Title: Takecab Tablets Special Drug Use Surveillance "Maintenance therapy for reflux esophagitis: Long-term use"

NCT Number: NCT03214081

Statistical analysis plan Approve Date: 20-Feb-2019

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- Patient identifiers within the text, tables, or figures or in by-patient data listings.
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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   : Maintenance therapy for reflux esophagitis: long-term use

Protocol No.   : Vonoprazan-5003

Sponsor   : Takeda Pharmaceutical Company Limited

PPD   Takeda Pharmaceutical Company Limited

PPD

Version 2: Prepared on February 20, 2019

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List of terms/abbreviations

- The drug: Takecab Tablets

- PPI: Proton pump inhibitor is abbreviated to PPI.

- 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 other than "not related" to Takecab Tablets 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 for maintenance therapy is started is Day -1, and the day when Takecab Tablets for maintenance therapy is started is Day 1.

- Post-treatment days: The day after the completion of Takecab Tablets administration for maintenance therapy is post-treatment Day 1.

- Duration of disease (days): The start date of Takecab Tablets administration for maintenance therapy − The date of initial onset of reflux esophagitis + 1

  - For the date of initial onset of reflux esophagitis, since the survey form is designed to record only the year and month, "01-MM-YYYY" will be used to calculate the duration of disease.

  - For the date of initial onset of reflux esophagitis, if the month is unknown, "01-JAN-YYYY" will be used to calculate the duration of disease.

- Duration of use (days): The end date of Takecab Tablets administration for maintenance therapy − The start date of Takecab Tablets administration for maintenance therapy + 1

  - If "Ongoing after 12 months of Takecab Tablets administration" is recorded in the survey form, "365 days" will be used.

- 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/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.

- Endoscopic relapse rate: The percentage of patients assessed as having Los Angeles classification grade A to D disease, among patients in the efficacy analysis set with recorded endoscopic findings during the therapy period and at Month 12 (or discontinuation of the 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.

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 15 days or later after prescription of Takecab Tablets
- 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 disease
  - Patients found as not having the target disease based on the enrollment data meeting "Exclusion criterion 1" or the comment recorded under "Other" reason for discontinuation
- Meeting any exclusion criterion
- No evaluable paired efficacy data at baseline (i.e., at the start of the maintenance therapy) and post-treatment
  - For endoscopy and subjective symptoms at baseline and post-treatment, all are "Not performed" or are outside the Time Window.
- Initial episode of reflux esophagitis
  - The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is <4 weeks.
    - For "the date of initial onset of reflux esophagitis" in patients with "the start date of Takecab therapy – The date of initial onset of reflux esophagitis + 1" being <28 days, see the "Duration of disease" section under "List of terms/abbreviations".
  - The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is 4 to <8 weeks and use of antacids before initiation of Takecab therapy was recorded, and the surveillance investigator judged that the current

disease is the initial episode of reflux esophagitis.

- Off-label prescription
  - ➢ Patients given Takecab Tablets at 40 mg

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.

  - Fracture: An AE falling under any of the PT codes listed in Table 1 is handled as a fracture.

  - Neuroendocrine tumor due to increased serum gastrin: An AE falling under SMQ code 20000090 [Malignancies (SMQ) narrow] is handled as a neuroendocrine tumor due to increased serum gastrin.

