Statistical Analysis Plan

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Study Number: Vedolizumab-5033

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statistical analysis plan

(Final analysis)

Product name Entyvio for Intravenous Infusion 300 mg

Survey title Special Investigation "Ulcerative Colitis"

Protocol Number :Vedolizumab-5033

Sponsor : Takeda Pharmaceutical Company Limited.

Takeda Pharmaceutical Company Limited.

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1 Definitions of Terms

1.1 List of Terms and Abbreviations

- This drug: Entyvio for I. V. Infusion 300 mg is abbreviated as this drug.
- Adverse event: AE that occurred after receiving Entyvio.
- Adverse events (induction phase): Adverse events that occurred by the day before the fourth dose in patients who received the fourth or higher dose and all events in patients who received the third or lower dose.
- Adverse events (maintenance period): Adverse events that occurred on or after the day of the fourth dose.
- Adverse reactions, etc.: Acronym of the term "adverse reactions/infections." Adverse events for which the causal relationship with Entyvio is other than “Not related ” in the assessment of the investigator. The term "adverse drug reactions/infections" is used in the title of this SAP, and "adverse drug reactions" is used in the text and tables.
- Adverse drug reactions, etc. (induction phase): Adverse drug reactions, etc.: Events that occurred by the day before the fourth dose in patients who received the fourth or more doses, and all events in patients who received the third or less doses.
- Adverse drug reactions, etc. (maintenance period): Adverse drug reactions, etc. that occurred on or after the day of the fourth dose.
- Serious adverse events: Adverse events assessed as “serious ” by the investigator. Events listed in the MedDRA code list of the Important Medical Events List will be handled as serious even if the investigator's assessment is “non-serious.”
- Related to Entyvio: Any AE other than 'Not related' for Entyvio.
- Not Related to Entyvio: AEs assessed as not related to Entyvio.
- Summary statistics: A general term for the number of patients, mean, standard deviation, maximum, minimum, and quartiles.
- Patients whose CRFs were not collected: Registered patients whose CRFs were not collected.
- Patients whose CRFs were collected: Registered patients whose CRFs were collected.
- Age: When the month of start of administration of Entyvio is the month of birth, it shall be calculated as the year of start of administration of Entyvio - year of birth -1. If the month of start of administration of Entyvio is equal to or greater than the month of birth, it shall be calculated as the year of start of administration of Entyvio - year of birth. If the month of birth is unknown, the month shall be calculated as January.

- Duration of disease (year): Actual number (unit: year) = Year of the first administration of Entyvio − Date of diagnosis of UC +1
- Timing of onset of adverse events (or adverse reactions, etc.): Calculated as the date of onset of adverse events (or adverse reactions, etc.) - the start date of Entyvio treatment +1. If the onset date of an adverse event (or adverse drug reaction) is unknown, it should be counted as the first day. However, if the start date of administration of Entyvio = the onset date of adverse event (or adverse reaction, etc.), it should be calculated as the start date of the first administration of Entyvio.
- Partial Mayo score: Sum of the stool frequency subscore, rectal bleeding subscore, and Physician's Global Assessment subscore. If any of the subscores used for the sum is missing, the partial Mayo score will be considered missing.
- Complete Mayo score: Sum of the stool frequency subscore, rectal bleeding subscore, Physician's Global Assessment subscore, and endoscopic subscore. If any of the subscores used for the sum is missing, the complete Mayo score will be considered missing.
- Complete Mayo score remission: Patients with a complete Mayo score of ≤ 2 points and no individual Mayo subscore > 1 point will have a complete Mayo score remission. Otherwise, if the complete Mayo score is not missing, the status will be "complete Mayo score non-remission."
- Partial Mayo score remission: A patient with a partial Mayo score ≤ 2 points and all Mayo subscores (Stool Frequency, Blood in the Stool, Physician's Global Assessment) ≤ 1 point will be classified as "Partial Mayo score remission." Otherwise, if the partial Mayo score is not missing, the status will be "Partial Mayo score non-remission."
- Complete Mayo score improvement: Cases meeting both of the following two conditions will be regarded as “complete Mayo score improvement.” Otherwise, if the complete Mayo score is not missing, the response will be "complete Mayo score not improved."
    - Decrease from Entyvio baseline in complete Mayo score of ≥ 3 points and ≥ 30%
    - Decrease in the rectal bleeding subscore by ≥ 1 point from the start of Entyvio treatment or absolute rectal bleeding subscore of ≤ 1 point
- Partial Mayo score improvement: Cases meeting both of the following two conditions will be regarded as “partial Mayo score improvement.” Otherwise, if the partial Mayo score is not missing, the response will be "Partial Mayo score not improved."
    - Decrease in partial Mayo score by ≥ 2 points and ≥ 25% from the start of Entyviotreatment
    - Decrease in the rectal bleeding subscore by ≥ 1 point from the start of Entyvio treatment or absolute rectal bleeding subscore of ≤ 1 point
- If the complete Mayo score is missing after the third dose of Entyvio or at the time of treatment discontinuation, the following 3 methods will be applied to the evaluation of remission/improvement in the complete Mayo score. This approach will apply to all patients with a nonmissing complete Mayo score at the start of Entyvio even if they did not

have a record of a complete Mayo score after the third dose of Entyvio or at the end of treatment. For data on the third dose of Entyvio in the maintenance phase, 54 weeks after the start of treatment with Entyvio, and at treatment discontinuation, handling of missing data (2) and (3) should be applied. This approach will apply to all patients with a nonmissing complete Mayo score at the start of Entyvio treatment even if they did not have a record of complete Mayo score at the time after the 3 doses of Entyvio, 54 weeks after the start of Entyvio treatment, or at the time of treatment discontinuation.

- Handling of missing data (1): If only the endoscopic subscore is missing and the partial Mayo score is not missing, the assessment of remission/improvement will be regarded as missing and excluded from the analysis. Patients with non-missing endoscopic subscore who have received at least one dose of Entyvio will be excluded from the analysis, assuming the assessment of remission/improvement is missing. If the endoscopic subscore is non-missing and there is no administration after the 4th dose, the assessment of remission/improvement will be handled as non-remission/non-improvement.
- Handling of missing data (2): If only the endoscopic subscore is missing and the partial Mayo score is not missing, the assessment of remission/improvement will be regarded as missing and excluded from the analysis. If the endoscopic subscore is non-missing, the assessment of remission/improvement will be handled as non-remission/non-improvement.
- Handling of missing data (3): The assessment of remission/improvement will be handled as non-remission/non-improvement.

