



Title: Clinical effectiveness and safety of vedolizumab intravenous in real world clinical practice in ulcerative colitis Korean patients: a multicenter postmarketing observational study

NCT Number: NCT03535649

Protocol Approve Date: 24 September 2018

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## Non-Interventional Study Protocol

**Title:** Clinical effectiveness and safety of vedolizumab intravenous in real world clinical practice in ulcerative colitis Korean patients: a multicenter post-marketing observational study

**Short title:** Vedolizumab in ulcerative colitis Korean patients

**Study ID:** Vedolizumab-5045

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**Study phase:** Medical Affairs, Post-Approval Company Sponsored (Observational)

**Date of final version 4.1 of protocol:** 24 September 2018 (Amendment 4)

## 1 Administrative Information

### 1.1 Contacts

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Adverse events and pregnancy reporting	Takeda Korea Pharmacovigilance Team Email: <a href="mailto:DSO-KR@takeda.com">DSO-KR@takeda.com</a> Fax: +82 2 501 7489 Tel: +82 10 3054 2482
Study Manager (conduct of the study)	PPD
Trial Clinician (medical advice on protocol, compound, and medical management of patients)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

## 1.2 Approval

### REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation (ICH), E6 Good Clinical Practice (GCP): Consolidated Guideline.
- Guidelines for Good Pharmacovigilance Practices (GVP).
- Guidelines for Good Pharmacoepidemiology Practices (GPP).
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

### SIGNATURES

PPD



**INVESTIGATOR SIGNATURE PAGE**

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

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Signature of Investigator

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Date

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*<Investigator Name (print or type)>*

---

*<Investigator's Title>*

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*<Location of Facility (City, State/Province)>*

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*<Location of Facility (Country)>*

## STUDY SUMMARY

<b>Name of Sponsor(s):</b> Takeda Korea	<b>Compound/Product [if applicable]:</b> Vedolizumab
<b>Title of Protocol:</b> Clinical effectiveness and safety of vedolizumab intravenous in real world clinical practice in ulcerative colitis Korean patients: a multicenter post-marketing observational study	
<b>Study Number:</b> Vedolizumab-5045	<b>Phase:</b> 4 (observational)
<p><b>Study Design:</b></p> <p>This is an observational, multicenter, post-marketing study that will analyze real world data on the effectiveness and safety of vedolizumab intravenous (IV) in South Korean patients presenting ulcerative colitis (UC) and having failed tumor necrosis factor (TNF)-<math>\alpha</math> antagonist therapy (as per the approved label).</p> <p>Patients will be identified from the medical records and enrolled in the study if they meet the inclusion and exclusion criteria. Screening logs of potential patients will be maintained at each of the sites, to record reasons why the patient failed eligibility screening. Both retrospective and prospective patient data will be collected, with prospective data collected for treatment baseline visit (i.e. first date of vedolizumab treatment) and follow up visits. Prospective data will be collected according to each site's IRB definition (i.e. whether treatment baseline and follow up visits happens post initial IRB submission date, or post initial IRB approval date, etc).</p> <p>The study will collect information on demographics, risk factors, clinical data, laboratory and endoscopic data, previous UC medications and surgeries, UC medications and concomitant treatments at baseline (start of vedolizumab treatment) and follow-up. The safety outcome measures will include: adverse events of special interest (AESIs) (serious infections, opportunistic infections, hepatitis viral infection, gastrointestinal infections, respiratory infections, other clinically significant infections, malignancies, infusion-related reactions, and hepatic injury), serious adverse events (SAEs), and pregnancy outcomes. The data will be abstracted, if available, from the medical charts.</p> <p>Data on pregnancy and pregnancy outcomes will be collected subject to a written informed consent from the patient or the patient's partner.</p>	
<p><b>Primary Objectives:</b></p> <ul style="list-style-type: none"> <li>To assess the clinical effectiveness of vedolizumab IV in UC Korean patients by the clinical response at 6 weeks.</li> <li>To assess the safety of vedolizumab IV in UC Korean patients.</li> </ul>	
<p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To assess the clinical effectiveness of vedolizumab IV in UC Korean patients by the clinical response at 14 weeks and clinical remission at 6 and 14 weeks.</li> <li>To assess the clinical effectiveness of vedolizumab IV in UC Korean patients on mucosal healing at 6 and 14 weeks.</li> </ul>	

**Exploratory Objectives:**

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**Patient Population:**

Adult patients ( $\geq 19$  years of age) diagnosed with moderately to severely active UC, having failed TNF- $\alpha$  antagonist therapy and who have been prescribed vedolizumab IV (and received at least one dose) in a routine clinical practical setting.

**Number of Patients:**

100 patients

**Study Sites:**

Approximately 15 sites in South Korea

**Dose Level(s):**

As per standard of care

**Route of Administration:**

IV

**Duration of Study:**

Approximately 15 months

**Criteria for Inclusion:**

- Female or male patient with moderately to severely active UC and having failed TNF- $\alpha$  antagonist therapy.
- Patient was  $\geq 19$  years of age at time of initiating vedolizumab IV.

**Criteria for Exclusion:**

- Patient was treated with vedolizumab IV outside of the locally approved label in South Korea.
- Patient was enrolled in an interventional Inflammatory Bowel Disease clinical trial at time of using vedolizumab IV.

**Criteria for Evaluation and Analyses:****Primary Outcomes:**

- Clinical response to vedolizumab IV at 6 weeks will be assessed using the partial Mayo score: reduction of at least 3 points and a decrease of at least 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscale, or an absolute rectal bleeding score of 0 or 1.
- Safety of vedolizumab IV will be assessed by the incidence rates of AESIs, SAEs, and pregnancy outcomes occurred during the study period.

**Secondary Outcomes:**

- Clinical response to vedolizumab IV at 14 weeks, and clinical remission at 6 and 14 weeks (i.e., score  $\leq 2$  and no sub-score  $> 1$ ) will be assessed using the complete Mayo score\*.
- Clinical effectiveness of vedolizumab IV on mucosal healing at 6 and 14 weeks (i.e., level of mucosal damage in comparison to baseline) will be assessed by the Mayo endoscopic sub-score of 0 or 1.

**Exploratory Outcomes:**

CCI

**Statistical Considerations:**

All collected data will be summarized using descriptive statistics because of the exploratory nature of this study. The full analysis set will comprise all patients fulfilling all inclusion and exclusion criteria, subject to either a waiver of requirement to obtain informed consent or a written informed consent, depending on each site's IRB policy on collecting prospective data (i.e. whether a site defines prospective data as data collected from treatment baseline and follow up visits occurring post the initial IRB submission data, or initial IRB approval date, etc). Pregnancy and pregnancy outcomes data will only be analyzed if collected under a written informed consent from the patient or the patient's partner.

