patients are enrolled in more than one department in one medical institution, the number of the medical institution is counted as one. Number of patients excluded from safety evaluation and efficacy evaluation are counted by reason of exclusion, and a list will be prepared.

* “Patients targeted for safety evaluation” indicates “safety analysis set”.

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

(1) Frequency count

2 Patient demographics

2.1 Patient demographics

Analysis	Safety analysis set	
population:		
Analysis items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
	Inpatient/outpatient classification	[Outpatient, Inpatient]
	Existence of hypersensitivity predisposition	[Yes or No or Unknown]
	Existence of complication	[Yes or No]
	Breakdown of complication (multiple counts)	
	Lifestyle-related disease	[Diabetes mellitus, Hypertension, Dyslipidaemia, Hyperuricaemia]
	Gastrointestinal disease (reflux oesophagitis)	
	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]
	Others	
	Details of previous <i>H. pylori</i> eradication	[PPI + AMPC + CAM 400 mg, PPI + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800

	mg, Unknown]
Height (cm)	
Weight (kg)	
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 (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
<i>H. pylori</i> infection diagnostic method (multiple counts)	[Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> antibody assay]
Treatment details	
First-line eradication	[Takecab Tablets + AMPC + CAM, Takecab Tablets + AMPC + MTZ]
Second-line eradication	

Analysis method: 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 drug

3.1 Treatment details

Analysis Safety analysis set

population:

Analysis items:	Triple therapy	[Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM other doses, Takecab Tablets + AMPC + MTZ]
	Whether triple therapy was discontinued or not	[Yes or No]
	Breakdown of reasons of discontinuation of triple therapy	[Incidence of AE, No patient visit due to reasons such as changing hospital, Pregnancy, Others]
	Method of determination of <i>H. pylori</i> eradication at the completion of triple therapy (multiple counts)	[Rapid urease test, Microscopic method, Culture method, Urea breath test, Anti- <i>H. pylori</i> antibody assay, Stool <i>H. pylori</i> antibody assay, not yet conducted]

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

(1) Frequency count

3.2 Concomitant drug

Analysis Safety analysis set

population:

Analysis items:	Existence of concomitant drug	[Yes or No]
	Type of concomitant drug	

Analysis method: Following analysis will be conducted for the above analysis items. Concomitant drugs will be coded to terms in 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 one patient, one patient is counted for the drug (in generic name).

(1) Frequency count

4 Tabulated analysis on safety results

4.1 Incidence of AE and ADR/infection

4.1.1 Incidence of AE

Analysis Safety analysis set

population:

Analysis items: Adverse event

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs
- (3) Proportion of patients with AEs
- (4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed in a single patient, one patient will be counted for the PT.

4.1.2 Incidence of ADR/infection

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed in a single patient, one patient will be counted for the PT.

4.1.3 Incidence of AE and ADR/infection falling under the categories of important identified risks, important potential risks, and important missing information

4.1.3.1 Incidence 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

terms/abbreviations)

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs
- (3) Proportion of patients with AEs
- (4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed in a single patient, one patient will be counted for the PT.

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

Analysis Safety analysis set

population:

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

Analysis method: Following analyses will be conducted for the above analysis items by drug

combination (Takecab Tablets + AMPC + CAM and Takecab Tablets + AMPC + MTZ) and pooled data of combinations.

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed in a single patient, one patient will be counted for the PT.

4.2 Incidence of AE and ADR/infection in patients excluded from safety evaluation

4.2.1 Incidence of AE

Analysis Patients excluded from safety analysis set
population:

Analysis items: Adverse event

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs

(3) Proportion of patients with AEs

(4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed in a single patient, one patient will be counted for the PT.

4.2.2 Incidence of ADR/infection

Analysis population: Patients excluded from safety analysis set

Analysis items: ADRs, etc.

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed in a single patient, one patient will be counted for the SOC.
- PT will be presented with number and proportion of patients with ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed in a single patient, one patient will be counted for the PT.