- Important missing information: Not applicable

Table 1   List of PT codes related to fracture

PT_NAME	PT_CODE	PT_NAME	PT_CODE
Acetabulum fracture	10000397	Impacted fracture	10066386
Ankle fracture	10002544	Jaw fracture	10023149
Atypical femur fracture	10070884	Limb fracture	10074551
Atypical fracture	10072395	Lower limb fracture	10061599
Avulsion fracture	10066184	Lumbar vertebral fracture	10049947
Bone fissure	10064210	Maisonneuve fracture	10081343
Bone fragmentation	10064211	Metaphyseal corner fracture	10079667
Cervical vertebral fracture	10049946	Multiple fractures	10028200
Chance fracture	10073162	Open fracture	10030527
Clavicle fracture	10009245	Osteophyte fracture	10080550
Comminuted fracture	10052614	Osteoporotic fracture	10031290
Complicated fracture	10010149	Patella fracture	10034122
Compression fracture	10010214	Pathological fracture	10034156
Craniofacial fracture	10077603	Pelvic fracture	10061161
Epiphyseal fracture	10053962	Pubis fracture	10070286
Facial bones fracture	10016042	Radius fracture	10037802
Femoral neck fracture	10016450	Rib fracture	10039117
Femur fracture	10016454	Sacroiliac fracture	10074362
Fibula fracture	10016667	Scapula fracture	10039579
Foot fracture	10016970	Skull fracture	10061365
Forearm fracture	10016997	Skull fractured base	10040960
Fracture	10017076	Spinal compression fracture	10041541
Fracture blisters	10079423	Spinal fracture	10041569
Fracture displacement	10053206	Spinal fusion fracture	10074807
Fracture malunion	10017085	Stapes fracture	10081442
Fracture nonunion	10017088	Sternal fracture	10042015
Fracture of clavicle due to birth trauma	10017107	Stress fracture	10042212
Fractured coccyx	10049164	Subchondral insufficiency fracture	10079864
Fractured ischium	10017290	Thoracic vertebral fracture	10049948
Fractured sacrum	10017308	Tibia fracture	10043827
Fractured skull depressed	10017310	Torus fracture	10066094

Greenstick fracture	10018720	Traumatic fracture	10049514
Hand fracture	10019114	Ulna fracture	10045375
Hip fracture	10020100	Upper limb fracture	10061394
Humerus fracture	10020462	Wrist fracture	10048049
Ilium fracture	10021343		

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), serum gastrin, endoscopy

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of therapy	Post-treatment days: -1	-8 to 1
At the completion of therapy	Post-treatment days: 337	2 or more

Subjective symptoms

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of therapy	Post-treatment days: -1	-8 to 1
At Month 6 of therapy	Post-treatment days: 169	2 to 253
At Month 12 of therapy	Post-treatment days: 337	254 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

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 15 days or later after prescription of Takecab Tablets, Unknown whether any AE developed or not]

Patients targeted for safety evaluation*

Patients excluded from efficacy evaluation*

Reason of exclusion (multiple counts)
[Other than the target disease, Meeting any exclusion criterion, No valuable paired efficacy data at baseline (i.e., at the start of the maintenance therapy) and post-treatment, Initial episode of reflux esophagitis (i.e., The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is <4 weeks. / The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is 4 to <8 weeks and use of antacids before initiation of Takecab therapy was recorded, and the surveillance investigator judged that

the current disease is the initial episode
of reflux esophagitis), Off-label
prescription]

Patients targeted for efficacy
evaluation[*]

Analysis method: Frequency will be counted 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".

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]
Duration of disease (days)	
Inpatient/outpatient classification	[Outpatient, Inpatient]
Existence of hypersensitivity predisposition	[No, Yes, Unknown]
Existence of complication	[No, Yes]
Breakdown of complication (multiple counts)	
Life-style 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]
Bone or joint disease	[Osteoporosis, Rheumatoid arthritis, Osteoarthritis]
Malignancy	[Gastric cancer, Lung cancer, Colorectal cancer, Esophageal cancer]
Others	
Height (cm)	
Weight (kg)	
BMI (kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
Helicobacter pylori infection	[Negative, Positive, Unknown]
Existence of hiatus hernia	[No, Yes, Unknown]
Smoking history	[Non-smoker, Current smoker,

	Ex-smoker, Unknown]
Drinking history (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
Endoscopy assessment	[Grade N, Grade M, Not performed]
Any antacid before Takecab therapy Breakdown of drug (multiple counts)	[No, Yes, Unknown] [Takecab Tablets, lansoprazole, omeprazole, rabeprazole, esomeprazole, H2 blocker]
Reason for use	[Treatment of reflux esophagitis, maintenance therapy for reflux esophagitis]

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 population: Safety analysis set

Analysis items:

	Starting daily dose	[10 mg, 20 mg]
	Treatment status	[Continued, Ended, Not specified]
	Reason for discontinuation	[Incidence of AE, No patient visit due to reasons such as changing hospital, Pregnancy, Inadequate response, Prolonged remission with no anticipated likelihood of recurrence, Others]

Analysis method: 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 concomitant drug	[No, Yes]
	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). If the generic name is missing, the drug term will be alternatively used.