- If the partial Mayo score is missing after the third dose of Entyvio or at the time of discontinuation, the following 2 methods will be applied to the evaluation of remission/improvement in the partial Mayo score. This approach will apply to all patients with a nonmissing partial Mayo score at initiation of Entyvio even if they did not have a record of partial Mayo score after the third dose of Entyvio or at discontinuation. For data after the 3rd dose of Entyvio in the maintenance phase, 54 weeks after the start of treatment with Entyvio, and at the time of treatment discontinuation, missing data handling (2) will be applied. This approach will apply to all patients with a non-missing partial Mayo score at initiation of Entyvio treatment even if they did not have a record of partial Mayo score at 54 weeks after the 3 doses of Entyvio, or at discontinuation of Entyvio treatment.
  - Handling of missing data (1): Patients who received the 4th or later dose of Entyvio at least once will be excluded from the analysis by assuming the assessment of remission/improvement as missing. For patients without the 4th and subsequent administrations of Entyvio, the assessment of remission/improvement will be handled as non-remission/non-improvement.
  - Handling of missing data (2): The assessment of remission/improvement will be handled as non-remission/non-improvement.
- SIBDQ is the sum of the scores for all questions (Q1, Q2, Q3, Q4, Q5, Q6, Q7, Q8, Q9, Q10). The SIBDQ will be set as missing if one or more questions are missing.

- SIBDQ subscores are calculated as follows: If one or more questions for calculation are missing, then the subscore will be set to missing.
    - Systemic symptom subscore: The mean of Q1 and Q7.
    - Social function subscore: The mean of Q2 and Q3.
    - Abdominal symptom subscore: The mean of Q4, Q6 and Q9.
    - Emotional subscore: The mean of Q5, Q8 and Q10.

1.2 Analysis Sets

In this study, the analysis sets are defined as "safety analysis set," "safety analysis set (maintenance phase)," "efficacy analysis set," and "efficacy analysis set (maintenance phase)." The analysis sets are defined as follows:

- Safety analysis set

  Defined as "Among patients with locked CRF, who received Entyvio at least once, have no major protocol violations, and are evaluable for safety." Patients with locked CRFs who meet the following conditions will be excluded from the safety analysis set.

  - Entyvio naïve
  - Enrollment outside the enrollment period
  - Enrollment from 15 days after the start date of treatment with Entyvio
  - Presence/absence of adverse event unknown
  - Withdrew consent

- Safety analysis set (maintenance phase)

  Defined as "Patients who received the 4th or later dose of Entyvio at least once among the patients evaluable for safety." Patients who meet the following conditions will be excluded from the safety analysis set (maintenance phase).

  - Patients without the 4th or subsequent administration of Entyvio

- Efficacy analysis set

  Defined as "Patients evaluable for efficacy without major protocol violations among patients eligible for safety evaluation." Patients eligible for the safety evaluation who meet any of the following conditions will be excluded from the efficacy evaluation.

  - Other than target disease
  - Inclusion criteria deviation
  - Exclusion criteria deviation
  - Patients who have received Entyvio in the past
  - Patients with a history of colectomy or stoma

- Efficacy analysis set (maintenance phase)

  Defined as "Patients who received the 4th or later dose of Entyvio at least once among the patients evaluable for efficacy." Patients meeting the following conditions will be excluded from the efficacy analysis set (maintenance phase).

  - Patients without the 4th or subsequent administration of Entyvio

1.3 Number of digits to be displayed

- Percentage (%)

  Incidence of AEs or ADRs:

  Round off to 2 decimal places.

  Other than the above:

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

- Summary statistics

  Mean, 14 quantiles, median, 34 quantiles:

  Round the second digit of the source data to display up to the first digit of the source data.

  Standard deviation:

  Round the third digit of the source data to display to the second digit of the source data.

  Min, Max:

  The same number of digits as that of the source data will be displayed.

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

- Important identified risks
  - Infusion reactions including hypersensitivity reactions: The following adverse events are defined as infusion reactions including hypersensitivity reactions.
    - Events identified by the SMQ "anaphylactic reactions" broad search OR the SMQ "anaphylactic/anaphylactoid shock conditions" broad search OR the SMQ "angioedema" broad search OR the SMQ "hypersensitivity" broad search

*In the Risk Management Plan at the time of the final analysis of this study, "infusion reaction and hypersensitivity reaction" were defined as important identified risks.In the Risk Management Plan, the event term was changed from "infusion reaction including hypersensitivity reaction" to "infusion reaction and hypersensitivity reaction" at the time of obtaining marketing approval for Entyvio Subcutaneous Injection 108 mg Pen and Entyvio Subcutaneous Injection 108 mg Syringe, but only the term was changed and the definition of the event was not changed. The term “infusion reaction including hypersensitivity reaction ” is continuously used because this survey was conducted with ENTYVIO for I.V. Infusion 300 mg.

- Important potential risks
  - Infections (other than progressive multifocal leukoencephalopathy): Infections (other than progressive multifocal leukoencephalopathy) are AEs that:
    - Events in the SOC "Infections and infestations"

      However, events corresponding to progressive multifocal leukoencephalopathy are excluded.
  - Progressive multifocal leukoencephalopathy: Adverse events applicable to Appendix 1 are defined as progressive multifocal leukoencephalopathy.
  - Malignancies: AEs meeting any of the following criteria will be considered malignancies.
    - Events in SOC"Neoplasms benign, malignant and unspecified (incl cysts and polyps)"
- Important missing information: Not applicable

1.5 Handling of TIME WINDOW

For each test, evaluable data (Data that are not missing and determined to be adopted) should be handled as described below. Evaluable data within the allowable window should be employed. If there are more than one evaluable data within the same acceptable range, the data with the test date closest to the reference implementation date will be adopted, and if the magnitude of difference from the reference implementation date is the same or the reference implementation date is not specified, the data at the last evaluation will be adopted. The magnitude of the difference from the reference day will be determined based on the number of days after administration.

Laboratory tests (Hemoglobin, white blood cell count, lymphocytes, albumin, CRP), Mayo score, stool frequency/bloody stool

Evaluation time point	Reference Date	Acceptable range
		Days after administration
At the start of administration of Entyvio	Days after treatment: 1	-28 ~ 1
Patients who received up to the third dose: After the third dose of Entyvio or at the time of discontinuation For patients who received 4 doses or more: After 3 doses of Entyvio	Days after treatment: 99	Patients who received up to the third dose: 2~126 Patients who received ≥ 4 doses: Days of the 2nd to 4th doses
54 weeks after the start of administration of Entyvio or at the time of discontinuation of administration	Days after treatment: 376	From the day after the 4th administration to 406

For SIBDQ (inflammatory bowel disease quality of life questionnaire), CRF time points will be used.