Continuous variables will be summarized as the number of patients, mean, standard deviation, median, 1st and 3rd quartiles, minimum and maximum. Summary for categorical variables will include frequency counts and percentages, and number of missing data. Percentages will be based on the number of non-missing data as the denominator. There will not be imputation of missing data.

Effectiveness analyses will present change from baseline in partial and/or complete Mayo scores. Baseline is defined as the date of first vedolizumab IV dose. All patients would have active disease at baseline. If Mayo score at baseline is less than 3 (e.g., patients who were prescribed vedolizumab because of unacceptable adverse events (AEs) related to TNF- $\alpha$  antagonist therapy), these patients will be excluded from the effectiveness analyses due to TNF- $\alpha$  intolerance.

Safety analyses will present number of patients with an event and crude incidence rates with 95% confidence intervals according to Pearson-Clopper. Additionally, safety analysis will be presented (1) based on events occurring between first and last dose of vedolizumab (also AEs at 14 weeks of post-discontinuation in occurred cases) and (2) based on events occurring between first dose of vedolizumab and end of study follow-up.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at time of final data analysis.

All planned analyses will be documented in the statistical analysis plan.



**Sample Size Justification:**

The sample size for the study is not based on statistical considerations because it does not consider hypothesis testing/power calculation or precision around an estimate. The sample size of approximately 100 patients was selected because of potential availability of patients treated with vedolizumab IV in South Korea during the study period.

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**Table of Contents**

1	Administrative Information .....	2
1.1	Contacts .....	2
1.2	Approval .....	3
2	Introduction.....	14
2.1	Ulcerative Colitis.....	14
2.2	Vedolizumab .....	15
2.3	Study Rationale .....	16
3	Study Objectives and Outcomes .....	17
3.1	Objectives .....	17
3.1.1	Primary Objectives.....	17
3.1.2	Secondary Objectives.....	17
3.1.3	Exploratory Objectives .....	17
3.2	Outcomes.....	17
3.2.1	Primary Outcomes.....	18
3.2.2	Secondary Outcomes.....	18
3.2.3	Exploratory Outcomes .....	18
4	Study Administrative Structure .....	19
4.1	National Coordinating Principal Investigator.....	19
4.2	Study Institutions and Investigators.....	19
4.3	Sponsor Personnel .....	20
4.4	Contract Research Organization.....	20
5	Ethics .....	21
5.1	Ethical Conduct of the Study.....	21
5.2	Independent Ethics Committee / Institutional Review Board and Authorities.....	21
5.3	Authorities.....	22
5.4	Patient Information and Informed Consent .....	22
6	Study Design and Plan.....	24
6.1	Study Schedule .....	24
6.2	Discussion of Study Design.....	25
6.3	Study Population .....	26
6.4	Selection of Study Population .....	26
6.4.1	Inclusion Criteria.....	26
6.4.2	Exclusion Criteria .....	26
6.5	Study Variables .....	26

6.5.1	Demographics and Risk Factors Data .....	27
6.5.2	Clinical Data .....	28
6.5.3	Laboratory and Endoscopic Data .....	28
6.5.4	Treatment Data .....	28
6.5.5	Adverse Events Data .....	29
6.6	Study Plan .....	32
7	Safety Reporting .....	34
7.1	Definitions .....	34
7.1.1	Adverse Event .....	34
7.1.2	Adverse Drug Reaction .....	34
7.1.3	Special Situation Reports and Product Quality Issues .....	34
7.1.4	Serious Adverse Event .....	35
7.2	Collection and Notification of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance .....	37
7.3	Reporting of Adverse Drug Reactions and Special Situation Reports to Regulatory Agencies .....	37
8	Data Quality Control and Assurance .....	38
8.1	Quality Control .....	38
8.2	Audit from Quality Assurance Unit .....	38
8.3	Inspection by Institutional Review Board / Institutional Ethics Committee or Competent Authority .....	38
8.4	Data Management .....	38
8.4.1	Data Collection Tools .....	39
9	Statistical Methods and Determination of Sample Size .....	40
9.1	Description of Analysis Set .....	40
9.2	Method of Statistical Analysis .....	40
9.3	Analysis of Study Outcomes .....	40
9.3.1	Analysis of Primary Outcomes .....	41
9.3.2	Analysis of Secondary Outcomes .....	41
9.3.3	Analysis of Exploratory Outcomes .....	41
9.2	Interim Analyses .....	42
9.3	Determination of Sample Size .....	42
10	Reports .....	43
11	Plans for Disseminating and Communicating Study Results .....	43
12	Archiving of Study Documentation .....	43
13	References .....	45

14	Appendices .....	47
14.1	Annex 1. Mayo Score.....	47

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**List of Abbreviations and Definition of Terms**

5-ASA:	5-Aminosalicylic Acid
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
CA:	Competent Authority
CD:	Crohn's Disease
CI:	Confidence Interval
CMV:	Cytomegalovirus
CRO:	Contract Research Organization
EMA:	European Medicines Agency
GCP:	Good Clinical Practice
GI:	Gastrointestinal
GPP:	Good Pharmacoepidemiology Practices
GVP:	Good Pharmacovigilance Practices
HLT:	High-Level Term
HR:	Hazard Ratio
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
ISPE:	International Society for Pharmacoepidemiology
IV:	Intravenous
JCV:	John Cunningham Virus
mAb:	Monoclonal Antibodies
MAdCAM-1:	Mucosal Addressin Cell Adhesion Molecule-1
MedDRA:	Medical Dictionary for Regulatory Activities
PML:	Progressive Multifocal Leukoencephalopathy
PY:	Person-Year
SADR:	Serious Adverse Drug Reaction
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SD:	Standard Deviation

SIS:	Subject Information Sheet
SMQ:	Sub-standardized MedDRA query
SOC:	System Organ Class
SSR:	Special Situation Report
TB:	Tuberculosis
TNF- $\alpha$ :	Tumor Necrosis Factor alpha
UC:	Ulcerative Colitis

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## 2 Introduction

### 2.1 Ulcerative Colitis

Ulcerative Colitis (UC) is a chronic, relapsing, remitting inflammatory disease of the colonic mucosa and submucosa. The incidence and prevalence of UC in South Korea (Korea) is low compared to other regions, but has showed a 10-fold increase in the last 20 years [[Kim 2010](#), [Ng 2016](#)]. Globally, the highest incidences have been found in northern Europe and North America: 11.4 and 12.9 per 100,000 persons, respectively [[Burisch 2013](#), [Loftus 2016](#), [Rocchi 2012](#)]. While the mean annual incidence rates of UC in Korea are lower, they have increased from 1.3 to 5.0 per 100,000 inhabitants between 2001 and 2006 [[Kim 2010](#), [Kim 2015](#)].