(1) Frequency count

4   Tabulated analysis on safety results

4.1   Incidence of AE and ADR/infection

4.1.1   Incidence of AE

Analysis
population: Safety analysis set

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
population: 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.

4.1.3   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

"Important identified risks, important potential risks and important missing information" section)

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

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section)

Analysis method: Following analyses 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.

4.1.3.3 Incidence of ADRs/infections listed in the safety specification (by risk)

Analysis population:
    Safety analysis set

Analysis items: ADRs, etc. listed in the safety specification (listed in the "Important identified risks, important potential risks and important missing information" section)

Subgroup items: Seriousness   [Serious, Non-serious]

Analysis method: For each risk, following analysis will be conducted for the above analysis items in each subgroup. The definition of each risk is provided in the "important identified risks, important potential risks and important missing information"

section.

[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. However, if such events had different seriousness categories, the patient will be counted once each under serious and non-serious categories.

- 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, if such events had different seriousness categories, the patient will be counted once each under serious and non-serious categories.

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

4.2.1 Incidence of AE

Analysis population: Patients excluded from safety analysis set

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 population:	Safety analysis set	
Analysis items:	Adverse event	
Subgroup items:	Seriousness	[Serious, Non-serious]
	Time of onset	[Day 1–84, Day 85–168, Day 169–252, Day 253–336, Day 337 or later, Unknown]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to the event), 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 Takecab therapy was started

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

4.3.2 Incidence of ADR/infection 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 1–84, Day 85–168, Day 169–252, Day 253–336, Day 337 or later, Unknown]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to the event), Unknown]
Analysis method:	Following analyses 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. 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 Takecab therapy was started

  Outcome: Death (due to the event) → 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 population:	Safety analysis set	
Analysis items:	ADRs, etc.	
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]

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Existence of complication	[No, Yes]
Breakdown of complication (multiple counts)	[Lifestyle related disease, Hepatic disease, Renal disease, Allergic disease, Bone/joint disease, Malignancy, Others]
BMI (kg/ m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
Hypersensitive diathesis	[No, Yes, Unknown]
Treatment status	[Continued, Ended, Not specified]
Existence of concomitant drug	[No, Yes]

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 population: Safety analysis set

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 population: Safety analysis set

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 presence/absence of complication

Analysis population: Safety analysis set

Analysis items: ADRs, etc.

Subgroup items: Existence of complication   [No, Yes]

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.

4.4.5 Incidence of ADR/infection by breakdown of complication

Analysis population: Safety analysis set

Analysis items: ADRs, etc.

Subgroup items: Breakdown of complication (multiple counts)   [Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Bone/joint disease, Malignancy, 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.

4.4.6   Incidence of ADR/infection by BMI subgroup

Analysis   Safety analysis set
population:

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: 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 presence/absence of concomitant drug

Analysis   Safety analysis set
population:

Analysis items: ADRs, etc.

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

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 breakdown of antacid used before initiation of Takecab therapy

Analysis population:	Safety analysis set
Analysis items:	ADRs, etc.
Subgroup items:	Breakdown of antacid used before initiation of Takecab therapy (multiple counts) [Takecab Tablets, lansoprazole, omeprazole, rabeprazole, esomeprazole, H2 blocker]
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 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 of each evaluation period [at the start of therapy, Month 12] for the above analysis items. In addition, summary statistics and 95% confidence interval of mean change from the start of therapy will be calculated.

4.4.10 Change of serum gastrin

Analysis population:	Safety analysis set
Analysis items:	Serum gastrin (pg/mL)
Analysis method:	Summary statistics will be calculated for the measured values of each evaluation period [at the start of therapy, Month 12] for the above analysis item. In addition, summary statistics and 95% confidence interval of mean change from the start of therapy will be calculated.