1.6 Other Handling

- Nothing in particular

2 Number of medical institutions, number of patients enrolled, and patient composition

2.1 Disposition of patients

Analyzed:	All registered patients (registered patients)	
Analysis item:	Enrolled patients	
	Number of medical institutions	
	Patients with no CRF collected	
	CRF collected patients	
	Patients excluded from safety evaluation *	
	Reason for exclusion (multiple counts)	[No administeration, enrollment outside the enrollment period, enrollment on or after Day 15 of the first dose of Entyvio, adverse event status unknown, consent withdrawal]
	Patients included in the safety evaluation *	
	Patients excluded from the safety evaluation (maintenance phase)	
	Reason for exclusion	[Patients without the fourth and subsequent doses of Entyvio]
	Safety analysis set (maintenance phase)	
	Patients excluded from efficacy evaluation *	
	Reason for exclusion (multiple counts)	[Patients with other diseases than the target disease, patients who violated the inclusion criteria, patients who violated the exclusion criteria, patients who have received Entyvio in the past, patients with a history of large intestine resection, stoma, etc.]
	Patients included in efficacy evaluation *	
	Patients excluded from efficacy evaluation (maintenance phase)	
	Reason for exclusion	[Patients without the fourth and subsequent doses of Entyvio]
	Efficacy analysis set (maintenance phase)	

Analytical method: For the above analytical variables, the following analyses will be performed, and a figure of patient composition will be prepared.

For patients enrolled, the number of study sites will also be calculated. A medical institution with different clinical departments in the study will be counted as one medical institution. If there is no patient meeting the reason for exclusion, 0 patient will be displayed. For patients excluded from the safety evaluation and efficacy evaluation, the number of patients by reason for exclusion will be tabulated and a list will be prepared.

*"Patients excluded from safety evaluation" refer to patients excluded from "patients included in safety evaluation" among patients whose case report forms are collected. Similarly, “patients excluded from efficacy evaluation ” refer to patients who are excluded from the“ efficacy evaluation population ” among the “safety evaluation population.”

（1） Calculation of frequencies

3 Patient characteristics

3.1 Patient characteristics

Analyzed:	Safety analysis set, safety analysis set (maintenance phase)	
Analysis item:	Sex	[Male, Female]
	Age (years)	Summary statistics
		[Min<= - <35, 35<= - <=Max, unknown]
		[Min<= - <18, 18<= - <65, 65<= - <=Max, unknown]
		[Min<= - <15, 15<= - <65, 65<= - <=Max, unknown]
	Duration of disease (years)	Summary statistics
		[Min<= - <1, 1<= - <5, 5<= - <10, 10<= - <=Max]
	Presence or absence of medical history	[No, Yes, unknown]
	Presence or absence of complications	[No, Yes]
	UC severity	[Moderate, severe]
	Extent of UC Disease	[pancolitis, left-sided colitis, proctitis, right-sided or segmental colitis]
	Family history	[No, Yes, unknown]
	Family history (multiple counts)	[Parents, children, grandparents, siblings, grandchildren]
	History of tuberculosis infection	[No, Yes, unknown]
	Steroid refractory	[No, Yes, unknown]
	Steroid dependence	[No, Yes, unknown]
	Steroid intolerance	[No, Yest, unknown]
	Prior UC therapies (excluding anti-TNFα therapies) other than Entyvio within 3 months prior to starting Entyvio	[No, Yes, unknown]
	Prior treatment with anti-TNFα antibody	[No, Yes]
	Details of prior treatment with anti-TNFα antibody (multiple counts)	
	Prior Adalimumab Therapy	[No, Yes]
	Prior infliximab therapy	[No, Yes]
	Prior Golimumab Treatment	[No, Yes]
	Prior Adalimumab Treatment Disposition *Only if the patient has a history of treatment with adalimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Details of prior infliximab therapy *Only if the patient has a history of treatment with infliximab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]
Prior Golimumab Treatment Disposition *Only if the patient has previously received golimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Analytical method: For the above analytical variables, frequency tabulation of categorical data and summary statistics of continuous data will be calculated.

3.2 Past history and complications

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Past history and complications

Analytical method: For the above analytical variable, the following analyses should be performed.

（1） Number of patients with events

（2） Incidence

（3） Type

The following accounting methods will be used for each analysis.

[Number of cases]

- Number of cases.

[Incidence]

- Calculate with the number of patients with events/the number of patients evaluated for safety ×100.

[Type]

- Coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with events and the incidence should be presented in SOC internationally agreed order. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC.
- As for PT, the number of patients with events and the incidence will be entered in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT.

4 Details of treatment

4.1 Administration status of Entyvio

Analyzed:	Safety analysis set	
Analysis item:	Daily dose	[300 mg, others]
Analytical method:	For the above analytical variables, frequencies will be presented for each dose (1st, 2nd ..., 9th). For the breakdown of others, frequency will be presented for each administration.	

4.2 Administration status of concomitant drugs

Analyzed:	Safety analysis set	
Analysis item:	Presence/absence of concomitant drug administration	[No, Yes]
	Purpose of administration (multiple counts)	[For treatment of UC, for treatment of adverse events, for treatment of complications, Others (prophylactic administration, etc.)]
Analytical method:	For the above analytical variables, frequency distribution will be performed.	

4.3 Concomitant Therapy Status

Analyzed:	Safety analysis set	
Analysis item:	Presence/absence of concomitant therapy	[No, Yes]
	Purpose of implementation (duplicate counting)	[For treatment of UC, for treatment of adverse events, for treatment of complications, Others (prophylactic therapy, etc.)]
Analytical method:	For the above analytical variables, frequency distribution will be performed.	

4.4 Surgical Procedures

Analyzed:	Safety analysis set	
Analysis item:	Presence or absence of surgical procedure	[No, Yes]
Analytical method:	For the above analytical variables, frequency distribution will be performed.	

5 Matters concerning safety

5.1 Adverse Events and Adverse Drug Reactions/Infections

5.1.1 Data on adverse events

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse events, adverse events (induction phase), adverse events (maintenance phase)

Analytical method:

- Analysis of Adverse Events in the Safety Analysis Set
- Analysis of Adverse Events (Induction Period) in the Safety Analysis Set
- Analysis of adverse events (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the following analyses should be performed.

（1） Number of patients with adverse events

（2） Number of adverse events

（3） Incidence of adverse events

（4） Types of Adverse Events

The following accounting methods will be used for each analysis.

[Number of patients with adverse events]

- Number of patients with AEs.

[Number of adverse events]

- Number of adverse events experienced. When the same adverse event occurred more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- It is calculated as the number of patients with adverse events/the number of patients evaluated for safety ×100.

[Types of adverse events]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC.
- For PT, the number of patients with adverse events and the incidence will be described in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT.