UC is a lifelong disease that causes considerable morbidity in a relatively young patient population. The etiology is not fully understood. The risk factors include: a history of a recent bacterial infection (e.g., Salmonella, Campylobacter), immune system malfunction, family history of the disease, young age (usually UC begins before 30), Caucasians' and Jews' ethnicities (compared to Asian), and smoking [[Ananthakrishnan 2017](#), [Adams 2013](#), [Choi 2017](#)]. Many patients require frequent hospitalizations, enteral nutrition, and surgical procedures (e.g., colectomies). The majority will have flares alternating with periods of remission, with a small proportion of patients having progressive or persistent symptoms [[Ananthakrishnan 2017](#)]. UC patients are often unable to function normally in society by virtue of having uncontrolled disease.

Current UC treatments have been effective for many patients but have numerous limitations for those with moderate to severe disease. Pharmacologic treatments for UC include 5-aminosalicylic acids (5-ASAs), corticosteroids, and immunomodulators (thiopurines such as azathioprine and 6-mercaptopurine, along with methotrexate). Monoclonal antibodies (mAb) directed against tumor necrosis factor alpha (TNF- $\alpha$ ) are recommended when adequate dosage and duration of treatment with corticosteroid or combination of corticosteroid and thiopurine do not improve symptoms, or if the treatment is not tolerable to the patient [[Choi 2017](#)]. In Korea, infliximab, adalimumab, and golimumab are used as anti-TNF therapies, all of which showed therapeutic effects in terms of remission induction and maintenance in patients with moderate to severe active UC [[Choi 2017](#)]. Although TNF- $\alpha$  antagonists

represent an important addition to the pharmacologic armamentarium, they are effective in only a subset of patients, with approximately two-thirds of patients in controlled trials failing treatment at the end of the first year of therapy [[Hanauer 2002](#), [Rutgeerts 2005](#), [Colombel 2007](#)].

## 2.2 Vedolizumab

Vedolizumab is a humanized immunoglobulin G1 mAb directed against the human lymphocyte integrin  $\alpha_4\beta_7$ . The  $\alpha_4\beta_7$  integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interactions with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa. Vedolizumab exclusively targets the  $\alpha_4\beta_7$  integrin, antagonizing its adherence to MAdCAM-1 and thus impairing the migration of leukocytes into GI mucosa. By virtue of its gut-selective mechanism of action, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with current treatments for UC.

The efficacy of vedolizumab in UC patients was demonstrated in a phase III randomized, double-blind, placebo-controlled, multicenter study that assessed the effect of vedolizumab induction and maintenance treatment on UC clinical response in 374 and 521 (open-label) patients with active moderate to severe disease. Vedolizumab patients had a statistically significant improvement in clinical response (i.e., reduction in the Mayo score of  $\geq 3$  points and  $\geq 30\%$  from baseline, and decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1) and remission (i.e., Mayo score  $\leq 2$  and no subscore  $> 1$ ) at 6 weeks, mucosal healing (i.e., endoscopic sub-score of 0 or 1), durable clinical response (i.e., remission at both weeks 6 and 52) and remission at 52 weeks, and corticosteroid-free remission at week 52 in patients receiving glucocorticoids at baseline compared to placebo. Response rates at week 6 were 47.1% and 25.5% among patients in the vedolizumab and placebo groups, respectively (difference with adjustment for stratification factors, 21.7 percentage points; 95% confidence interval [CI]: 11.6 to 31.7;  $P < 0.001$ ). At week 52, 41.8% of patients who continued to receive vedolizumab every 8 weeks and 44.8% of patients who continued to receive vedolizumab every 4 weeks were in clinical remission, as compared with 15.9% of patients who switched to placebo (adjusted difference, 26.1 percentage points for vedolizumab every 8 weeks vs. placebo [95% CI: 14.9 to 37.2;



P<0.001] and 29.1 percentage points for vedolizumab every 4 weeks vs. placebo [95% CI: 17.9 to 40.4; P<0.001]) [[Feagan 2013](#)].

Vedolizumab has also shown a favorable safety profile with low incidence rates of serious infections, infusion-related reactions and malignancies over an extended treatment period in another phase III, open-label, multicenter study which enrolled 2830 UC and Crohn's Disease (CD) patients treated with vedolizumab. In this study, safety data from 6 trials were integrated and adverse events (AEs) were evaluated in patients who received  $\geq 1$  dose of vedolizumab or placebo. In total, these patients accumulated 4811 person-years (PYs) of vedolizumab exposure (median exposure range: 1-1977 days). No increased risk of any infection or serious infection was associated with this exposure. Serious clostridial infections, sepsis and tuberculosis (TB) were reported infrequently ( $\leq 0.6\%$  of patients). No cases of progressive multifocal leukoencephalopathy (PML) were observed. Independent risk factors for serious infection in UC were prior failure of a TNF- $\alpha$  antagonist (Hazard Ratio (HR): 1.99; 95% CI: 1.16 to 3.42; p=0.0122) and narcotic analgesic use (HR: 2.68; 95% CI: 1.57 to 4.58; p=0.0003). Investigator-defined infusion-related reactions were reported for  $\leq 5\%$  of patients in each study. Eighteen vedolizumab-exposed patients ( $< 1\%$ ) were diagnosed with a malignancy [[Colombel 2017](#)].

Vedolizumab was approved in Korea on June 19<sup>th</sup>, 2015 for use in both UC and CD patients with inadequate response, lost response, or who were intolerant to TNF- $\alpha$  antagonist [[Choi 2017](#)].

### 2.3 Study Rationale

Despite that there are several observational studies assessing the clinical effectiveness of vedolizumab, including a consecutive cohort of 115 UC German patients reporting 23.5% of clinical remission at 14 weeks [[Baumgart 2016](#)], there is currently no observational study assessing the effectiveness and safety of vedolizumab intravenous (IV) in a real world clinical setting in Korea. This post-marketing observational study aims to show that real world effectiveness and safety outcomes from daily clinical practice in Korean patients diagnosed with UC and having failed TNF- $\alpha$  antagonist therapy are consistent with those reported in randomized controlled trials.

### 3 Study Objectives and Outcomes

#### 3.1 Objectives

##### 3.1.1 Primary Objectives

- To assess the clinical effectiveness of vedolizumab IV in UC Korean patients by the clinical response at 6 weeks.
- To assess the safety of vedolizumab IV in UC Korean patients.