5 Tabulated analysis on efficacy results

5.1 Endoscopic relapse rate

Analysis population: Patients in the efficacy analysis set with recorded endoscopic findings during the therapy period and at Month 12 (or discontinuation of the therapy)

Analysis items: Endoscopic relapse rate (%)

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

5.2 Change of severity of subjective symptoms

Analysis population: Efficacy analysis set

Analysis items: Subjective symptoms

Heartburn	[None, Mild, Moderate, Severe, Unknown]
Acid reflux	[None, Mild, Moderate, Severe, Unknown]
Heavy stomach feeling	[None, Mild, Moderate, Severe, Unknown]
Early satiety	[None, Mild, Moderate, Severe, Unknown]
Epigastric pain	[None, Mild, Moderate, Severe, Unknown]
Epigastric burning sensation	[None, Mild, Moderate, Severe, Unknown]
Bloating	[None, Mild, Moderate, Severe, Unknown]
Nausea/vomiting	[None, Mild, Moderate, Severe, Unknown]
Belching	[None, Mild, Moderate, Severe, Unknown]
Inappetence	[None, Mild, Moderate, Severe, Unknown]

Analysis method: Frequency will be counted for the above analysis items at each time point of evaluation [at the start of therapy, Month 6, Month 12], and point estimates will be calculated.

5.3 Factors which may affect efficacy

5.3.1 Endoscopic relapse rate

Analysis population: Patients in the efficacy analysis set with recorded endoscopic findings during the therapy period and at Month 12 (or discontinuation of the therapy)

Analysis items: Endoscopic relapse rate (%)

Subgroup items:
Sex	[Male, Female]
Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
Existence of complication	[No, Yes]

Breakdown of complication (multiple counts)	[Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Bone/joint disease, Malignancy, 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]
Treatment status	[Continued, Ended, Not specified]
Existence of concomitant drug	[No, Yes]
Helicobacter pylori infection	[Negative, Positive, Unknown]
Existence of hiatus hernia	[No, Yes, Unknown]
Any antacid before Takecab therapy	[No, Yes, Unknown]

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

6   Incidence of ADR/infection in the additional pharmacovigilance plan

6.1   Incidence of ADR/infection in the additional pharmacovigilance plan (Attached Form No. 12)

Analysis population:	Safety analysis set
Analysis items:	ADRs, etc. listed in the safety specification (listed in the "Important identified risks, important potential risks and important missing information" section)
Subgroup items:	Seriousness [Serious, Non-serious]
Analysis method:	Following analysis will be conducted for the above analysis items in each subgroup, in accordance with Notes 1 to 4 for Attached Form No. 12 in Notification No. 1128-2 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (Notification regarding reexamination) dated November 28, 2017.

(1) Number and proportion of patients

The risk terms and the order of their listing will be in accordance with the "Important identified risks, important potential risks and important missing information" section.

7   Summary of cases in post-marketing surveillance etc.

7.1   Summary of cases in post-marketing surveillance etc. (Attached Form No. 16)

Analysis population: Patients whose survey forms have not been collected

Analysis items: Case number

Name of institution

Sex

Date of birth

Reason for use (Disease code, Disease name)

Complication (Disease code, Disease name)

Route of administration

Maximum dose

Average dose

Unit

Duration of use

Concomitant drug (Drug code, Drug name)

Extent of effectiveness

ADR (Disease code, Disease name, Outcome)

Survey form number

Dropout

Analysis method: A list will be prepared for the above analysis items, in accordance with Notes 1 to 3 for Attached Form No. 16 in the Notification No. 1128-2 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (Notification regarding reexamination) dated November 28, 2017.

Revision history (version control)

Version	Date	Person who prepared/ revised this document	Comment
Version 1	December 25, 2018	PPD	Preparation of Version 1
Version 2	February 20, 2019	PPD	Preparation of Version 2 Changes from Version 1 are listed in Attachment 1.

