Clinical Study Protocol

NCT Number: NCT03824561

Title: Special Drug-Use Surveillance Study on Entyvio for IV Infusion 300 mg [Ulcerative Colitis]

Study Number: Vedolizumab-5033

Document Version and Date: Version 9 / 29-JUL-2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

A summary of changes to previous protocol versions is appended to the end of the document.

Note; This document was translated into English as the language on original version was Japanese.

Protocol for Special Drug Use-Results Surveillance Study
Entyvio for IV Infusion 300 mg
Special Drug Use-Results Surveillance Study
[Ulcerative Colitis]

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**Vedolizumab-5033**
Version No.	**Version 9**
Date of preparation	**July 29, 2024**

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1.0 BACKGROUND

Ulcerative colitis (UC) is an inflammatory bowel disease that relapses and remits repeatedly. Since no radical treatment has been established, the basic medical treatment strategy is to promptly induce remission by drugs and maintain remission for a long period of time (remission maintenance).

Entyvio for intravenous (IV) infusion 300 mg (hereafter referred to as "Entyvio") is a recombinant humanized immunoglobulin G1 monoclonal antibody that binds specifically to α4β7 integrin on human lymphocytes and inhibits the binding of α4β7 integrin to the mucosal addressin cell adhesion molecule 1 (MadCAM1) ligand on the vascular endothelium of the intestine, thereby inhibiting the entry of pro-inflammatory memory T-cells into the intestinal mucosa. Entyvio, thus, inhibits intestinal inflammation with its gut-selective immunomodulatory activity not associated with systemic immunosuppression. Based on shipment data, the cumulative number of patients using Entyvio after the first marketing approval in May 2014 is estimated to be approximately 510,259 patient-years overseas as of May 19, 2020. The evidence of statistically significant and clinically meaningful efficacy of Entyvio has been demonstrated through multiple clinical studies in participants with moderate to severe active UC.

Therefore, a special drug use-results surveillance study (hereafter referred to as this study) was planned to investigate the safety and effectiveness of the long-term use of Entyvio in participants with UC during actual and the routine clinical setting in Japan. This study will be conducted in compliance with the applicable regulatory requirements, including the Good Post-marketing Study Practice (GPSP) Ordinance.

2.0 OBJECTIVES

To examine and evaluate the safety and effectiveness of Entyvio in UC participants for long-term and actual use during the routine clinical setting in Japan.

3.0 PLANNED SAMPLE SIZE AND RATIONALE

3.1 PLANNED SAMPLE SIZE

1,000 participants including:

≥ 300 participants with a history of treatment with anti-tumor necrosis factor alpha (TNFα) antibody, and

≥ 300 participants without any history of treatment with anti-TNFα antibody

3.2 RATIONALE

In the 300 mg group of Entyvio during the CCT-101 study, the incidence of adverse events related to infusion-related reactions was 4.2% (12/287 participants) and the incidence of adverse events in the infections and infestations system organ class (SOC), was 67.6% (194/287 participants). Adverse events in the infections and infestations SOC occurred in ≥3% of participants by preferred term were nasopharyngitis (45.6%, 131/287 participants), gastroenteritis (6.6%, 19/287 participants), influenza (4.9%, 14/287

participants), bronchitis (3.8%, 11/287 participants), pharyngitis (3.5%, 10/287 participants), enteritis infectious (3.5%, 10/287 participants), and tonsillitis (3.1%, 9/287 participants).

To examine these safety specifications and the other adverse drug reactions in the routine clinical setting, the sample size was set at 1,000 participants. A sample size of 1,000 participants will provide the power to detect at least one adverse drug reaction with an incidence of ≥ 0.3% with a confidence level over 95%.

Of the planned 1,000 participants, ≥ 300 participants each with or without a history of treatment with anti-TNFα antibody will be enrolled to evaluate the safety and effectiveness of long-term administration of Entyvio. As an interim analysis, the effectiveness of induction therapy with Entyvio in the induction phase will be evaluated when the evaluable data after 3 doses of Entyvio are obtained from ≥ 90 participants each with or without a history of treatment with anti-TNFα antibody, along with the safety as necessary.