##### 3.1.2 Secondary Objectives

- To assess the clinical effectiveness of vedolizumab IV in UC Korean patients by the clinical response at 14 weeks and clinical remission at 6 and 14 weeks.
- To assess the clinical effectiveness of vedolizumab IV in UC Korean patients on mucosal healing at 6 and 14 weeks.

##### 3.1.3 Exploratory Objectives



#### 3.2 Outcomes

### 3.2.1 Primary Outcomes

- Clinical response to vedolizumab IV at 6 weeks will be assessed using the partial Mayo score: reduction of at least 3 points and a decrease of at least 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscale, or an absolute rectal bleeding score of 0 or 1.
- Safety of vedolizumab IV will be assessed by the incidence rates of adverse events of special interest (AESIs), SAEs, and pregnancy outcomes occurred during the study period.

### 3.2.2 Secondary Outcomes

- Clinical response to vedolizumab IV at 14 weeks, and clinical remission at 6 and 14 weeks (i.e., score  $\leq 2$  and no sub-score  $> 1$ ) will be assessed using the complete Mayo score\*.
- Clinical effectiveness of vedolizumab IV on mucosal healing at 6 and 14 weeks (i.e., level of mucosal damage in comparison to baseline) will be assessed by the Mayo endoscopic sub-score of 0 or 1.

### 3.2.3 Exploratory Outcomes

CCI



## 4 Study Administrative Structure

### 4.1 National Coordinating Principal Investigator

The National Coordinating Principal Investigator for this study is:

Professor Byong Duk Ye

Inflammatory Bowel Disease Center

Asan Medical Center

88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505 Korea

### 4.2 Study Institutions and Investigators

This study is planned to be conducted in academic / general hospitals across South Korea, and is estimated to recruit approximately 100 patients. The list of study institutions, investigators, and approximate target patient numbers – selected based on UC treatment experience and capability of available resources – are given below. The Sponsor will keep a record of the Site Study Responsibles.

Study Site	Principal Investigator	Approximate Target Patient Number
PPD		18
		3
		3
		13
		18
		9
		3
		10
		10
		2

PPD

4

3

9

15

6

PPD

#### 4.3 Sponsor Personnel

Takeda Korea will keep a record of all relevant sponsor personnel.

#### 4.4 Contract Research Organization

The Contract Research Organization (CRO) will keep a record of all involved CRO personnel.

## 5 Ethics

This is an observational chart review study, where the existence of the study poses no medical risk for the patient.

### 5.1 Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki [[WMA 2008](#)], International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) consolidated guideline, European Medicines Agency (EMA) Good Pharmacovigilance Practices [[EMA 2014](#)], International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) guideline [[ISPE 2016](#)] and any local regulations. Special attention will be paid to data protection.

The Sponsor and the CRO will ensure that the protocol and any amendments are submitted to the relevant Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) according to local requirements.

The Sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs / IRBs, if applicable.

### 5.2 Independent Ethics Committee / Institutional Review Board and Authorities

The CRO or the Site Study Responsible will coordinate the submissions to the IECs (or IRB or Research Ethics Board [REB]) and any other necessary authorities, as per international and local requirements. The study protocol will be submitted by the CRO to the central/local board for its review. Subject enrolment will not start at any site before the Sponsor has obtained waiver of requirement to obtain informed consent from the IECs to collect retrospective data, where the retrospective data collection cut-off is defined according to each site's IRB policy (i.e. until one day prior initial IRB submission date, or until one day prior initial IRB approval date, etc).

For patients whose treatment baseline (i.e. first date of vedolizumab treatment) and follow up visits occur prospectively (as defined by each site's IRB policy, as above), a signed informed consent must be obtained from each subject prior to any prospective data collection. Collection of pregnancy and pregnancy outcomes data is also subjected to a signed informed

consent from the patient or the patient's partner. Otherwise, only retrospective data will be collected for the study. For details on both the rationale for the waiver of requirement to obtain informed consent and the informed consent for collection of treatment baseline and follow up visits data, see Section 5.4 on Patient Information and Informed Consent.

According to applicable regulations, the appointed CRO or the Site Study Responsible will notify or obtain approval from the relevant IEC / IRB of the protocol and any amendments. The CRO or the Site Study Responsible will submit required documents to the IEC / IRB, such as:

- Periodic updates on the progress of the study.
- Notification of the end-of-study.
- A summary of the study results.

The Sponsor or the CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Site Study Responsible with a copy of this list. Copies of the documents will be distributed upon request.

### **5.3 Authorities**

The Sponsor or the CRO may send study documents to the competent authority (CA) and / or other national or regional authorities, if required per the local regulation. The Sponsor or the CRO will keep an updated list of submission and approval dates and a copy of all documents submitted.

### **5.4 Patient Information and Informed Consent**

The rights, safety, and well-being of the trial patients are the most important considerations and should prevail over interests of science and society. This study will comply with ethical and regulatory requirements for each participating country.

No informed consent will be obtained to collect retrospective data (where the retrospective data collection cut-off is defined according to each site's IRB policy i.e. until one day prior initial IRB submission date, or until one day prior initial IRB approval date, etc), as only retrospective observational chart-abstracted data is included, and no patient identifier data (e.g. name, initials, national identity number, resident registration number, date and month of

birth, etc) will be collected. A waiver of requirement to obtain informed consent will be sought, allowing for inclusion of patients treated with vedolizumab intravenous (IV) during a specific period in a participating center. In particular, a waiver of requirement to obtain informed consent allows for inclusion of data from deceased patients, and from patients who have completed UC therapy and are not actively followed-up. All data collected will be encrypted to ensure confidentiality and data protection.

Detailed explanation of data protection, data encryption, and patient confidentiality measures will be included in each application for local ethics approval. Where necessary, these will include country-specific measures. Patient data will be entered only where a locally-applicable informed consent waiver is granted.

For patients whose treatment baseline (i.e. first date of vedolizumab treatment) and follow up visits occur prospectively (as defined by each site's IRB policy, as above), it is the responsibility of the investigator to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study (with written assent for underage subjects). Additionally, collection of pregnancy and pregnancy outcomes data is also subjected to a written informed consent from the patient or the patient's partner.

For subjects not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the subject and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.



## 6 Study Design and Plan

This is an observational, multicenter, post-marketing study that will analyze real world data on the effectiveness and safety of vedolizumab IV in Korean patients presenting UC and having failed TNF- $\alpha$  antagonist therapy (as per the approved vedolizumab label in Korea).