[Attachment 1] Comparison Table of revision of Vonoprazan-5003

Section	Before change	After change	Reason for change
4.1.3.3	-	4.1.3.3 Incidence of ADRs/infections listed in the safety specification (by risk)	Version 2 Tabulation of the incidence by PT by risk is newly added as necessary information for CSR Attached Form 12
6	6 Incidence of ADR/infection in the additional pharmacovigilance plan (Attached Form No. 12)	6 Incidence of ADR/infection in the additional pharmacovigilance plan 6.1 Incidence of ADR/infection in the additional pharmacovigilance plan (Attached Form No. 12)	Version 2 Editorial improvement
6.1	Analysis items: ADRs, etc. falling under the important potential risks (specified under the "Important identified risks, important potential risks and important missing information" section)	Analysis items: ADRs, etc. listed in the safety specification (listed in the "Important identified risks, important potential risks and important missing information" section)	Version 2 Editorial improvement
7	7 Summary of cases in post-marketing surveillance etc. (Attached Form No. 16)	7 Summary of cases in post-marketing surveillance etc. 7.1 Summary of cases in post-marketing surveillance etc. (Attached Form No. 16)	Version 2 Editorial improvement

Statistical Analysis Plan

(Analysis of final results)

Product Name   : Takecab Tablets

Title of Surveillance   : Maintenance therapy for reflux esophagitis: long-term use

Protocol No.   : Vonoprazan-5003

Sponsor   : Takeda Pharmaceutical Company Limited

PPD   Takeda Pharmaceutical Company Limited

PPD

Version 1: Prepared on December 25, 2018

<p align="center">Table of contents</p>

List of terms/abbreviations

The drug: Takecab Tablets

PPI: Proton pump inhibitor is abbreviated to PPI.

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 other than "not related" to Takecab Tablets 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 for maintenance therapy is started is Day -1, and the day when Takecab Tablets for maintenance therapy is started is Day 1.

Post-treatment days: The day after the completion of Takecab Tablets administration for maintenance therapy is post-treatment Day 1.

Duration of disease (days): The start date of Takecab Tablets administration for maintenance therapy − The date of initial onset of reflux esophagitis + 1

• For the date of initial onset of reflux esophagitis, since the survey form is designed to record only the year and month, "01-MM-YYYY" will be used to calculate the duration of disease.

• For the date of initial onset of reflux esophagitis, if the month is unknown, "01-JAN-YYYY" will be used to calculate the duration of disease.

Duration of use (days): The end date of Takecab Tablets administration for maintenance therapy − The start date of Takecab Tablets administration for maintenance therapy + 1

• If "Ongoing after 12 months of Takecab Tablets administration" is recorded in the survey form, "365 days" will be used.

- 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/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.

Endoscopic relapse rate: The percentage of patients assessed as having Los Angeles classification grade A to D disease, among patients in the efficacy analysis set with recorded endoscopic findings during the therapy period and at Month 12 (or discontinuation of the 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.

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 15 days or later after prescription of Takecab Tablets
- 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 disease
  - Patients found as not having the target disease based on the enrollment data meeting "Exclusion criterion 1" or the comment recorded under "Other" reason for discontinuation
- Meeting any exclusion criterion
- No evaluable paired efficacy data at baseline (i.e., at the start of the maintenance therapy) and post-treatment
  - For endoscopy and subjective symptoms at baseline and post-treatment, all are "Not performed" or are outside the Time Window.
- Initial episode of reflux esophagitis
  - The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is <4 weeks.
    - For "the date of initial onset of reflux esophagitis" in patients with "the start date of Takecab therapy – The date of initial onset of reflux esophagitis + 1" being <28 days, see the "Duration of disease" section under "List of terms/abbreviations".
  - The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is 4 to <8 weeks and use of antacids before initiation of Takecab therapy was recorded, and the surveillance investigator judged that the current

disease is the initial episode of reflux esophagitis.

- Off-label prescription
  - ➤ Patients given Takecab Tablets at 40 mg

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.

  - Fracture: An AE falling under any of the PT codes listed in Table 1 is handled as a fracture.

  - Neuroendocrine tumor due to increased serum gastrin: An AE falling under SMQ code 20000090 [Malignancies (SMQ) narrow] is handled as a neuroendocrine tumor due to increased serum gastrin.