5.1.2 Status of onset of ADRs/infections

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the following analyses should be performed.

（1） Number of patients with adverse drug reactions, etc.

（2） Number of adverse drug reactions

（3） Incidence of adverse drug reactions, etc.

（4） Types of adverse drug reactions, etc.

The following accounting methods will be used for each analysis.

[Number of patients with adverse reactions, etc.]

- Number of patients with adverse drug reactions, etc.

[Number of adverse drug reactions]

- Number of adverse drug reactions, etc. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse drug reactions, etc.]

- Calculate with the number of patients with adverse reactions, etc./the number of patients evaluated for safety ×100.

[Types of adverse drug reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC.
- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT.

5.2 Incidences of adverse events and adverse drug reactions/infections in patients excluded from safety evaluation

5.2.1 Incidences of adverse events in patients excluded from safety evaluation

Analyzed: Patients excluded from safety evaluation

Analysis item: Adverse Events

Analytical method: For the above analytical variable, the following analyses should be performed.

（1） Number of patients with adverse events

（2） Number of adverse events

（3） Incidence of adverse events

（4） Types of Adverse Events

The following accounting methods will be used for each analysis.

[Number of patients with adverse events]

- Number of patients with AEs.

[Number of adverse events]

- Number of adverse events experienced. When the same adverse event occurred more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- Calculate as the number of patients with adverse events/the number of patients excluded from safety evaluation ×100.

[Types of adverse events]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC.
- For PT, the number of patients with adverse events and the incidence will be described in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT.

5.2.2 ADRs/infections in patients excluded from safety evaluation

Analyzed: Patients excluded from safety evaluation

Analysis item: Adverse Reactions, etc.

Analytical method: For the above analytical variable, the following analyses should be performed.

（1） Number of patients with adverse drug reactions, etc.

（2） Number of adverse drug reactions

（3） Incidence of adverse drug reactions, etc.

（4） Types of adverse drug reactions, etc.

The following accounting methods will be used for each analysis.

[Number of patients with adverse reactions, etc.]

- Number of patients with adverse drug reactions, etc.

[Number of adverse drug reactions]

- Number of adverse drug reactions, etc. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse drug reactions, etc.]

- Calculate as the number of patients with adverse reactions, etc./the number of patients excluded from safety evaluation ×100.

[Types of adverse drug reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC.
- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT.

5.3 Adverse Events and Adverse Drug Reactions/Infections Corresponding to Important Identified and Important Potential Risks

5.3.1 Incidences of adverse events included in safety specifications (tabulation by risk)

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse events included in safety specifications (important identified risks and important potential risks)

Adverse events included in safety specifications (important identified risks and important potential risks) (induction period)

Adverse events included in safety specifications (important identified risks and important potential risks) (maintenance phase)

Stratification items: Total

Seriousness [Serious, non-serious]

Analytical method:

- Analyses of adverse events included in the safety specification (important identified risks and important potential risks) in the safety analysis set
- Analyses of adverse events included in the safety specification (important identified risks and important potential risks) (induction phase) in the safety analysis set
- Analyses of adverse events included in the safety specification (important identified risks and important potential risks) (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of the analysis set and analysis items, the following analyses should be performed for each risk and each stratum of the stratification factors. The risks covered shall be in accordance with Paragraph 1.4 of the definition of terms, etc.

[Types of adverse events]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC. However, if the seriousness is different, serious and non-serious cases will be counted as 1 case each.
- For PT, the number of patients with adverse events and the incidence will be described in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT. However, if the seriousness is different, serious and non-serious cases will be counted as 1 case each.

5.3.2 Incidences of ADRs/infections included in safety specifications (tabulation by risk)

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse reactions, etc. included in safety specifications (important identified risks and important potential risks)

Adverse drug reactions, etc. included in safety specifications (important identified risks and important potential risks) (induction phase)

Adverse drug reactions, etc. included in safety specifications (important identified risks and important potential risks) (maintenance phase)

Stratification items: Total

Seriousness [Serious, non-serious]

Analytical method:

- Analyses of ADRs included in the safety specifications (important identified risks and important potential risks) in the safety analysis set
- Analyses of adverse drug reactions, etc. (induction phase) included in the safety specification (important identified risks and important potential risks) in the safety evaluation population
- Analyses of adverse drug reactions, etc. (maintenance phase) included in the safety specifications (important identified risks and important potential risks) in the safety evaluation population (maintenance phase)

For the above combination of the analysis set and analysis items, the following analyses should be performed for each risk and each stratum of the stratification factors. The risks covered shall be in accordance with Paragraph 1.4 of the definition of terms, etc.

[Types of adverse drug reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC. However, if the seriousness is different, serious and non-serious cases will be counted as 1 case each.
- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT. However, if the seriousness is different, serious and non-serious cases will be counted as 1 case each.

5.4 Adverse events and adverse reactions/infections by seriousness, time to onset, outcome, and causal relationship with Entyvio

5.4.1 Incidences of AEs by seriousness, time to onset, outcome, and causal relationship to Entyvio

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse events, adverse events (induction phase), adverse events (maintenance phase)

Stratification items: Total

Seriousness	[Serious, non-serious]
Time of onset	[1 to 28 days, 29 to 56 days, 57 to 112 days, 113 to 168 days, 169 to 224 days, 225 to 280 days, 281 to 336 days, ≥ 337 days]
Outcome	[Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to the event), unknown]
Relationship to Entyvio	[Related, Not Related]

Analytical method:

- Analysis of Adverse Events in the Safety Analysis Set
- Analysis of Adverse Events (Induction Period) in the Safety Analysis Set
- Analysis of adverse events (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of the analysis set and analysis items, the following analyses should be performed for each stratum of the stratification factor.

（1） Number of patients with adverse events

（2） Number of adverse events

（3） Incidence of adverse events

（4） Types of Adverse Events

The following accounting methods will be used for each analysis.

[Number of patients with adverse events]

- Number of patients with AEs.

[Number of adverse events]

- Number of adverse events experienced. When the same adverse event occurred more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- It is calculated as the number of patients with adverse events/the number of patients evaluated for safety ×100.

[Types of adverse events]

- Adverse events will be coded using the MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse events and the incidence of adverse events should be described in SOC internationally agreed order. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC. However, one case of the same SOC will be adopted in accordance with the last priority.
- For PT, the number of patients with adverse events and the incidence will be described in ascending order of PT code. If the same PT occurs more than once in the same patient, the

patient will be counted as 1 patient in the PT. However, 1 case of the same PT will be adopted in the following order of priority.