It is anticipated that at least 100 patients in a total of about 15 sites will be treated with vedolizumab IV from August 2017, when vedolizumab IV became available in Korea, to the end of the eligibility period. Patients will be identified from the medical records and enrolled in the study if they meet the inclusion and exclusion criteria. Screening logs of potential patients will be maintained at each of the sites, to record reasons why the patient failed eligibility screening. If available, basic demographic information will be recorded in the screening log to allow comparisons between patients who are enrolled and not enrolled. Only available patient data will be collected, which includes data until the day of enrollment to the study or until the earliest occurrence of any of the following: end of treatment, lost to follow-up, or death.

An interim analysis will be performed after approx. 50 patients are included. Primary and secondary outcomes will be considered for such analysis.

This is a non-interventional chart review study. All decisions on clinical management and treatment have been made by the investigator as part of routine of standard of care, and independently of participation in the study. Data are collected if available per clinical routine.

### 6.1 Study Schedule

Planned eligibility period:	From August 2017, up until a 100 patients (at least) are enrolled
Planned collection of the first data point:	August 2018
Planned collection of the last data point:	100 patients (at least) are enrolled
Planned analysis completion:	January 2019
Planned completion of study report:	March 2019

Note: the study schedule may be changed based on the protocol approval date and progress.

## 6.2 Discussion of Study Design

The study has several limitations, among them:

### *Selection bias*

Selection bias is the selection of individuals, groups or sites in such a way that the sample obtained is not representative of the population intended to be analyzed. As there is no probabilistic selection of sites or randomization of patients (i.e., if not all eligible patients will be approached for study participation), a selection bias cannot be ruled out.

### *Information bias*

In observational study designs the investigator has restricted control over the data that is collected in the medical record. Furthermore, since the medical charts used were not designed for the study, the available data may be of insufficient quality. These data may be incomplete, inaccurate, or inconsistently measured between patients, especially in the case of safety assessments.

### *Channeling bias*

Channeling bias is a form of allocation bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences. As vedolizumab is a new and first-in-class treatment for UC, it is possible that patients receiving vedolizumab in the early months of commercialization will have more severe disease or will be in greater need of a new therapy than those seen in subsequent years. This channeling of such patients into vedolizumab therapy may yield a safety and effectiveness profile different to that observed in later years.

### *Limited use of vedolizumab*

It is anticipated that approximately 100 patients will be treated with vedolizumab in Korea during the study period and enrolled in the study. Because of this small study population, the clinical effectiveness assessments and the safety incidence rates may be based on low numbers / few events and thus have wide 95% CIs. In addition, for outcomes with few events it may not be possible to undertake stratified analyses.

### 6.3 Study Population

The study population will be adult patients ( $\geq 19$  years of age) diagnosed with moderately to severely active UC, having failed TNF- $\alpha$  antagonist therapy and who have been prescribed vedolizumab IV (and received at least one dose) in a routine clinical practical setting. Patients who are eligible (i.e., fulfill all inclusion criteria and none of the exclusion criteria) will be enrolled into the study.

### 6.4 Selection of Study Population

#### 6.4.1 Inclusion Criteria

Patient eligibility is determined according to the following criteria prior to entry into the study:

- Female or male patient with moderately to severely active UC and having failed TNF- $\alpha$  antagonist therapy.
- Patient was  $\geq 19$  years of age at time of initiating vedolizumab IV.

#### 6.4.2 Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for entry into the study:

- Patient was treated with vedolizumab IV outside of the locally approved label in Korea.
- Patient was enrolled in an interventional Intestinal Bowel Disease clinical trial at time of using vedolizumab IV.

### 6.5 Study Variables

The study will collect information on demographics, risk factors, clinical data, laboratory and endoscopic data, previous UC medications and surgeries, UC medications and concomitant treatments at baseline (i.e., start of vedolizumab treatment) and follow-up.

- **Index date:** the index date is defined as the date of the first treatment with vedolizumab, between August 1, 2017 and the date when at least 100 cases are collected.
- **Index period:** the index period is defined from August 1, 2017 up until 100 cases (at least) are collected; when eligible patient medical records (defined by index treatment date) should be identified.

- **Follow-up period:** the follow-up period is defined as the time between the index date and when all relevant data for outcomes will be collected until the occurrence of any of following: end of treatment, lost to follow up, or death.

The safety outcome measures will include: AESIs (i.e., serious infections, opportunistic infections, hepatitis viral infection, GI infections, respiratory infections, other clinically significant infections, malignancies, infusion-related reactions, and hepatic injury), SAEs, and pregnancy outcomes.

The data will be abstracted, if available, from the medical charts.

### 6.5.1 Demographics and Risk Factors Data

- Year of birth.
- Sex.
- Body mass index, or height and weight, at baseline (i.e., start of vedolizumab treatment).
- Previous and current (at baseline) smoking status.
- UC/Inflammatory Bowel Disease family history.
- Selected comorbidities:
  - Multiple sclerosis.
  - Rheumatoid arthritis.
  - Psoriatic arthropathy.
  - Vasculitis.
  - Systemic lupus erythematosus.
  - Dermatomyositis.
  - Systemic sclerosis.
  - Ankylosing spondylitis.
  - Primary sclerosing colangitis.
  - Autoimmune hepatitis.
  - Diabetes Mellitus.
  - Hypertension.
  - Dyslipidemia.

### 6.5.2 Clinical Data

- Date of first UC signs/symptoms.
- Date of UC diagnosis.
- UC intestinal location/s (i.e., rectal and sigmoid colon only, left side of colon only, proximal to the splenic flexure only, all of the colon) and extraintestinal manifestations at baseline.
- Partial or complete Mayo score at baseline and follow-up, respectively. This score comprises 4 sections assessing the severity and activity of UC in terms of: ‘stool pattern’, ‘most severe rectal bleeding of the day’, ‘endoscopic findings’, and ‘global assessment by physician’. All 4 items are ranked based on severity with 0 being normal and 3 being most severe. Each item acquires 0-3 points, resulting in a maximum final score of 12. Partial score does not include endoscopic findings (Section 14.1 [Annex 1](#)).

### 6.5.3 Laboratory and Endoscopic Data

- Clinical laboratory values: fecal calprotectin and C-reactive protein at baseline and follow-up.
- Blood laboratory values: erythrocyte sedimentation rate, hemoglobin, albumin, platelet count and *Clostridium difficile* at baseline and follow-up.
- Endoscopic data at baseline and follow-up.
- Biopsy / histologic findings at baseline and follow-up.

### 6.5.4 Treatment Data

- UC medication history prior to start of vedolizumab IV (especially, TNF- $\alpha$  antagonist therapy).
- UC-related hospitalizations, emergency department and outpatient medical visits. Note: planned hospital admissions for vedolizumab IV therapy are not to be considered AEs and not to be collected as hospitalizations.
- UC-related surgeries.
- Start and all dates of vedolizumab infusions, dose and dose escalation (if any).
- Concurrent use of other UC medications at time of starting vedolizumab IV, including dates start / stop:
  - Other biologic agents (infliximab, adalimumab, golimumab).