4.0 STUDY POPULATION

Target population is patients with UC. Participants must meet all of the following inclusion criteria and none of the exclusion criteria. Refer to the precautions in the package insert.

4.1 INCLUSION CRITERIA

Patients who meet both of the following criteria will be included.

[1] Patients in the active phase of moderate or severe UC.
[2] Patients with an inadequate response to conventional therapy.

4.2 EXCLUSION CRITERIA

Patients who meet the following criterion will not be included.

Patients for whom Entyvio is contraindicated.

5.0 DOSAGE AND ADMINISTRATION

The usual dose is 300 mg of vedolizumab (recombinant) per administration via intravenous infusion for adults. Entyvio should be administered at Week 2 and Week 6 after receiving the initial dose, and then every 8 weeks thereafter. Refer to the precautions in the package insert for details.

6.0 PLANNED NUMBER OF MEDICAL INSTITUTIONS BY DEPARTMENT

Department of gastroenterological medicine and others Approximately 250 institutions

7.0 METHODS

7.1 OBSERVATION PERIOD

54 weeks

7.2 Data Collection Method

Web-based Electronic Data Capture (EDC) system will be used. Data on stool frequency and rectal bleeding as part of Quality of life (QOL) and Mayo scores will be collected via the participant diary (Medidata ePRO) in principle.

7.3 Participant Registration Method

The “central registration system” will be used. The investigator or a person appointed by the investigator will enter participant registration information into the EDC system and electronically sign it within 14 days after the start of the treatment with Entyvio (the day of treatment initiation is defined as “Day 0” and the day after initiation is defined as “Day 1”).

7.4 Entry in the Survey Form (electronic) and Electronic Signature

The investigator or a person appointed by the investigator will enter the participant's background and treatment information into the EDC system after 3 doses of Entyvio and within approximately 1 month after the end of observation at Week 54. The investigator will then electronically sign it.

For participants who discontinue the treatment during observation period for any reasons, the investigator or a person appointed by the investigator will enter the participant's background and treatment information into the EDC system within approximately 1 month after the completion of the observation required. The investigator will then electronically sign it. However, for participants who discontinue treatment due to adverse events, the investigator will continue to observe until the adverse event has resolved or is alleviated or until the end of the observation period, to the extent possible even after treatment discontinuation. The investigator or a person appointed by the investigator will enter the observation results into the EDC system, and the investigator will electronically sign it.

8.0 SCHEDULED IMPLEMENTATION PERIOD

Study period: February 2019 to October 31, 2024

Participant registration period: February 2019 to June 30, 2023*

Date of study completion (date of completion of the final analysis): June 30, 2025 (planned)

* Even for patients for whom Entyvio has been prescribed by June 30, 2023, registration (entry into the EDC system) will not be accepted from July 1, 2023.
If the number of participants registered for the study reaches the planned number before June 30, 2023, the registration will be closed before the end of the participant registration period. If the participant registration period is shortened, the study period will be changed accordingly.

9.0 ITEMS

The investigator or a person appointed by the investigator will enter the following items into the EDC system. The schedule of the study is shown in Appendix 1.

9.1 INFORMED CONSENT

The investigator will obtain informed consent from the participant or a legally acceptable representative before registration. Patients who provide informed consent will be assigned an identification number.

9.2 PARTICIPANT REGISTRATION

1) Items

Presence or absence of consent, start date of treatment with Entyvio, participant identification number, sex, month and year of birth, assessment of inclusion criteria, assessment of exclusion criteria, presence or absence of history of treatment with anti-TNFα antibody, and severity of UC.

2) Timing

At participant registration.

9.3 PARTICIPANT BACKGROUND

1) Items

Time of UC diagnosis, range of UC lesions, medical history/complications, familial history, history of tuberculosis infection, steroid resistance/dependence/intolerance, presence or absence and details of previous therapies for UC other than Entyvio within 3 months before the start of treatment with Entyvio (excluding anti-TNFα antibody drugs), and details of history of treatment with anti-TNFα antibody.

2) Timing

At the start of treatment with Entyvio.