Seriousness: Serious → Non-serious

Onset time: 1 to 28 days →29 to 56 days →57 to 112 days →113 to 168 days →169 to 224 days →225 to 280 days →281 to 336 days → ≥ 337 days

Outcome: Fatal (due to the event) → recovered with sequelae → not recovered → recovering → recovered → unknown

Causal relationship with Entyvio: Related → Not related

5.4.2 ADRs/infections by seriousness, time to onset, and outcome

Analyzed:	Safety analysis set, safety analysis set (maintenance phase)	
Analysis item:	Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)	
Stratification items:	Total	
	Seriousness	[Serious, non-serious]
	Time of onset	[1 to 28 days, 29 to 56 days, 57 to 112 days, 113 to 168 days, 169 to 224 days, 225 to 280 days, 281 to 336 days, ≥ 337 days]
	Outcome	[Recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, death (due to the event), unknown]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of the analysis set and analysis items, the following analyses should be performed for each stratum of the stratification factor.

（1） Number of patients with adverse drug reactions, etc.

（2） Number of adverse drug reactions

（3） Incidence of adverse drug reactions, etc.

（4） Types of adverse drug reactions, etc.

The following accounting methods will be used for each analysis.

[Number of patients with adverse reactions, etc.]

- Number of patients with adverse drug reactions, etc.

[Number of adverse drug reactions]

- Number of adverse drug reactions, etc. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse drug reactions, etc.]

- Calculate with the number of patients with adverse reactions, etc./the number of patients evaluated for safety ×100.

[Types of adverse drug reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. Data will be broadly classified by SOC, and tabulated by PT within the SOC. If the SOC is "investigations," they will be summarized by HLGT (Sort in ascending order of HLGT code, but not output) and by PT.
- For SOC, the number of patients with adverse drug reactions, etc. and the incidence should be described in the order of SOC international consensus. A patient who experiences the same SOC more than once will be counted as 1 patient in the SOC. However, one case of the same SOC will be adopted in accordance with the last priority.
- For PT, the number of patients with adverse drug reactions, etc. and the incidence should be entered in ascending order of PT code. If the same PT occurs more than once in the same patient, the patient will be counted as 1 patient in the PT. However, 1 case of the same PT will be adopted in the following order of priority.

  Seriousness: Serious → Non-serious

  Onset time: 1 to 28 days →29 to 56 days →57 to 112 days →113 to 168 days →169 to 224 days →225 to 280 days →281 to 336 days → ≥ 337 days

  Outcome: Fatal (due to the event) → recovered with sequelae → not recovered → recovering → recovered → unknown

5.5 ADRs/Infections Leading to Treatment Discontinuation for Entyvio

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse drug reactions etc., Adverse drug reactions etc. (induction period), Adverse drug reactions etc. (maintenance period) for which [Cause for discontinuation of administration of Entyvio] in [Adverse events] is [Yes]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, analyses should be performed in the same manner as in Section 5.1.2.

5.6 Factors that may affect safety

5.6.1 Status of onset of ADRs/infections by patient background and treatment factors

Analyzed:	Safety analysis set, safety analysis set (maintenance phase)	
Analysis item:	Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)	
Stratification items:	Sex	[Male, Female]
	Age (years)	[Min<= - <35, 35<= - <=Max, unknown]
		[Min<= - <18, 18<= - <65, 65<= - <=Max, unknown]
		[Min<= - <15, 15<= - <65, 65<= - <=Max, unknown]
	Duration of disease (years)	[Min<= - <1, 1<= - <5, 5<= - <10, 10<= - <=Max]
	Presence or absence of medical history	[No, Yes, unknown]
	Presence or absence of complications	[No, Yes]
	UC severity	[Moderate, severe]
	Extent of UC Disease	[pancolitis, left-sided colitis, proctitis, right-sided or segmental colitis]
	Family history	[No, Yes, unknown]
	Family history (multiple counts)	[Parents, children, grandparents, siblings, grandchildren]
	History of tuberculosis infection	[No, Yes, unknown]
	Steroid refractory	[No, Yes, unknown]
	Steroid dependence	[No, Yes, unknown]
	Steroid intolerance	[No, Yes, unknown]
	Prior UC therapies (excluding anti-TNFα therapies) other than Entyvio within 3 months prior to starting Entyvio	[No, Yes, unknown]
	Prior treatment with anti-TNFα antibody	[No, Yes]
	Details of prior treatment with anti-TNFα antibody (multiple counts)	
	Prior Adalimumab Therapy	[No, Yes]
	Prior infliximab therapy	[No, Yes]
	Prior Golimumab Treatment	[No, Yes]
	Prior Adalimumab Treatment Disposition *Only if the patient has a history of treatment with adalimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Details of prior infliximab therapy *Only if the patient has a history of treatment with infliximab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]
Prior Golimumab Treatment Disposition *Only if the patient has previously received golimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of the analysis set and analysis items, the following analyses should be performed for each stratum of the stratification factor.

（1） Number of patients with adverse drug reactions, etc.

（2） Incidence of adverse drug reactions, etc.

The following accounting methods will be used for each analysis.

[Number of patients with adverse reactions, etc.]

- Number of patients with adverse drug reactions, etc.

[Incidence of adverse drug reactions, etc.]

- Calculate with the number of patients with adverse reactions, etc./the number of patients evaluated for safety ×100.

5.6.2 Incidences of ADRs/infections by gender

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Sex [Male, Female]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.3 Incidences of ADRs and infections by age group

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Age (years) [Min<= - <35, 35<= - <=Max, unknown]
[Min<= - <18, 18<= - <65, 65<= - <=Max, unknown]
[Min<= - <15, 15<= - <65, 65<= - <=Max, unknown]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.4 Status of occurrence of ADRs/infections by duration of disease

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Duration of disease (years) [Min<= - <1, 1<= - <5, 5<= - <10, 10<= - <=Max]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.5 Status of occurrence of ADRs/infections by presence/absence of medical history

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Presence or absence of medical history [No, Yes, unknown]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.6 Status of occurrence of ADRs/infections by presence/absence of complications

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Presence or absence of complications [No, Yes]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.7 Adverse Reactions/Infections by Severity of UC

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: UC severity [Moderate, severe]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.8 Status of occurrence of ADRs/infections by the extent of UC lesions

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Extent of UC Disease [pancolitis, left-sided colitis, proctitis, right-sided or segmental colitis]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.9 ADRs/infections by family history

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Family history [No, Yes, unknown]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.10 ADRs/infections by family medical history relationship

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Family history (multiple counts) [Parents, children, grandparents, siblings, grandchildren]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.11 Status of occurrence of ADRs/infections by history of tuberculosis infection

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: History of tuberculosis infection [No, Yes, unknown]

Analytical method:
- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.12 Status of occurrence of ADRs/infections by steroid resistance