- Immunomodulators.
  - 5-ASAs.
  - Corticosteroids.
  - Antibiotics.
  - Opioid pain medications.
  - Others.
- Date and reasons for vedolizumab IV discontinuation, and type of medication switch.

#### **6.5.5 Adverse Events Data**

- AESIs (including dates and pre-index occurrence, if any):
  - Serious infections.
  - Opportunistic infections, including but not limited to: TB infection or reactivation, including extrapulmonary TB, and PML.
  - Hepatitis viral infection.
  - GI infections.
  - Respiratory infections.
  - Malignancies.
  - Infusion-related reactions and hypersensitivity.
  - Hepatic injury.
- SAEs.
- Pregnancy outcomes.

All AEs occurring on or after start of vedolizumab IV therapy will be abstracted from the medical charts and categorized as defined below. Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

##### *Serious Infections*

Serious infection is defined as any event coded to MedDRA terms within the MedDRA SOC of Infections and Infestations that meets the seriousness definition (see Section 7.1.4).

##### *Opportunistic Infections*

Opportunistic infections include:

- Candidiasis of bronchi, trachea, esophagus, or lungs. This is defined as any events coded to a MedDRA term for candidiasis of the bronchi, trachea, esophagus, or lung.
- Coccidioidomycosis. This is defined as any events coded to a MedDRA term for coccidioidomycosis, pulmonary coccidioidomycosis, cutaneous coccidioidomycosis or extrapulmonary coccidioidomycosis.
- Cryptococcosis. This is defined as any events coded to a MedDRA term for cryptococcosis, pulmonary cryptococcosis, extrapulmonary cryptococcosis, disseminated cryptococcosis and recurrent cryptococcosis.
- Cryptosporidiosis. This is defined as any events coded to a MedDRA term for cryptosporidiosis or recurrent cryptosporidiosis.
- Cytomegalovirus (CMV) disease. This is defined as events coded to a MedDRA term for CMV disease, including CMV chorioretinitis, colitis, duodenitis, enteritis, gastritis, hepatitis, mononucleosis, mucocutaneous ulcer, myelomeningoradiculitis, myocarditis, esophagitis, pancreatitis, pericarditis, proctocolitis, urinary tract infection, encephalitis, CMV pneumonia, and CMV syndrome.
- Encephalopathy-related infections. This is defined as encephalitis or encephalopathy due to infections, excluding those transmitted by arthropod (such as Japanese B encephalitis) or rodents, or due to influenza, measles, mumps, polio or rabies. Includes PML (see below).
- Herpes simplex. This is defined as events coded to MedDRA terms for herpes simplex esophagitis, bronchitis, or pneumonitis, or to herpes esophagitis, bronchitis or pneumonia.
- Histoplasmosis. This is defined as events coded to any MedDRA term for histoplasmosis, and includes both acute and chronic infections of any site.
- Isosporiasis, chronic intestinal. This is defined as events coded to MedDRA terms for isosporiasis of the MedDRA high-level term (HLT) isospora infection.
- Kaposi's sarcoma. This is defined as events coded to the MedDRA HLT Kaposi's sarcoma.
- Mycobacterium avium complex. This is defined as events coded to the MedDRA term Mycobacterium avium complex infection.
- TB: This is defined as all events coded to the MedDRA HLT TB infections, including new infections and reactivation of latent infections, of pulmonary and extrapulmonary sites.

- *Pneumocystis carinii* pneumonia. This is defined as events coded to the MedDRA terms *Pneumocystis carinii* pneumonia and acute *Pneumocystis carinii* pneumonia.
- *Pneumonia, recurrent*. This is defined as events coded to the MedDRA term *pneumonia recurrent*.
- *PML*: This includes events coded to the MedDRA terms *PML*, *human polyomavirus infection*, *John Cunningham virus (JCV) infection*, *JCV test positive*, *leukoencephalopathy*, and *polyomavirus test positive*. Cases of *PML* shall meet the histopathological, radiological, laboratory, and clinical criteria of the American Academy of Neurology guidelines for *PML* diagnosis [[Berger JR 2013](#)].
- *Salmonella septicemia, recurrent*. This is defined as events coded to the MedDRA terms *Salmonella sepsis* or *Salmonella septicemia*.
- *Toxoplasmosis of brain*. This is defined as events coded to MedDRA term *cerebral toxoplasmosis*.

Other rare infections that are not normally seen in immunocompetent persons may also be considered as opportunistic infections.

#### *Hepatic Viral Infections*

This is defined as events within the Hepatitis viral infections MedDRA HLT, and includes all types of viral infections of the hepatic system. Where number of events permit, sub-analyses of specific types of infection (hepatitis B and hepatitis C) will be undertaken.

#### *Gastrointestinal Infections*

This is defined as events within the Infections and Infestation SOC that are coded to the MedDRA HLT GI infections.

#### *Respiratory Infections*

This is defined as events within the Respiratory, Thoracic and Mediastinal Disorders SOC that are coded to the MedDRA HLT respiratory tract infection.

#### *Malignancies*



This is defined as all malignant and benign neoplasms within the MedDRA Malignant tumors sub-standardized MedDRA query (SMQ). This SMQ includes all malignancies and carcinomas in situ.

#### *Infusion-Related Reactions and Hypersensitivity*

This is defined as events occurring within 1 day after each vedolizumab IV administration that are coded to terms in the following MedDRA SMQs and will be considered as suspected reports of hypersensitivity:

- Anaphylactic reaction SMQ.
- Anaphylactic/anaphylactoid shock conditions SMQ.
- Hypersensitivity SMQ.
- Angioedema SMQ.

#### *Hepatic Injuries*

Events coded to terms in the following MedDRA SMQs will be considered as suspected reports of drug-induced liver injury:

- Cholestasis and jaundice of hepatic origin SMQ.
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ.
- Hepatitis non-infectious SMQ.
- Liver-related investigations signs and symptoms (Narrow SMQ).
- Liver infections SMQ.
- Abnormal liver function is defined as levels  $>2 \times$  Upper Limit of Normal.

#### *Serious Adverse Events*

All AEs that meet the seriousness criteria (see Section 7.1.4).

### **6.6 Study Plan**

All eligible UC patient medical records will be identified, wherever feasible, through the following steps:

1. Participating sites will be asked to list exhaustively all UC patients with at least 1 prescription of vedolizumab IV up to site initiation.
2. Full eligibility criteria will be confirmed by the principal investigator or any designee.