- Important missing information: Not applicable

Table 1   List of PT codes related to fracture

PT_NAME	PT_CODE	PT_NAME	PT_CODE
Acetabulum fracture	10000397	Impacted fracture	10066386
Ankle fracture	10002544	Jaw fracture	10023149
Atypical femur fracture	10070884	Limb fracture	10074551
Atypical fracture	10072395	Lower limb fracture	10061599
Avulsion fracture	10066184	Lumbar vertebral fracture	10049947
Bone fissure	10064210	Maisonneuve fracture	10081343
Bone fragmentation	10064211	Metaphyseal corner fracture	10079667
Cervical vertebral fracture	10049946	Multiple fractures	10028200
Chance fracture	10073162	Open fracture	10030527
Clavicle fracture	10009245	Osteophyte fracture	10080550
Comminuted fracture	10052614	Osteoporotic fracture	10031290
Complicated fracture	10010149	Patella fracture	10034122
Compression fracture	10010214	Pathological fracture	10034156
Craniofacial fracture	10077603	Pelvic fracture	10061161
Epiphyseal fracture	10053962	Pubis fracture	10070286
Facial bones fracture	10016042	Radius fracture	10037802
Femoral neck fracture	10016450	Rib fracture	10039117
Femur fracture	10016454	Sacroiliac fracture	10074362
Fibula fracture	10016667	Scapula fracture	10039579
Foot fracture	10016970	Skull fracture	10061365
Forearm fracture	10016997	Skull fractured base	10040960
Fracture	10017076	Spinal compression fracture	10041541
Fracture blisters	10079423	Spinal fracture	10041569
Fracture displacement	10053206	Spinal fusion fracture	10074807
Fracture malunion	10017085	Stapes fracture	10081442
Fracture nonunion	10017088	Sternal fracture	10042015
Fracture of clavicle due to birth trauma	10017107	Stress fracture	10042212
Fractured coccyx	10049164	Subchondral insufficiency fracture	10079864
Fractured ischium	10017290	Thoracic vertebral fracture	10049948
Fractured sacrum	10017308	Tibia fracture	10043827
Fractured skull depressed	10017310	Torus fracture	10066094

Greenstick fracture	10018720	Traumatic fracture	10049514
Hand fracture	10019114	Ulna fracture	10045375
Hip fracture	10020100	Upper limb fracture	10061394
Humerus fracture	10020462	Wrist fracture	10048049
Ilium fracture	10021343		

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), serum gastrin, endoscopy

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of therapy	Post-treatment days: -1	-8 to 1
At the completion of therapy	Post-treatment days: 337	2 or more

Subjective symptoms

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the start of therapy	Post-treatment days: -1	-8 to 1
At Month 6 of therapy	Post-treatment days: 169	2 to 253
At Month 12 of therapy	Post-treatment days: 337	254 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

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 15 days or later after prescription of Takecab Tablets, Unknown whether any AE developed or not]

Patients targeted for safety evaluation*

Patients excluded from efficacy evaluation*

    Reason of exclusion (multiple counts) [Other than the target disease, Meeting any exclusion criterion, No valuable paired efficacy data at baseline (i.e., at the start of the maintenance therapy) and post-treatment, Initial episode of reflux esophagitis (i.e., The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is <4 weeks. / The interval between the date of initial onset of reflux esophagitis and the start date of Takecab maintenance therapy is 4 to <8 weeks and use of antacids before initiation of Takecab therapy was recorded, and the surveillance investigator judged that

the current disease is the initial episode of reflux esophagitis), Off-label prescription]

Patients targeted for efficacy evaluation[*]

Analysis method: Frequency will be counted 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".

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]
Duration of disease (days)	
Inpatient/outpatient classification	[Outpatient, Inpatient]
Existence of hypersensitivity predisposition	[No, Yes, Unknown]
Existence of complication	[No, Yes]
Breakdown of complication (multiple counts)	
Life-style 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]
Bone or joint disease	[Osteoporosis, Rheumatoid arthritis, Osteoarthritis]
Malignancy	[Gastric cancer, Lung cancer, Colorectal cancer, Esophageal cancer]
Others	
Height (cm)	
Weight (kg)	
BMI (kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
Helicobacter pylori infection	[Negative, Positive, Unknown]
Existence of hiatus hernia	[No, Yes, Unknown]
Smoking history	[Non-smoker, Current smoker,