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Steroid refractory [No, Yes, unknown]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.13 Status of occurrence of ADRs/infections by steroid dependence

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Steroid dependence [No, Yes, unknown]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.14 Incidences of ADRs and infections by steroid intolerance

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Steroid intolerance [No, Yes, unknown]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.15 Data on adverse reactions and infections by prior treatment history for UC other than Entyvio within 3 months prior to the start of Entyvio administration (excluding anti-TNFα antibody drugs)

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items:

Prior UC therapies (excluding anti-TNFα therapies) other than Entyvio within 3 months prior to starting Entyvio	[No, Yes, unknown]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.16 Incidences of ADRs and infections by history of anti-TNFα antibody treatment

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items:

Prior treatment with anti-TNFα antibody	[No, Yes]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.17 Adverse Reactions/Infections by Details of Prior Anti-TNFα Antibody Treatment

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items:

Prior Adalimumab Therapy	[No, Yes]
Prior infliximab therapy	[No, Yes]
Prior Golimumab Treatment	[No, Yes]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set

- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.18 Incidence of ADRs/infections by adalimumab treatment history

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Prior Adalimumab Treatment Disposition [Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.19 Adverse Reactions/Infections by History of Infliximab Treatment

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items: Details of prior infliximab therapy [Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.6.20 ADRs/infections by prior golimumab use

Analyzed: Safety analysis set, safety analysis set (maintenance phase)

Analysis item: Adverse Drug Reactions, etc., Adverse Drug Reactions, etc. (Induction Period), Adverse Drug Reactions, etc. (Maintenance Period)

Stratification items:	Prior Golimumab Treatment Disposition	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Analytical method:

- Analysis of adverse drug reactions, etc. in the safety analysis set
- Analysis of adverse drug reactions, etc. (induction period) in the safety analysis set
- Analysis of adverse drug reactions, etc. (maintenance phase) in the safety analysis set (maintenance phase)

For the above combination of analysis set and analysis items, the same analyses as in Section 5.1.2 should be performed for each of the subgroups of the stratification factors.

5.7 Laboratory Evaluations

Analyzed: Patients evaluable for safety, patients evaluable for safety (maintenance phase)

Analysis item: Hemoglobin (g/dL)
WBC (/uL)
Lymphocytes (%)
Albumin (g/dL)
CRP(mg/dL)

Analytical method: The safety analysis set will be analyzed by evaluation timing (At the start of administration of Entyvio, after the third dose of Entyvio, or at the time of discontinuation).
Patients included in the safety evaluation (maintenance phase) will be analyzed by evaluation timing (At the start of administration of Entyvio, after the 3 doses of Entyvio, 54 weeks after the start of administration of Entyvio, or at the time of discontinuation of administration).
For the above combinations of analysis sets and evaluation time points, summary statistics of observed values and changes from the start of Entyvio treatment will be presented.

6 Matters concerning efficacy

6.1 Presence/absence of therapeutic response, continuation of treatment

Analyzed:	Efficacy analysis set	
Analysis item:	Presence or absence of therapeutic response after the third dose or at the time of discontinuation	[No, Yes, missing]
	Continuation of treatment (4th dose)	[No, Yes]
Analytical method:	Frequency tabulation will be performed for the above analytical variables.	

6.2 Change in complete and partial Mayo scores

Analyzed:	Efficacy analysis set, efficacy analysis set (maintenance phase)	
Analysis item:	Complete Mayo Score	
	Partial Mayo Score	
	Complete Mayo score remission (Missing handling (1))	[Remission, non-remission]
	Complete Mayo score remission (handling of missing data (2))	[Remission, non-remission]
	Complete Mayo score remission (Missing handling (3))	[Remission, non-remission]
	Improvement in complete Mayo score (Missing handling (1))	[Improved, not improved]
	Improvement in complete Mayo score (Missing handling (2))	[Improved, not improved]
	Improvement in complete Mayo score (Missing handling (3))	[Improved, not improved]
	Partial Mayo score remission (handling of missing data (1))	[Remission, non-remission]
	Partial Mayo score remission (handling of missing data (2))	[Remission, non-remission]
	Partial Mayo score improvement (handling of missing data (1))	[Improved, not improved]
	Partial Mayo score improved (missing handling (2))	[Improved, not improved]
	Stool Frequency	
	Stool Frequency Score	[0, 1, 2, 3]
	Blood in stool score	[0, 1, 2, 3]
	Mucosal score	[0, 1, 2, 3]
	Physician's Global Assessment Score	[0, 1, 2, 3]
Analytical method:	Patients included in the efficacy evaluation will be analyzed by evaluation timing (At the start of administration of Entyvio, after the third dose of Entyvio, or at the time of discontinuation). Patients included in the efficacy evaluation (maintenance phase) will be analyzed by evaluation timing (At the start of administration of Entyvio, after the 3 doses of Entyvio, 54 weeks after the start of administration of Entyvio, or at the time of discontinuation of administration). For the above combination of analysis sets and evaluation time points, the following analyses should be performed. For remission and response, frequency tabulation will be performed.	

For complete Mayo score, partial Mayo score, and stool frequency, summary statistics of observed values and changes from the start of Entyvio administration will be presented.
For the stool frequency score, bloody stool score, endoscopic score, and physician's global assessment score, summary statistics of measured values and changes from the start of Entyvio treatment will be performed, and frequency tabulation using 4 categories of 0, 1, 2, and 3 will be performed.

The complete Mayo score, complete Mayo score remission, and complete Mayo score improvement will be summarized separately for patients whose complete Mayo score and endoscopic score at the start of administration of Entyvio meet the following conditions.

・Complete Mayo score ≥ 6 with endoscopic subscore ≥ 2
・Complete Mayo score ≥ 5 with endoscopic subscore ≥ 2
・Complete Mayo score ≥ 4 with endoscopic subscore ≥ 2
・No condition

For partial Mayo score, partial Mayo score remission and partial Mayo score improvement, partial Mayo score at the start of administration of Entyvio will be tabulated for patients who met the following conditions.

・Partial Mayo score ≥ 5
・Partial Mayo score ≥ 4
・Partial Mayo score ≥ 3
・No condition

6.3 QOL survey

6.3.1 QOL survey

Analyzed:	Patients without colectomy, stoma, etc. during the observation period among the efficacy analysis set, and patients without colectomy, stoma, etc. during the observation period among the efficacy analysis set (maintenance phase)
Analysis item:	SIBDQ SIBDQ subscore (Systemic symptoms, social function, abdominal symptoms, emotional state) SIBDQ Question 1~10
Analytical method:	Patients included in the efficacy evaluation will be analyzed by evaluation timing (At the start of administration of Entyvio, after the third dose of Entyvio, or at the time of discontinuation).

