Title: Special drug use surveillance of Takecab tablets for "prevention of recurrence of gastric/duodenal ulcer in patients receiving low-dose aspirin:long-term use"

NCT Number: NCT03214094

Statistical analysis plan　Approve Date: 07-AUG-2019

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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	: Prevention of recurrent gastric or duodenal ulcer during low-dose aspirin therapy: long-term use
Protocol No.	: Vonoprazan-5004
Sponsor	: Takeda Pharmaceutical Company Limited

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Version 1: Prepared on August 7, 2019

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List of terms/abbreviations

- The drug: Takecab Tablets
- 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 Medially 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 not assessed as "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 is started is Day -1, and the day when Takecab Tablets is started is Day 1.
- Duration (days) of treatment with Takecab Tablets: Completion date of treatment with Takecab Tablets - start date of treatment with Takecab Tablets + 1 (excluding days without treatment)
    - For patients with "under treatment with Takecab Tablets 12 months after the start of treatment" entered on the survey form, the duration of treatment is handled as 365 days (excluding days without treatment).
- Duration (days) of low-dose aspirin therapy: Completion date of low-dose aspirin therapy - start date of low-dose aspirin therapy + 1 (excluding days without treatment)
    - For patients with missing completion date of low-dose aspirin therapy or "under low-dose aspirin therapy at the completion of survey" entered on the survey form, the duration of therapy is handled as missing (unknown).
    - For other patients with "therapy started before the start of treatment with Takecab Tablets" described as the status of low-dose aspirin on the survey form, but with missing start date, the duration of therapy is calculated by imputing "start time of low-dose aspirin therapy" described as patient demographics (the first date of the month is the start date of therapy). If only the month is missing, "January 1" is imputed as the start date of therapy. Otherwise

(both the year and month are missing or “unknown”), the duration of therapy is handled as missing (unknown).

- 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.

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 [found later]
- Enrollment in this survey 15 days or later after prescription of Takecab Tablets [found later]
- 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 target disease [found later]
- Patient failing to meet all of the inclusion criteria
- Patient meeting any of the exclusion criteria
- Patient with no post-baseline efficacy data
    - A post-baseline examination was not conducted or was conducted outside the time window to determine the "development of gastric ulcer, duodenal ulcer, or hemorrhagic lesions in stomach or duodenum."

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.
    - Fracture: An AE falling under any of the PT codes listed in Table 1 is handled as fracture.
    - Gastrointestinal infection with clostridium difficile: An AE falling under SMQ code 20000080 (Pseudomembranous colitis [SMQ] narrow) is handled as gastrointestinal infection with clostridium difficile.
    - Neuroendocrine tumour due to increased serum gastrin: An AE falling under SMQ code 20000090 (Malignancies [SMQ] narrow) is handled as neuroendocrine tumour due to increased serum gastrin.
- Important missing information: Not applicable

Table 1 Fracture-related PT codes

PT NAME	PT CODE	PT NAME	PT CODE
Acetabulum fracture	10000397	Ilium fracture	10021343
Ankle fracture	10002544	Impacted fracture	10066386
Atypical femur fracture	10070884	Jaw fracture	10023149
Atypical fracture	10072395	Limb fracture	10074551
Avulsion fracture	10066184	Lower limb fracture	10061599
Bone fissure	10064210	Lumbar vertebral fracture	10049947
Bone fragmentation	10064211	Maisonneuve fracture	10081343
Cervical vertebral fracture	10049946	Metaphyseal corner fracture	10079667
Chance fracture	10073162	Multiple fractures	10028200
Clavicle fracture	10009245	Open fracture	10030527
Comminuted fracture	10052614	Osteophyte fracture	10080550
Complicated fracture	10010149	Osteoporotic fracture	10031290
Compression fracture	10010214	Patella fracture	10034122
Craniofacial fracture	10077603	Pathological fracture	10034156
Cuboid syndrome	10081921	Pelvic fracture	10061161
Epiphyseal fracture	10053962	Pubis fracture	10070286

PT NAME	PT CODE	PT NAME	PT CODE
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

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 or the standard day is not specified, 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)

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

Development of gastric ulcer, duodenal ulcer, or hemorrhagic lesions in stomach or duodenum