	Ex-smoker, Unknown]
Drinking history (taking alcohol-containing beverages almost daily)	[Yes or No or Unknown]
Endoscopy assessment	[Grade N, Grade M, Not performed]
Any antacid before Takecab therapy Breakdown of drug (multiple counts)	[No, Yes, Unknown] [Takecab Tablets, lansoprazole, omeprazole, rabeprazole, esomeprazole, H2 blocker]
Reason for use	[Treatment of reflux esophagitis, maintenance therapy for reflux esophagitis]

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
population: Safety analysis set

Analysis items: Starting daily dose   [10 mg, 20 mg]

                   Treatment status   [Continued, Ended, Not specified]

                   Reason for discontinuation   [Incidence of AE, No patient visit due
                                                    to reasons such as changing hospital,
                                                    Pregnancy, Inadequate response,
                                                    Prolonged remission with no
                                                    anticipated likelihood of recurrence,
                                                    Others]

Analysis method: 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 concomitant drug   [No, Yes]

                   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). If the
                   generic name is missing, the drug term will be alternatively used.

                   (1) Frequency count

4 Tabulated analysis on safety results

4.1 Incidence of AE and ADR/infection

4.1.1 Incidence of AE

Analysis population: Safety analysis set

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 population: 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.

4.1.3 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

"Important identified risks, important potential risks and important missing information" section)

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

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section)

Analysis method: Following analyses 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.

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

4.2.1 Incidence of AE

Analysis population: Patients excluded from safety analysis set

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 population:	Safety analysis set	
Analysis items:	Adverse event	
Subgroup items:	Seriousness	[Serious, Non-serious]
	Time of onset	[Day 1–84, Day 85–168, Day 169–252, Day 253–336, Day 337 or later, Unknown]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to the event), 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 Takecab therapy was started

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

4.3.2 Incidence of ADR/infection 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 1–84, Day 85–168, Day 169–252,

| | Day 253–336, Day 337 or later, Unknown] |
| Outcome | [Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to the event), Unknown] |

Analysis method: Following analyses 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. 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 Takecab therapy was started

Outcome: Death (due to the event) → 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 population:	Safety analysis set
Analysis items:	ADRs, etc.

Subgroup items:		
	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Existence of complication	[No, Yes]
	Breakdown of complication (multiple counts)	[Lifestyle related disease, Hepatic disease, Renal disease, Allergic disease, Bone/joint disease, Malignancy, Others]
	BMI (kg/ m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <30.0, 30.0<= - <=Max]
	Hypersensitive diathesis	[No, Yes, Unknown]
	Treatment status	[Continued, Ended, Not specified]
	Existence of concomitant drug	[No, Yes]

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 population:	Safety analysis set

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
population: Safety analysis set

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 presence/absence of complication

Analysis
population: Safety analysis set

Analysis items: ADRs, etc.

Subgroup items: Existence of complication   [No, Yes]

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.

4.4.5 Incidence of ADR/infection by breakdown of complication

Analysis population:	Safety analysis set
Analysis items:	ADRs, etc.

Subgroup items:	Breakdown of complication (multiple counts)	[Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Bone/joint disease, Malignancy, 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.

4.4.6 Incidence of ADR/infection 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:　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 presence/absence of concomitant drug

Analysis population:	Safety analysis set

population:

Analysis items:	ADRs, etc.
Subgroup items:	Existence of concomitant drug [No, Yes]
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 breakdown of antacid used before initiation of Takecab therapy

Analysis population:	Safety analysis set
Analysis items:	ADRs, etc.
Subgroup items:	Breakdown of antacid used before initiation of Takecab therapy (multiple counts) [Takecab Tablets, lansoprazole, omeprazole, rabeprazole, esomeprazole, H2 blocker]
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 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 of each evaluation period [at the start of therapy, Month 12] for the above analysis items. In addition, summary statistics and 95% confidence interval of mean

change from the start of therapy will be calculated.