3. Retrospective Patient's data defined per IRB policy will be abstracted only after reception of the waiver of requirement to obtain informed consent.
4. Prospective Patient's data defined per IRB policy will be abstracted only for patients who consented to participate in the study.

The medical records data collection will follow this schedule (see **Table 1**):

**Table 1. Study data collection schedule.<sup>1</sup>**

	Enrollment	Baseline <sup>2</sup>	Follow-up period <sup>3</sup>
<b>Review inclusion/exclusion criteria</b>	X		
<b>Demographics and risk factors data <sup>4</sup></b>		X	
<b>Clinical data</b> (including Mayo score)		X	X
<b>Laboratory and endoscopic data</b>		X	X
<b>UC medication and surgeries history</b>		X	X
<b>UC current medications</b> (including vedolizumab data)		X	X
<b>Adverse Events data</b>		X	X

<sup>1</sup> Data will be collected only if available in the medical charts.

<sup>2</sup> Baseline refers to the start of vedolizumab treatment. Index date will be considered as the baseline patient data.

<sup>3</sup> The follow-up data for each patient will be data from index date until the occurrence of any of following: end of treatment, lost to follow up, or death.

<sup>4</sup> Demographics and risk factors data include year of birth, sex, body mass index, or height and weight at baseline (i.e., start of vedolizumab treatment), previous and current (at baseline) smoking status, and UC/Inflammatory Bowel Disease family history.

## 7 Safety Reporting

### 7.1 Definitions

#### 7.1.1 Adverse Event

An AE is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE.
- A laboratory test result that requires the subject / patient to receive specific corrective therapy.
- A laboratory abnormality that leads to discontinuation of therapy.
- A laboratory abnormality that the health care provider considers to be clinically significant.

#### 7.1.2 Adverse Drug Reaction

An ADR is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

#### 7.1.3 Special Situation Reports and Product Quality Issues

A Special Situation Report (SSR) includes any of the following events:

- **Pregnancy:** any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- **Breastfeeding:** infant exposure from breast milk.
- **Overdose:** all information of any accidental or intentional overdose.

- Drug abuse, misuse or medication error: all information on medicinal product abuse, misuse or medication error (potential or actual).
- Suspected transmission of an infectious agent: all information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product.
- Occupational exposure.
- Use outside the terms of the marketing authorization, also known as “off-label”.
- Use of falsified medicinal product.

A Product Quality Issue refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

#### **7.1.4 Serious Adverse Event**

A SAE is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event, so the event(s) causing the death should be recorded.
- In the view of the health care provider, places the subject / patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability / incapacity.
- Results in a congenital anomaly / birth defect.

A SAE may also be any other medically important event that, in the opinion of the health care provider, may jeopardize the subject / patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization and includes any event or synonym described in the Takeda Medically Significant AE List (see **Table 2**).

**Table 2. Takeda medically significant AE list.**

Term	
<b>General</b>	<b>Hepatobiliary System</b>
Malignancy	Acute hepatic failure
Endotoxic shock	Fulminant hepatitis
Sepsis	<b>Immune system</b>
Transmission of an infectious agent by a medicinal product	Anaphylaxis
Necrotic conditions including Gangrene	Progressive multifocal leukoencephalopathy
<b>Blood and Lymphatic System</b>	Transplant rejection
Bone marrow failure	<b>Musculoskeletal System</b>
Disseminated intravascular coagulation	Rhabdomyolysis
Thrombotic thrombocytopenic purpura	<b>Nervous System</b>
Acquired hemoglobinopathies	Cerebrovascular accident
Hemolysis	Coma
<b>Cardiovascular System</b>	Convulsive seizures
Cardiac arrest	Hyperthermia malignant
Cardiac failure	Macular edema
Cardiomyopathy acute	Psychosis
Malignant hypertension	Meningoencephalitis
Ventricular arrhythmias	Neuroleptic malignant syndrome
Embolisms and infarctions	Suicidal behavior
Dissection and rupture of important vessels	<b>Reproductive System</b>
<b>Endocrine System</b>	Abortion
Adrenal crisis	Uterine perforation
<b>Gastrointestinal System</b>	<b>Respiratory System</b>
Acute pancreatitis	Acute respiratory failure
GI hemorrhage	Pulmonary hypertension
GI perforation	<b>Skin and subcutaneous tissue</b>
GI obstruction	Toxic epidermal necrolysis
Necrotizing colitis	Stevens-Johnson syndrome
Peritonitis	<b>Urinary System</b>
	Acute renal failure

GI: gastrointestinal

## **7.2 Collection and Notification of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance**

Events / issues which are part of the study objectives or outcomes will be systematically identified and collected from medical records or other applicable source records, and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Korea Pharmacovigilance.

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or Product Quality Issue where the event / issue pertains to a Takeda product (or unbranded generic), such information should be notified to the local Takeda Pharmacovigilance department within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. As such reports are spontaneously notified, causality of any AEs should be assumed unless there is evidence to the contrary.

## **7.3 Reporting of Adverse Drug Reactions and Special Situation Reports to Regulatory Agencies**

The expedited reporting of AEs and SSRs that are study endpoints to regulatory agencies is not required. Such events should be included in the Clinical Study Report.

For spontaneously reported events that are not study endpoints, sponsor shall notify regulatory agencies in accordance with local regulatory requirements.

## **8 Data Quality Control and Assurance**

### **8.1 Quality Control**

Sponsor's standard operating procedures for the analysis of observational studies shall be followed. Any deviation from the Statistical Analysis Plan (SAP) or additional unplanned analyses shall be identified as such in the study report.

### **8.2 Audit from Quality Assurance Unit**

The Quality Assurance unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

### **8.3 Inspection by Institutional Review Board / Institutional Ethics Committee or Competent Authority**

Representatives from IRB / IEC or CA may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Site Study Responsible must immediately contact the Sponsor and CRO, and must make the records available as requested.

### **8.4 Data Management**

Data management will be carried out according to a Data Management Plan, which must be written and approved before the design of the study database is finalized. The data management provider should approve all data formats before the data collection tools are made available to the sites. Collected data will be encrypted to ensure confidentiality and data protection.

If the waiver of requirement to obtain informed consent or written informed consent required for collection of prospective data and of pregnancy-related data is known not to be available in spite of it being required, data is not entered into or is deleted from the database.

If a patient is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant (i.e., if collected within the time frame of the first follow-up period).

If a patient is included in the study in spite of being treated off-label (not according to the summary of product characteristics), data is kept in the database and analyzed separately and as part of the overall analyses as described in the SAP.

The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and AEs/ADRs (MedDRA) must be followed.

#### **8.4.1 Data Collection Tools**

The Study Site will receive data collection tools (case report forms, access to electronic data capture, etc.) from Takeda. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard.