Assessment time	Standard day of conduct	Time window
		Post-treatment days
At the completion of survey	Post-treatment days: –	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	
	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 [found later], Enrollment 15 days or later after prescription of Takecab Tablets [found later], Unknown whether any AE developed or not]
	Patients targeted for safety evaluation*	
	Patients excluded from efficacy evaluation*	
	Reason of exclusion (multiple counts)	[Other than target disease [found later], Patient failing to meet all of the inclusion criteria, Patient meeting any of the exclusion criteria, Patient with no post-baseline efficacy data]
	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]
	Previous medical history (multiple counts)	[Gastric ulcer, Duodenal ulcer]
	Purpose of low-dose aspirin therapy (multiple counts)	[Angina pectoris, Myocardial infarction, Transient ischemic attack (TIA), Cerebral infarction, Others]
	Existence of coronary arterial stent	[Yes or No]
	Inpatient/outpatient classification	[Outpatient, Inpatient]
	Existence of hypersensitivity predisposition	[Yes or No or Unknown]
	Existence of complication	[Yes or No]
	Height (cm)	
	Weight (kg)	
	BMI (kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	Existence of *H. pylori* infection	[Positive or Negative or Unknown]
	Smoking history	[Non-smoker, Current smoker, Ex-smoker, Unknown]
	Drinking history	[Yes or No or Unknown]
	Existence of stress, a risk factor for developing gastric or duodenal ulcer	[Yes or No or Unknown]
	Existence of acid-suppressant therapy before the start of treatment with Takecab Tablets to prevent recurrent gastric or duodenal ulcer	[Yes or No or Unknown]
	Breakdown of drugs in patients with “Yes”	[Lansoprazole, Omeprazole, Rabeprazole, Esomeprazole, H_2-blocker]
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 Status of treatment with Takecab Tablets

Analysis population:	Safety analysis set	
Analysis items:	Initial daily dose of Takecab Tablets	[10 mg, Others]
	Duration (days) of treatment with Takecab Tablets	[1<= - <=84, 85<= - <=168, 169<= - <=Max]
	Reasons for discontinuation of treatment with Takecab Tablets	[Incidence of AE, No patient visit due to reasons such as changing hospital, Pregnancy, Development of gastric ulcer/duodenal ulcer/hemorrhagic lesions in stomach or duodenum, Discontinuation of low-dose aspirin therapy, Others]
Analysis method:	Following analysis will be conducted for the above analysis items. (1) Frequency counts of countable data, and summary statistics of quantitative data	

3.2 Status of low-dose aspirin therapy

Analysis population:	Safety analysis set	
Analysis items:	Initial daily dose of low-dose aspirin	[81 mg, 100 mg, 162 mg, 200 mg, Others]
	Duration (days) of low-dose aspirin therapy	[1<= - <=84, 85<= - <=168, 169<= - <=Max, Unknown]
	Purpose of treatment with Takecab Tablets after the completion of low-dose aspirin therapy	[Treatment of complication, Development of gastric ulcer/duodenal ulcer/hemorrhagic lesions in stomach or duodenum, Development of new gastrointestinal disease not mentioned above after treatment with Takecab Tablets, Others (e.g., prophylactic treatment)]
Analysis method:	Following analysis will be conducted for the above analysis items. (1) Frequency counts of countable data, and summary statistics of quantitative data	

3.3 Concomitant drug (excluding low-dose aspirin)

Analysis population:	Safety analysis set	
Analysis items:	Existence of concomitant drug (excluding low-dose aspirin)	[Yes or No]

Type of concomitant drug (excluding low-dose aspirin)

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 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 category of safety specification (count by risk)

Analysis population: Safety analysis set

Analysis items: AEs, etc. falling under the category of safety specification (described as important identified risks, important potential risks, and important missing information)

Subgroup items: Seriousness [Serious, Non-serious]

Analysis method: Following analyses will be conducted for the above analysis items in each subgroup by risk. The risks are important identified risks, important potential risks, and as defined in important missing information.

[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, when the multiple events differ in seriousness, one patient will be counted as both serious and non-serious.
- 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, when the multiple events differ in seriousness, one patient will be counted as both serious and non-serious.

4.1.3.2 Incidence ADRs/infections falling under the category of safety specification (count by risk)

Analysis population: Safety analysis set

Analysis items: ADRs, etc. falling under the category of safety specification (described as important identified risks, important potential risks, and important missing information)

Subgroup items: Seriousness [Serious, Non-serious]

Analysis method: Following analyses will be conducted for the above analysis items in each subgroup by risk. The risks are important identified risks, important potential risks, and as defined in important missing information.

[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, when the multiple events differ in seriousness, one patient will be counted as both serious and non-serious.
- 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, when the multiple events differ in seriousness, one patient will be counted as both serious and non-serious.

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 (days)	[1<= - <=84, 85<= - <=168, 169<= - <=Max, Unknown]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to the relevant 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 Tablets was started
  Outcome: Death (due to the relevant 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 (days)	[1<= - <=84, 85<= - <=168, 169<= - <=Max, Unknown]
	Outcome	[Resolved, Resolving, Not resolved, Resolved with sequelae, Death (due to the relevant event), Unknown]

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 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 Tablets was started

  Outcome: Death (due to the relevant 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]
	Purpose of low-dose aspirin therapy (multiple counts)	[Angina pectoris, Myocardial infarction, Transient ischemic attack (TIA), Cerebral infarction, Others]
	Existence of complication	[Yes or No]
	Existence of renal disease	[Yes or No]
	Existence of hepatic disease	[Yes or No]
	BMI (kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	Initial daily dose of low-dose aspirin	[81 mg, 100 mg, 162 mg, 200 mg, Others]
	Existence of concomitant drug (excluding low-dose aspirin)	[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 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 purpose of low-dose aspirin therapy

Analysis population: Safety analysis set

Analysis items: ADRs, etc.