4.4.10 Change of serum gastrin

Analysis population:	Safety analysis set
Analysis items:	Serum gastrin (pg/mL)
Analysis method:	Summary statistics will be calculated for the measured values of each evaluation period [at the start of therapy, Month 12] for the above analysis item. In addition, summary statistics and 95% confidence interval of mean change from the start of therapy will be calculated.

5　Tabulated analysis on efficacy results

5.1　Endoscopic relapse rate

Analysis population:　Patients in the efficacy analysis set with recorded endoscopic findings during the therapy period and at Month 12 (or discontinuation of the therapy)

Analysis items:　Endoscopic relapse rate (%)

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

5.2　Change of severity of subjective symptoms

Analysis population:　Efficacy analysis set

Analysis items:　Subjective symptoms

Heartburn	[None, Mild, Moderate, Severe, Unknown]
Acid reflux	[None, Mild, Moderate, Severe, Unknown]
Heavy stomach feeling	[None, Mild, Moderate, Severe, Unknown]
Early satiety	[None, Mild, Moderate, Severe, Unknown]
Epigastric pain	[None, Mild, Moderate, Severe, Unknown]
Epigastric burning sensation	[None, Mild, Moderate, Severe, Unknown]
Bloating	[None, Mild, Moderate, Severe, Unknown]
Nausea/vomiting	[None, Mild, Moderate, Severe, Unknown]
Belching	[None, Mild, Moderate, Severe, Unknown]
Inappetence	[None, Mild, Moderate, Severe, Unknown]

Analysis method:　Frequency will be counted for the above analysis items at each time point of evaluation [at the start of therapy, Month 6, Month 12], and point estimates will be calculated.

5.3　Factors which may affect efficacy

5.3.1　Endoscopic relapse rate

Analysis population:　Patients in the efficacy analysis set with recorded endoscopic findings during the therapy period and at Month 12 (or discontinuation of the therapy)

Analysis items:　Endoscopic relapse rate (%)

Subgroup items:

Sex	[Male, Female]
Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
Existence of complication	[No, Yes]

Breakdown of complication (multiple counts)	[Lifestyle-related disease, Hepatic disease, Renal disease, Allergic disease, Bone/joint disease, Malignancy, Others]
BMI (kg/ m²)	[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]
Treatment status	[Continued, Ended, Not specified]
Existence of concomitant drug	[No, Yes]
Helicobacter pylori infection	[Negative, Positive, Unknown]
Existence of hiatus hernia	[No, Yes, Unknown]
Any antacid before Takecab therapy	[No, Yes, Unknown]

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

6 Incidence of ADR/infection in the additional pharmacovigilance plan (Attached Form No. 12)

Analysis population: Safety analysis set

Analysis items: ADRs, etc. falling under the important potential risks (listed in the "Important identified risks, important potential risks and important missing information" section)

Subgroup items: Seriousness   [Serious, Non-serious]

Analysis method: Following analysis will be conducted for the above analysis items in each subgroup, in accordance with Notes 1 to 4 for Attached Form No. 12 in Notification No. 1128-2 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (Notification regarding reexamination) dated November 28, 2017.

(1) Number and proportion of patients with manifestations of important potential risks

The risk terms and the order of their listing will be in accordance with the "Important identified risks, important potential risks and important missing information" section.

7   Summary of cases in post-marketing surveillance etc. (Attached Form No. 16)

Analysis
population:

Patients whose survey forms have not been collected

Analysis items:

Case number

Name of institution

Sex

Date of birth

Reason for use (Disease code, Disease name)

Complication (Disease code, Disease name)

Route of administration

Maximum dose

Average dose

Unit

Duration of use

Concomitant drug (Drug code, Drug name)

Extent of effectiveness

ADR (Disease code, Disease name, Outcome)

Survey form number

Dropout

Analysis method:

A list will be prepared for the above analysis items, in accordance with Notes 1 to 3 for Attached Form No. 16 in Notification No. 1128-2 of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau (Notification regarding reexamination) dated November 28, 2017.

Revision history (version control)

Version	Date	Person who prepared/ revised this document	Comment
Version 1	December 25, 2018	PPD	Preparation of Version 1

[Attachment 1] Comparison Table of revision of Vonoprazan-5003