Patients included in the efficacy evaluation (maintenance phase) will be analyzed by evaluation timing (At the start of administration of Entyvio, after the 3 doses of Entyvio, 54 weeks after the start of administration of Entyvio, or at the time of discontinuation of administration).
For the above combinations of analysis sets and evaluation time points, summary statistics of observed values and changes from the start of Entyvio treatment will be presented.

6.3.2 QOL Survey by Complete Mayo Score and Partial Mayo Score

Analyzed:	Patients without colectomy, stoma, etc. during the observation period among the efficacy analysis set, and patients without colectomy, stoma, etc. during the observation period among the efficacy analysis set (maintenance phase)	
Analysis item:	SIBDQ SIBDQ subscore (Systemic symptoms, social function, abdominal symptoms, emotional state) SIBDQ Question 1~10	
Stratification items:	Complete Mayo score remission	[Remission, non-remission]
	Complete Mayo score improved	[Improved, not improved]
	Partial Mayo score remission	[Remission, non-remission]
	Partial Mayo score improved	[Improved, not improved]
Analytical method:	For the above combination of analysis set and analysis items, the same analyses as in Section 6.3.1 should be performed for each of the subgroups of the stratification factors.	

For the Mayo score, missing data handling (1) will be applied to efficacy evaluable patients, and missing data handling (2) will be applied to efficacy evaluable patients (maintenance phase).

The complete Mayo score remission and complete Mayo score improvement will be tabulated for patients whose complete Mayo score and endoscopic score at the start of Entyvio meet the following conditions.

- Complete Mayo score ≥ 6 with endoscopic subscore ≥ 2
- Complete Mayo score ≥ 5 with endoscopic subscore ≥ 2
- Complete Mayo score ≥ 4 with endoscopic subscore ≥ 2

Partial Mayo score remission and partial Mayo score improvement will be tabulated for patients who met the following criteria of partial Mayo score at the start of administration of Entyvio.

- Partial Mayo score ≥ 5
- Partial Mayo score ≥ 4
- Partial Mayo score ≥ 3

6.4 Factors that may affect efficacy

6.4.1 Patient characteristics, presence/absence of therapeutic response by treatment characteristics, treatment continuation, complete Mayo score and partial Mayo score (history of anti-TNFα antibody treatment: 1)

Analyzed:	Efficacy analysis set, efficacy analysis set (maintenance phase)	
Analysis item:	Presence or absence of therapeutic response after the third dose or at the time of discontinuation	[No, Yes, missing]
	Continuation of treatment (4th dose)	[No, Yes]
	Complete Mayo score remission	[Remission, non-remission]
	Complete Mayo score improved	[Improved, not improved]
	Partial Mayo score remission	[Remission, non-remission]
	Partial Mayo score improved	[Improved, not improved]
Stratification item 1:	History of anti-TNFα antibody treatment: Part 1	[No, Yes]
Stratification item 2:	Sex	[Male, Female]
	Age (years)	[Min<= - <35, 35<= - <=Max, unknown]
		[Min<= - <18, 18<= - <65, 65<= - <=Max, unknown]
		[Min<= - <15, 15<= - <65, 65<= - <=Max, unknown]
	Duration of disease (years)	[Min<= - <1, 1<= - <5, 5<= - <10, 10<= - <=Max]
	Presence or absence of medical history	[No, Yes, unknown]
	Presence or absence of complications	[No, Yes]
	UC severity	[Moderate, severe]
	Extent of UC Disease	[pancolitis, left-sided colitis, proctitis, right-sided or segmental colitis]
	Family history	[No, Yes, unknown]
	Family history (multiple counts)	[Parents, children, grandparents, siblings, grandchildren]
	History of tuberculosis infection	[No, Yes, unknown]
	Steroid refractory	[No, Yes, unknown]
	Steroid dependence	[No, Yes, unknown]
	Steroid intolerance	[No, Yes, unknown]
	Prior UC therapies (excluding anti-TNFα therapies) other than Entyvio within 3 months prior to starting Entyvio	[No, Yes, unknown]

Prior treatment with anti-TNFα antibody	[No, Yes]
Details of prior treatment with anti-TNFα antibody (multiple counts)	[No, Yes]
Prior Adalimumab Therapy	[No, Yes]
Prior infliximab therapy	[No, Yes]
Prior Golimumab Treatment	
Prior Adalimumab Treatment Disposition *Only if the patient has a history of treatment with adalimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]
Details of prior infliximab therapy *Only if the patient has a history of treatment with infliximab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]
Prior Golimumab Treatment Disposition *Only if the patient has previously received golimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Analytical method: Efficacy analysis set will be analyzed after the third dose of Entyvio or at treatment discontinuation.

Efficacy analysis set (maintenance phase) will be analyzed at Week 54 of treatment with Entyvio or at treatment discontinuation.

For the combination of the above analysis set and analysis items, frequency tabulation will be performed for each stratum of Stratification Item 1. After stratification by stratification factor 1, frequency tabulation will be performed for each stratum of stratification factor 2.

For the Mayo score, missing data handling (1) will be applied to efficacy evaluable patients, and missing data handling (2) will be applied to efficacy evaluable patients (maintenance phase).

The complete Mayo score remission and complete Mayo score improvement will be tabulated for patients whose complete Mayo score and endoscopic score at the start of Entyvio meet the following conditions.

・Complete Mayo score ≥ 6 with endoscopic subscore ≥ 2

・Complete Mayo score ≥ 5 with endoscopic subscore ≥ 2

・Complete Mayo score ≥ 4 with endoscopic subscore ≥ 2

Partial Mayo score remission and partial Mayo score improvement will be tabulated for patients who met the following criteria of partial Mayo score at the start of administration of Entyvio.