Subgroup items: Purpose of low-dose aspirin therapy (multiple counts) [Angina pectoris, Myocardial infarction, Transient ischemic attack (TIA), Cerebral infarction, 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.

4.4.5 Incidence of ADR/infection by presence/absence of complication

Analysis population: Safety analysis set

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 presence/absence of renal disease

Analysis population: Safety analysis set

Analysis items: ADRs, etc.

Subgroup items: Existence of renal disease [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.

4.4.7 Incidence of ADR/infection by presence/absence of hepatic disease

Analysis population: Safety analysis set

Analysis items: ADRs, etc.

Subgroup items: Existence of hepatic disease [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.

4.4.8 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<= - <=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.

4.4.9 Incidence of ADR/infection by initial daily dose of low-dose aspirin

Analysis population:	Safety analysis set	
Analysis items:	ADRs, etc.	
Subgroup items:	Initial daily dose of low-dose aspirin	[81 mg, 100 mg, 162 mg, 200 mg, 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.

4.4.10 Incidence of ADR/infection by presence/absence of concomitant drug (excluding low-dose aspirin)

Analysis population:	Safety analysis set
Analysis items:	ADRs, etc.
Subgroup items:	Existence of concomitant drug (excluding low-dose aspirin) [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 Change of liver function test value

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

5 Tabulated analysis on efficacy results

5.1 Development of gastric ulcer, duodenal ulcer, or hemorrhagic lesions in stomach or duodenum

Analysis population:	Efficacy analysis set	
Analysis items:	Development of gastric ulcer, duodenal ulcer, or hemorrhagic lesions in stomach or duodenum	[Yes or No]
	Breakdown (multiple counts)	
	Development of gastric ulcer	[Yes or No]
	Development of duodenal ulcer	[Yes or No]
	Development of hemorrhagic lesions in stomach	[Yes or No]
	Development of hemorrhagic lesions in duodenum	[Yes or No]
Analysis method:	Frequency will be counted for the above analysis items, and point estimates and 95% confidence interval (two-sided) of proportions of patients who developed ulcer or hemorrhagic lesions will be calculated.	

5.2 Development of gastric ulcer, duodenal ulcer, or hemorrhagic lesions in stomach or duodenum (count in each subgroup)

Analysis population:	Efficacy analysis set	
Analysis items:	Development of gastric ulcer, duodenal ulcer, or hemorrhagic lesions in stomach or duodenum	[Yes or No]
	Breakdown (multiple counts)	
	Development of gastric ulcer	[Yes or No]
	Development of duodenal ulcer	[Yes or No]
	Development of hemorrhagic lesions in stomach	[Yes or No]
	Development of hemorrhagic lesions in duodenum	[Yes or No]
Subgroup items:	Sex	[Male, Female]
	Age (year)	[Min<= - <65, 65<= - <75, 75<= - <=Max]

	Existence of *H. pylori* infection	[Positive or Negative or Unknown]
	BMI (kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	Initial daily dose of low-dose aspirin	[81 mg, 100 mg, 162 mg, 200 mg, Others]

Analysis method: Frequency by each subgroup will be counted for the above analysis items, and point estimates and 95% confidence interval (two-sided) of proportions of patients who developed ulcer or hemorrhagic lesions will be calculated.

6 Incidence of ADR/infection in additional pharmacovigilance activities

6.1 Incidence of ADR/infection in additional pharmacovigilance activities (Attachment Form 12)

Analysis population:	Safety analysis set
Analysis items:	ADRs, etc. falling under the category of safety specification (described as important identified risks, important potential risks, and important missing information)
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 in Attachment Form 12 included in PSEHB/PED Notification No. 1128-2 (reexamination notification) dated November 28, 2017. (1) Number and proportion of patients with ADRs, etc. Risk terms and their order of listing will follow those of important identified risks, important potential risks, and important missing information.

7 Outline of patients in postmarketing surveillance, etc.

7.1 Outline of patients in postmarketing surveillance, etc. (Attachment Form 16)

Analysis population:	Patients whose survey forms have been collected
Analysis items:	Patient number Name of facility Sex Date of birth Indication (disease code, disease name) Complication (disease code, disease name) Route of administration Maximum dose Mean dose Unit Treatment period Concomitant drug (drug code, drug name) Level of effect ADR (disease code, disease name, outcome) Survey form No. Withdrawal
Analysis method:	A list will be prepared for the above analysis items in accordance with Notes 1 to 3 in Attachment Form 16 included in PSEHB/PED Notification No. 1128-2 (reexamination notification) dated November 28, 2017.

Revision history (version control)

Version	Date	Person who prepared/revised this document	Comment
Version 1	2019.8.7	PPD	Preparation of Version 1