The Site Study Responsible must sign-off the complete data set for each patient, confirming the collected data. AEs data reported according to Section 7 and data on SAEs collected according to Section 6 should be signed-off separately by a physician who is involved in the study.



## **9 Statistical Methods and Determination of Sample Size**

Statistical analysis will be performed using the SAS software (SAS Institute, North Carolina), version 9.4. A comprehensive SAP will be prepared before database lock. The SAP will detail the statistical analyses to be performed. It will describe the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed, as well as the final statistical analysis, will be described in a revised SAP before database lock. All later deviations and / or alterations will be summarized in the final study report.

Analyses will be performed using all available data. Due to the observational nature of the study, missing values are expected. However, no imputation of missing values will be considered unless otherwise stated in the SAP.

### **9.1 Description of Analysis Set**

The full analysis set will comprise all patients fulfilling all inclusion and exclusion criteria and any informed consent requirements.

### **9.2 Method of Statistical Analysis**

All collected data will be presented using descriptive statistics because of the exploratory nature of this study. Continuous variables will be summarized as the number of patients (n), mean, standard deviation (SD), median, 1<sup>st</sup> and 3<sup>rd</sup> quartiles (Q1 and Q3), minimum and maximum. Summary for categorical variables will include frequency counts and percentages and number of missing data. Percentages will be based on the number of non-missing data as the denominator.

Patient disposition will be presented, inclusive of discontinuation and reason for discontinuation. Patient demographics, risk factors, clinical characteristics and laboratory data (at baseline and follow-up, if applicable) will be summarized as descriptive statistics.

### **9.3 Analysis of Study Outcomes**

### 9.1.1 Analysis of Primary Outcomes

The primary outcomes of the study are:

- Clinical response to vedolizumab IV at 6 weeks using the partial Mayo score, defined as a reduction of at least 3 points and a decrease of at least 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscale, or an absolute rectal bleeding score of 0 or 1.
- Safety of vedolizumab IV will be assessed by the incidence rates of AESIs (as described in Section 6.5.5), SAEs, and pregnancy outcomes occurred during the study period. The proportion of patients experiencing AESIs, SAEs, and pregnancy outcomes, and their relation to study drug, will be summarized by presenting the rate and 95% CIs according to Pearson-Clopper. Additionally, safety analysis will be presented: (1) based on events occurring between first and last dose of vedolizumab (also AEs at 14 weeks of post-discontinuation in occurred cases), and (2) based on events occurring between first dose of vedolizumab and end of study follow-up.

### 9.1.2 Analysis of Secondary Outcomes

The secondary outcomes of the study are:

- Clinical response to vedolizumab at 14 weeks using the complete Mayo score (see definition above) and clinical remission at 6 and 14 weeks, defined as score  $\leq 2$  and no sub-score  $> 1$  relative to baseline.
- Clinical effectiveness of vedolizumab IV on mucosal healing at 6 and 14 weeks relative to baseline, defined by the Mayo endoscopic sub-score of 0 or 1.

### 9.1.3 Analysis of Exploratory Outcomes

The exploratory outcomes of the study are:

CCI



CCI

Baseline is defined as the date of first vedolizumab IV dose. If Mayo score at baseline is less than 3 (e.g., patients who were prescribed vedolizumab because of unacceptable AEs related to TNF- $\alpha$  antagonist therapy), these patients will be excluded from the effectiveness analyses.

## 9.2 Interim Analyses

An interim analysis will be performed after the approximately 50 patients are included. Primary and secondary outcomes will be considered for such analysis.

## 9.3 Determination of Sample Size

The sample size for the study is not based on statistical considerations because the study does not consider hypothesis testing / power calculation or precision around an estimate. The sample size of approximately 100 evaluable patients was selected because it is anticipated that around 100 patients will be treated with vedolizumab IV in South Korea during the study period and enrolled into the study.

## 10 Reports

Observational / non-interventional study reports will be prepared and submitted to Global Research for distribution. The interim and final study reports are planned to be available within a maximum of 3 months from collection of the last data point, and the participating sites should be informed about the results when the final report is finalized.

## 11 Plans for Disseminating and Communicating Study Results

Presentation of the study results in local, regional and / or international congresses, in addition to publication in a scientific journal, are envisaged as part as dissemination plans.

## 12 Archiving of Study Documentation

During the course of the study the Site Study Responsible must as a minimum file the below essential documents in the Study Site File:

- Written agreement between the Sponsor or representative (CRO) and the Site Study Responsible.
- The study protocol and any amendments.
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Study Responsible.
- Waiver of requirement to obtain informed consent (notified to / approved by IECs / IRBs, as locally required), including the original signed forms.
- Signed informed consent forms, for prospective data collection from treatment baseline and follow up visits, according to IRB policy.
- Signed informed consent forms of patient or of patient's partner, for collection of pregnancy and pregnancy outcomes data.
- The list of participating patients.
- Written IEC / IRB approval / vote according to local regulations.
- Authority approval according to local regulations, if required.
- The completed clinical report forms.

After final database lock the Site Study Responsible must at a minimum store the list of participating patients, the waiver of requirement to obtain informed consent and the signed informed consent forms for collection of pregnancy-related data and for prospective data

collection (according to IRB policy) from treatment baseline and follow up visits on site for 5 years. The Site Study Responsible should store additional study documentation for a longer period of time as required by any local regulations and / or hospital requirement.

Additionally, data collected via the clinical report forms and abstracted via Electronic Data Capture (EDC) must be archived by the site study responsible for 5 years after study completion. Data on the EDC will thereafter be destroyed, unless required to be store for a longer period of time by any local regulations and / or hospital requirement. The Sponsor, on top of the above onsite archiving requirements and according to local guidelines and standard operating procedures, will archive all study-related documentation and data (including data abstracted via an EDC) for 10 years after study completion.

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## 14 Appendices

### 14.1 Annex 1. Mayo Score.

Component	Score
<b>Stool Frequency</b>	
Normal	0
1–2 stools/day more than normal	1
3–4 stools/day more than normal	2
>4 stools/day more than normal	3
<b>Rectal Bleeding</b>	
None	0
Visible blood with stool less than half the time	1
Visible blood with stool half of the time or more	2
Passing blood alone	3
<b>Physician Rating of Disease Activity</b>	
Normal	0
Mild	1
Moderate	2
Severe	3
<b>Partial Mayo Score</b>	<b>(sum)</b>

Endoscopic Findings	Score
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern, mild friability)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe disease (spontaneous bleeding, ulceration)	3
<b>Full Mayo Score</b>	<b>(sum)</b>

Source [[Lewis 2008](#)].