9.4 TREATMENT DETAILS

1) Items

Status of treatment with Entyvio, lot number, status of treatment with concomitant medicines, implementation status of concomitant therapies, and implementation status of surgical procedures.

2) Timing

From the start of treatment with Entyvio to Week 54 (or treatment discontinuation).

9.5 EXAMINATION/OBSERVATION ITEMS

Each test/observation results will be recorded at each timing if performed in the routine clinical settings on treatment with Entyvio.

9.5.1 Presence or Absence of Therapeutic Response and Continuation of Treatment

1) Observation Items

Presence or absence of therapeutic response and continuation or discontinuation of treatment.

2) Timing

After 3 doses of Entyvio.

9.5.2 Complete Mayo Score

1) Observation Items

Endoscopy findings and physician's global assessment (stool frequency and rectal bleeding will be automatically entered from the participant diary, in principle).

2) Timing

Measurement timepoints at the start of treatment with Entyvio, after 3 doses, and at Week 54 (or treatment discontinuation).

9.5.3 QOL Survey

1) Observation Items

Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (QOL survey form for inflammatory bowel disease).

2) Timing

Measurement timepoints at the start of treatment with Entyvio, after 3 doses, and at Week 54 (or treatment discontinuation).

9.5.4 Laboratory Test Values

1) Observation Items

Hemoglobin, white blood cell count, lymphocytes, albumin, C-reactive protein (CRP), and calprotectin.

2) Timing

From the start of treatment with Entyvio to Week 54 (or treatment discontinuation).

9.5.5 Other Items for Observation

1) Observation Items

Pregnant or not pregnant during the observation period (women only) and withdrawal of consent.

2) Timing

From the start of treatment with Entyvio to Week 54 (or treatment discontinuation).

9.6 ADVERSE EVENTS

1) Items

Presence or absence of adverse events (see Table 1), name of adverse event, date of onset, time of onset after administration (only for infusion reactions including hypersensitivity reactions), seriousness and reasons for seriousness (see Table 2), cause of discontinuation of treatment with Entyvio, actions taken at the onset, date of outcome assessment, outcome, and causal relationship with Entyvio (see Table 3).

Table 1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a participant administered a pharmaceutical product. It does not necessarily have to have a causal relationship with the administration of the pharmaceutical product. An AE can therefore be any unfavorable or unintended sign (including abnormal laboratory test values), symptom, or disease that occurs when a pharmaceutical product is administered, whether or not related to the pharmaceutical product.

Table 2 Criteria for Seriousness

1. Results in death (death). 2. Is life threatening (life threatening). "Life threatening" refers to an event during which the participant was at risk of death. It does not refer to an event that hypothetically might have caused death if it were more severe. 3. Requires inpatient hospitalization or prolongation of current hospitalization (hospitalization/prolongation of hospitalization). 4. Results in persistent or significant disability or incapacity (disability). 5. Results in congenital anomaly/birth defect (congenital anomaly). 6. An event that may not be immediately life threatening or result in death or hospitalization, but may require an intervention to prevent one of the outcomes listed in 1–5 above or may jeopardize the participant. Note: However, if Takeda Pharmaceutical Company Limited considers the event to be serious, it will be handled as a serious adverse event, even if it was reported as non-serious by the reporter.

Table 3 Assessment Criteria for the Causal Relationship Between Adverse Events and Entyvio

Assessment	Assessment criteria
Related	An adverse event that follows a reasonable temporal sequence from administration of Entyvio (including the course after withdrawal of Entyvio), or for which possible involvement of Entyvio cannot be ruled out, although factors other than Entyvio, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not related	An adverse event that does not follow a reasonable temporal sequence from administration of Entyvio and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

2) Safety Specifications

The following events are defined as safety specifications, and detailed information

will be collected to the extent as possible at the time of onset.
- Infusion reactions including hypersensitivity reactions.
- Infections (other than progressive multifocal leukoencephalopathy).