4.3 Incidence of AE and ADR/infection by seriousness, time of onset, and outcome

4.3.1 Incidence of AE by seriousness, time of onset, and outcome

Analysis Safety analysis set

population:

Analysis items: Adverse event

Subgroup items:	Seriousness	[Serious, Non-serious]
	Time of onset	[During triple therapy, After completion of triple therapy]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown]

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

- (1) Number of patients with AEs
- (2) Number of incidence of AEs
- (3) Proportion of patients with AEs
- (4) Classification of AE

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

[Number of patients with AEs]

- Number of patients who experienced AEs.

[Number of incidence of AEs]

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

[Proportion of patients with AEs]

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

[Classification of AE]

- AEs will be coded to MedDRA/J terms. AEs will be counted by PT sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 developed 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 developed 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 which developed earliest after triple therapy was started

Outcome: Death → Resolved with sequelae → Not resolved → Resolving → Resolved → Unknown

4.3.2 Incidence of ADR/infection by seriousness, time of onset, and outcome

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Seriousness

[Serious, Non-serious]

Time of onset

[During triple therapy, After completion of triple therapy]

Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death, Unknown]
---------	---

Analysis method: Following analyses will be conducted for the above analysis items in each subgroup by drug combination (Takecab Tablets + AMPC + CAM and Takecab Tablets + AMPC + MTZ) and pooled data of combinations.

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 incidence of ADRs, etc.]

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

[Proportion of patients with ADRs, etc.]

- To be calculated with 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 sorted by SOC. When the SOC is “Investigations”, the event is counted by PT 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 ADR, etc. in the internationally agreed order of SOC. When multiple events coded to terms in an identical SOC developed 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 ADRs, etc. in ascending order of PT codes. When multiple events coded to terms in an identical PT developed 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 which developed earliest after triple therapy was started

Outcome: Death → Resolved with sequelae → Not resolved → Resolving
→ Resolved → Unknown

4.4 Incidence of ADR/infection by factor of patient demographics and treatment details

4.4.1 Incidence of ADR/infection by factor of patient demographics and treatment details

Analysis	Safety analysis set	
population:		
Analysis items:	ADRs, etc.	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
	Existence of complication	[Yes or No]
	Breakdown of complication (multiple counts)	[Lifestyle-related disease, Gastrointestinal disease, Hepatic disease, Renal disease, Allergic disease, Others]
	BMI (kg/ m ²)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	Triple therapy	[Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM other doses, Takecab Tablets + AMPC + MTZ]
	Classification of drugs	[Takecab Tablets + AMPC + CAM, Takecab Tablets + AMPC + MTZ]
	Existence of concomitant drug	[Yes or No]
Analysis method:	Following analysis will be conducted for the above analysis items in each subgroup, and 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 with number of patients with ADRs, etc./number of patients targeted for safety evaluation x 100.

4.4.2 Incidence of ADR/infection by sex

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Sex [Male, Female]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by age subgroup

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Age (year) [Min<= - <65, 65<= - <75, 75<= - <=Max]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by target disease of *H. pylori* eradication

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Target disease (multiple counts) [Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, *H. pylori* gastritis]
[Gastric ulcer or duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma or idiopathic thrombocytopenic purpura or stomach following endoscopic treatment of early gastric cancer or *H. pylori* gastritis]

Analysis method: Following analyses will be conducted for the above analysis items in each subgroup by drug combination (Takecab Tablets + AMPC + CAM and Takecab Tablets + AMPC + MTZ) and pooled data of combinations.

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by presence/absence of complication

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Existence of complication [Yes or No]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by breakdown of complication

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Breakdown of complication (multiple counts) [Lifestyle-related disease, Gastrointestinal disease, Hepatic disease, Renal disease, Allergic disease, Others]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by BMI subgroup

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: BMI (kg/ m²) [Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by triple therapy

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Triple therapy [Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM other doses, Takecab Tablets + AMPC + MTZ]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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 Incidence of ADR/infection by classification of drug

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Classification of drugs [Takecab Tablets + AMPC + CAM, Takecab Tablets + AMPC + MTZ]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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.

4.4.10 Incidence of ADR/infection by presence/absence of concomitant drug

Analysis Safety analysis set

population:

Analysis items: ADRs, etc.

Subgroup items: Existence of concomitant drug [Yes or No]

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

- (1) Number of patients with ADRs, etc.
- (2) Number of incidence 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.