・Partial Mayo score ≥ 5

・Partial Mayo score ≥ 4

・Partial Mayo score ≥ 3

6.4.2 Patient characteristics, presence/absence of therapeutic response by treatment characteristics, treatment continuation, complete Mayo score and partial Mayo score (history of anti-TNFα antibody treatment: 2)

Analyzed:	Efficacy analysis set, efficacy analysis set (maintenance phase)	
Analysis item:	Presence or absence of therapeutic response after the third dose or at the time of discontinuation	[No, Yes, missing]
	Continuation of treatment (4th dose)	[No, Yes]
	Complete Mayo score remission	[Remission, non-remission]
	Complete Mayo score improved	[Improved, not improved]
	Partial Mayo score remission	[Remission, non-remission]
	Partial Mayo score improved	[Improved, not improved]
Stratification item 1:	History of anti-TNFα antibody treatment: Part 2	[None, only 1 drug, 2 or more drugs]
Stratification item 2:	Sex	[Male, Female]
	Age (years)	[Min<= - <35, 35<= - <=Max, unknown] [Min<= - <18, 18<= - <65, 65<= - <=Max, unknown] [Min<= - <15, 15<= - <65, 65<= - <=Max, unknown]
	Duration of disease (years)	[Min<= - <1, 1<= - <5, 5<= - <10, 10<= - <=Max]
	Presence or absence of medical history	[No, Yes, unknown]
	Presence or absence of complications	[No, Yes]
	UC severity	[Moderate, severe]
	Extent of UC Disease	[pancolitis, left-sided colitis, proctitis, right-sided or segmental colitis]
	Family history	[No, Yes, unknown]

Family history (multiple counts)	[Parents, children, grandparents, siblings, grandchildren]
History of tuberculosis infection	[No, Yes, unknown]
Steroid refractory	[No, Yes, unknown]
Steroid dependence	[No, Yes, unknown]
Steroid intolerance	[No, Yes, unknown]
Prior UC therapies (excluding anti-TNFα therapies) other than Entyvio within 3 months prior to starting Entyvio	[No, Yes, unknown]
Prior treatment with anti-TNFα antibody	[None, only 1 drug, 2 or more drugs]
Details of prior treatment with anti-TNFα antibody (multiple counts)	[No, Yes]
Prior Adalimumab Therapy	[No, Yes]
Prior infliximab therapy	[No, Yes]
Prior Golimumab Treatment	
Prior Adalimumab Treatment Disposition *Only if the patient has a history of treatment with adalimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]
Details of prior infliximab therapy *Only if the patient has a history of treatment with infliximab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]
Prior Golimumab Treatment Disposition *Only if the patient has previously received golimumab	[Primary non-response, Secondary non-response, Intolerance, Discontinuation from response/remission, Other]

Analytical method: Efficacy analysis set will be analyzed after the third dose of Entyvio or at treatment discontinuation.

Efficacy analysis set (maintenance phase) will be analyzed at Week 54 of treatment with Entyvio or at treatment discontinuation.

For the combination of the above analysis set and analysis items, frequency tabulation will be performed for each stratum of Stratification Item 1. After stratification by stratification factor 1, frequency tabulation will be performed for each stratum of stratification factor 2.

For the Mayo score, missing data handling (1) will be applied to efficacy evaluable patients, and missing data handling (2) will be applied to efficacy evaluable patients (maintenance phase).

The complete Mayo score remission and complete Mayo score improvement will be tabulated for patients whose complete Mayo score and endoscopic score at the start of Entyvio meet the following conditions.

・Complete Mayo score ≥ 6 with endoscopic subscore ≥ 2

・Complete Mayo score ≥ 5 with endoscopic subscore ≥ 2

・Complete Mayo score ≥ 4 with endoscopic subscore ≥ 2

Partial Mayo score remission and partial Mayo score improvement will be tabulated for patients who met the following criteria of partial Mayo score at the start of administration of Entyvio.

・Partial Mayo score ≥ 5

・Partial Mayo score ≥ 4

・Partial Mayo score ≥ 3

Calprotectin will not be analyzed based on the decision of the case review committee.

7 Incidences of adverse reactions/infections in the additional pharmacovigilance plan

7.1 Incidences of adverse reactions and infections in the additional pharmacovigilance plan (Attached Form 12)

Analyzed:	Safety analysis set
Analysis item:	Adverse reactions, etc. included in safety specifications (Important identified risks, important potential risks, and important missing information)
Stratification items:	Seriousness [Serious, non-serious]
Analytical method:	For the above analytical variable, the following analyses should be performed for each stratum of the stratification factor in accordance with Attached Form 12, (Note) 1~4 of PSEHB/PED Notification No. 0325/10 dated March 25, 2020.

（1） Number of patients with events and incidence

Risk names and the order of risk names shall be in accordance with the definitions described in the safety specification (Important identified risks, important potential risks, and important missing information).

8 Incidence of adverse reactions/infections in post-marketing surveillance, etc.

8.1 Incidence of adverse reactions/infections in post-marketing surveillance, etc. (Attached Form 15)

Analyzed: Safety analysis set

Analysis item: Adverse Reactions, etc.

Analytical method: For the above analytical variable, the following analyses should be performed.

（1） Status of post-marketing surveillance, etc.

1） Number of patients in the safety analysis set *

2） Number of patients with adverse drug reactions, etc.

3） Incidence of adverse drug reactions, etc.

（2） Types of adverse drug reactions, etc.

1） Number of patients with all adverse drug reactions and incidences (by SOC)

2） Number of patients with all adverse drug reactions and incidences (by PT)

Adverse drug reactions will be coded using MedDRA. SOCs will be shown in internationally agreed order. PTs will be shown in ascending order of HLGT codes and ascending order of PT codes if the SOC is investigations, and otherwise in ascending order of PT codes.

In each analysis, events will be counted in the following manner.

[Number of patients with adverse drug reactions, etc. and incidence by type]

- When “frequency tabulation ” is performed

  A patient who experienced more than one event with the applicable SOC or PT should be counted as 1 patient with the event. In calculating the incidence, the denominator should be the number of patients in the safety analysis set.

*The "number of patients in the safety analysis set" refers to the "analysis set" (described above) for this analysis.

9 Case summary in post-marketing surveillance, etc.

9.1 Case summaries from post-marketing surveillance, etc. (Attached Form 16)

Analyzed:	CRF collected patients
Analysis item:	Case Number
	Name of medical institution
	Sex
	Age
	Reason for use (Disease code and name)
	Comorbidity (Disease code and name)
	Route of Administration
	Maximum Dose
	Mean dose
	Unit
	Duration of use (Entyvio treatment period)
	Concomitant medications (Drug code and name)
	Degree of efficacy
	Reactions (Disease code, name of disease, outcome)
	Survey form No.
	Dropout
	Reason for Dropout
Analytical method:	For the above analytical items, a list will be prepared in accordance with the guidelines for preparation of reexamination data entry file specified in PSEHB/PED Notification No. 1119 No. 3 dated November 19, 2020.

Appendix 1 Risk PTs

Risks	PT code	PT Japanese name
Progressive multifocal leukoencephalopathy	10057366	Human polyomavirus infection
	10023163	JC virus infection
	10070356	JC polyomavirus test positive
	10024382	Leukoencephalopathy
	10070342	Polyomavirus test positive
	10036807	Progressive multifocal leukoencephalopathy
	10078957	CSF JC virus test positive

Preparation history (version control)

Version	Date	Prepared/changed by	Comments
Original Version	2024.10.30	[redacted]	Preparation of the first version