Rationale for Safety Specifications

- Infusion reactions including hypersensitivity reactions.
  Infusion reactions are known as adverse reactions to biological products. Infusion reactions including hypersensitivity reactions to Entyvio have also been reported. Although most of symptoms have been reported to be mild or moderate and transient, and to resolve spontaneously, serious events such as anaphylaxis may occur. Therefore, these reactions were specified as safety specifications.

- Infections (other than progressive multifocal leukoencephalopathy).
  Entyvio is a gut-selective integrin antagonist and may impair immune functions in the gastrointestinal tract. However, infections outside the gastrointestinal tract have also been reported. Based on these, infection was specified as safety specifications.

3) Study period

From the start of treatment with Entyvio to Week 54 (or treatment discontinuation).

10.0 ANALYSIS ITEMS AND METHODS

10.1 Statistical Analysis Plan

A statistical analysis plan will be prepared before data lock. It will provide further details regarding the definition of endpoints and the analysis methods.

10.2 Analysis Sets

"Participants included in the safety evaluation" set will be identified for analysis.

10.3 Items Related to Participant Disposition

The number of registered participants, number of participants from whom survey forms (electronic) were collected, number of participants included in the safety evaluation, number of participants excluded from the evaluation, and reasons for exclusion will be tabulated.

10.4 Participant Background

As participant background, sex, age, disease duration, complications, presence or absence of history of treatment with anti-TNFα antibody, and severity of UC will be tabulated.

10.5 Treatment Details

Status of treatment with Entyvio, status of treatment with concomitant medicines, implementation status of concomitant therapies, and implementation status of surgical procedures will be tabulated.

10.6 ITEMS RELATED TO SAFETY

The following tabulation will be performed for participants included in the safety evaluation.

10.6.1 Status of Adverse Events

For adverse events that occur during the observation period, frequency tabulation will be performed by type, time of onset, seriousness, and causal relationship with Entyvio.

10.6.2 Factors That May Affect Safety

The frequency of adverse drug reactions that occur during the observation period will be tabulated by participants' background factors.

10.7 ITEMS RELATED TO EFFICACY

The following tabulation will be performed.

10.7.1 Presence or Absence of Therapeutic Response and Continuation of Treatment

Presence or absence of therapeutic response and continuation or discontinuation of treatment will be tabulated.

10.7.2 Time Course of Complete Mayo Score and Partial Mayo Score

The value, changes, remission rate, and improvement rate of complete and partial Mayo scores at each test time point will be tabulated.

10.7.3 QOL Survey

The QOL survey scores and changes at each test time point will be tabulated.

10.7.4 Calprotectin

The laboratory values and changes at each test time point will be tabulated.

10.8 INTERIM ANALYSIS

For early evaluation and analysis of the efficacy data obtained in this study, interim analysis will be performed when the evaluable data after 3 doses of Entyvio are obtained from ≥ 90 participants each with or without a history of treatment with anti-TNFα antibody. In interim analysis, the same analyses as in Sections 10.7.1–10.7.2 will be performed, along with the same analyses as in Sections 10.3–10.5 and 10.6.1 as necessary.

11.0 REGISTRATION OF STUDY INFORMATION

Prior to its start, the study information will be registered on the following public websites.

- Japan Pharmaceutical Information Center-Clinical Trials Information JapicCTI-194603
- Clinical study registration system of the United States National Institutes of Health:

12.0 ORGANIZATIONAL STRUCTURE

12.1 ORGANIZATIONAL CHART FOR OPERATIONS FOR POST-MARKETING SURVEILLANCE

See Appendix.

13.0 MEDICAL ADVISOR

Tasks to Be Delegated

- Advice on the preparation and revision of this protocol.
- Advice on the preparation and revision of the statistical analysis plan (tabulation/analysis items and methods).
- Advice on the preparation and revision of the clinical study report (safety and effectiveness conclusions and discussion).
- Advice on the preparation of feedback materials for medical institutions.
- Advice on journals/academic conferences in/at which the data could be published (if the data will be published outside the company).
- Further advice regarding implementation of this study requires various medical judgments.

Affiliation and Name

[redacted]

(random order)

14.0 CONTRACT RESEARCH ORGANIZATION

[redacted]

Service: Setting and management of the EDC related to the study.