4.4.11 List of outlines of patients targeted for analysis (Attachment Form 3)

Analysis population: Patients whose survey forms have been collected

Analysis items:

- Patient number
- Name of medical institution (company code)
- Main body of establishment/code
- Prefecture
- Patient initials
- Sex
- Date of birth
- Inpatient/outpatient classification
- Indication (disease code, disease name)
- Baseline severity
- Existence of complication (yes or no, number, term)
- Route of administration
- Maximum dose (daily dose/one dosage)
- Mean dose (daily dose/one dosage)
- Unit
- Daily dose frequency (maximum)
- Treatment period
- Concomitant drug (drug code, name of representative drug, number of drugs)
- Level of effect
- ADR (SOC code, ADR code, ADR term, yes or no, number)
- Outcome
- Survey form No.
- Withdrawal

Analysis method: A list will be prepared for the above analysis items.

4.4.12 Change of liver function test value

Analysis Safety analysis set

population:

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 of each evaluation period [at the start of triple therapy, at the completion of triple therapy] for the above analysis items. In addition, summary statistics and 95% confidence interval of mean change from the start of triple therapy will be calculated.

5 Tabulated analysis on efficacy results

5.1 Eradication rate of *H. pylori*

5.1.1 Eradication rate of first-line *H. pylori* eradication 4 weeks after completion of first-line eradication

Analysis population: Patients given first-line eradication in the efficacy analysis set

Analysis items: Eradication rate of first-line *H. pylori* eradication 4 weeks after completion of first-line eradication (%)

Analysis method: Frequency will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.

5.1.2 Eradication rate of second-line *H. pylori* eradication 4 weeks after completion of second-line eradication

Analysis population: Patients given second-line eradication in the efficacy analysis set

Analysis items: Eradication rate of second-line *H. pylori* eradication 4 weeks after the completion of the second-line eradication (%)

Analysis method: Frequency will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.

5.2 Factors which may affect efficacy

5.2.1 Eradication rate of *H. pylori* by patient demographic factor (patients of first-line eradication)

Analysis population: Patients given first-line eradication in the efficacy analysis set

Analysis items: Eradication rate of first-line *H. pylori* eradication 4 weeks after completion of first-line eradication (%)

Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic

	thrombocytopenic purpura, Stomach following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
Existence of complication	[Yes or No]
Breakdown of complication (multiple counts)	[Lifestyle-related disease, Gastrointestinal disease, Hepatic disease, Renal disease, Allergic disease, 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 (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
Daily dose of clarithromycin	[400 mg, 800 mg, Others]
Whether triple therapy was discontinued or not	[Yes or No]

Analysis method: Frequency by each subgroup will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.

5.2.2 Eradication rate of *H. pylori* by patient demographic factor (patients of second-line eradication)

Analysis population:	Patients given second-line eradication in the efficacy analysis set	
Analysis items:	Eradication rate of second-line <i>H. pylori</i> eradication 4 weeks after the completion of the second-line eradication (%)	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Target disease (multiple counts)	[Gastric ulcer, Duodenal ulcer, Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, Idiopathic thrombocytopenic purpura, Stomach

	following endoscopic treatment of early gastric cancer, <i>H. pylori</i> gastritis]
Existence of complication	[Yes or No]
Breakdown of complication (multiple counts)	[Lifestyle-related disease, Gastrointestinal disease, Hepatic disease, Renal disease, Allergic disease, Others]
Details of previous <i>H. pylori</i> eradication	[PPI + AMPC + CAM 400 mg, PPI + AMPC + CAM 800 mg, Takecab Tablets + AMPC + CAM 400 mg, Takecab Tablets + AMPC + CAM 800 mg, Unknown]
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 (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
Whether triple therapy was discontinued or not	[Yes or No]
Analysis method: Frequency by each subgroup will be counted for the above analysis items, and point estimates and two-sided 95% confidence interval of eradication rates will be calculated. When the eradication rate is calculated, the patients whose eradication is undeterminable are excluded from the denominator.	

Revision history (version control)

Version	Date	Person who prepared/revised this document	Comment
Version 1	August 18, 2017	PPD	Preparation of Version 1

[Attachment 1] Comparison Table of revision of Vonoprazan-5002

Not applicable