[redacted]

Service: Statistical analysis, construction of the EDC system, database creation, and medical writing.

[redacted]

Service: Data management, construction and operation of the EDC system, and storage of records.

[redacted]

Service: Operations related to monitoring.

15.0 OTHER NECESSARY MATTERS

15.1 REVISION OF PROTOCOL

During the implementation period, the status of progress, adverse drug reactions that cannot be predicted from precautions and serious adverse drug reactions, increase or stability in the incidence of specific adverse drug reactions, and appropriateness of items will be monitored and, if necessary, this protocol will be reviewed and revised. Additionally, when the application of partial changes in dosage and administration or indications are approved during the implementation period, the necessity for the revision of this protocol will be examined and the protocol will be revised if necessary.

15.2 MEASURES TO BE TAKEN IN CASES OF PROBLEMS OR QUESTIONS

If any safety and efficacy issue is identified, the data will be closely examined and corrective measures will be considered.

Appendix 1 Observation Schedule

Items \ Timing		Observation period			
		At participant registration	At treatment initiation	After 3 doses	Week 54/ at treatment discontinuation
Participant registration	Informed consent	X			
	Start date of treatment with Entyvio	X			
	Participant identification number	X			
	Sex	X			
	Month and year of birth	X			
	Assessment of inclusion criteria/assessment of exclusion criteria	X			
	Presence or absence of history of treatment with anti-TNFα antibody	X			
	Severity of UC	X			
Participant background	Time of UC diagnosis		X		
	Medical care category		X		
	Range of UC lesions		X		
	Complications		X		
	Medical history		X		
	Familial history		X		
	History of tuberculosis infection		X		
	Steroid resistance/dependence/ intolerance		X		
	History of previous therapies for UC within 3 months before the start of treatment with Entyvio		X		
	Details of history of treatment with anti-TNFα antibody		X		
Treatment details	Status of treatment with Entyvio/lot number		← X →		
	Status of treatment with concomitant medicines		← X →		
	Implementation status of concomitant therapies		← X →		
	Implementation status of surgical procedures		← X →		
Examination/observation items	Presence or absence of therapeutic response and continuation of treatment			X	
	Complete Mayo score Implementation of endoscopy/ physician's global assessment		X	X	X
	QOL survey		X	X	X
	Laboratory tests		← X →		
	Pregnant or not pregnant during the observation period (women only)		← X →		
	Adverse events		← X →		

X : To be implemented

← X → : To be implemented throughout the period

Document History

Version	Date	Comments
original version	December 6, 2018	New document
Version 2	January 7, 2019	7.3 Participant Registration Method 9.5.5 Other Items for Observation
Version 3	June 1, 2019	11.0 REGISTRATION OF STUDY INFORMATION 12.0 ORGANIZATIONAL STRUCTURE 12.1 Persons Responsible for Management 13.0 CONTRACT RESEARCH ORGANIZATION
Version 4	October 14, 2020	8.0 SCHEDULED IMPLEMENTATION PERIOD 13.0 CONTRACT RESEARCH ORGANIZATION
Version 5	January 15, 2021	9.4 Treatment Details 9.6 Adverse Events 13.0 CONTRACT RESEARCH ORGANIZATION Appendix 1 Observation Schedule Appendix 2 Takeda Medically Significant AE List
Version 6	July 5, 2021	1.0 BACKGROUND 3.2 Rationale 9.6 Adverse Events Table 2 Criteria for Seriousness 10.8 Interim Analysis 13.0 CONTRACT RESEARCH ORGANIZATION
Version 7	March 25, 2022	8.0. SCHEDULED IMPLEMENTATION PERIOD 11.0 REGISTRATION OF STUDY INFORMATION 12.0 ORGANIZATIONAL STRUCTURE 12.2 Medical Advisor
Version 8	April 28, 2022	12 0 ORGANIZATIONAL STRUCTURE
Version 9	July 29, 2024	8.0 SCHEDULED IMPLEMENTATION PERIOD 9.6 ADVERSE EVENTS Table 2 Criteria for Seriousness 14.0 CONTRACT RESEARCH ORGANIZATION