Title: Understand the Outcomes of Inflammatory Bowel Disease (IBD) Patients Treated with Biologics in Taiwan – A Decentralized Vedolizumab and Biologic Agents Core Assessments in IBD Collaboration

Protocol Approve Date: 11-Dec-2020

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Non-Interventional Study Protocol

Title: Understand the Outcomes of Inflammatory Bowel Disease (IBD) Patients Treated with Biologics in Taiwan – A Decentralized Vedolizumab and Biologic Agents Core Assessments in IBD Collaboration

Study ID: Vedolizumab-4030

Sponsor: *Takeda Pharmaceutical Co., Ltd.*
17F., No. 1, Songgao Rd., Xinyi Dist., Taipei City 11073, Taiwan (R.O.C.)
Phone: + 886-2-8729-9050
Fax: + 886-2-8789-2699

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

Date of final version 1.0 of protocol: 11-Dec-2020

1 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

Issue	<Country or region>Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol, compound, and medical management of subjects) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

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 Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- 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 subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for 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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- 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.

PPD

STUDY SUMMARY

Name of Sponsor(s): Takeda Pharmaceutical Co., Ltd.	**Compound/Product:** Vedolizumab
Title of Protocol: Understand the Outcomes of Inflammatory Bowel Disease (IBD) Patients Treated with Biologics in Taiwan – A Decentralized Vedolizumab and Biologic Agents Core Assessments in IBD Collaboration	
Study Number: Vedolizumab-4030	**Phase:** Medical Affairs, Post-Approval Company Sponsored (Observational)
Study Design: Retrospective cohort study	
Objectives: 1. To quantify the relapse rate post mandatory biologic discontinuation due to reimbursement limitation or reasons other than loss of response or adverse event and identify predictors (at the time of treatment discontinuation and off treatment) of relapse. 2. To quantify the treatment effectiveness of biologics including anti-TNF-α and vedolizumab in IBD patients and identify predictors of response to treatment. 3. To quantify the safety (particularly septic shock, pneumonia & tuberculosis [TB] reactivation) of biologics including anti-TNF-α and vedolizumab in IBD patients.	
Subject Population: Biologics treated IBD patients	
Number of Subjects: 724	**Study Sites:** Chang Gung Medical Foundation, Linkou China Medical University Hospital National Taiwan University Hospital Taichung Veterans General Hospital (Sites are subject to change per local Institutional Review Board [IRB] permitted.)
Dose Level(s): N/A	**Route of Administration:** N/A
Duration of Study: Overall Study Duration: Estimated to be 15 months (maximum) Data Collection Period: February 2007 to March 2020 (or per local IRB permitted date) Estimated Study Duration: July 2020 to July 2021	
Criteria for Inclusion of IBD Patients: 1. Aged ≥ 20 years old when IBD (Crohn's disease [CD] or ulcerative colitis [UC]) was first diagnosed during February 2008 to March 2020 (or per local IRB permitted date) - CD (ICD-9-CM: 555.X or ICD-10-CM: K50.XX, K50.XXX) - UC (ICD-9-CM: 556.X or ICD-10-CM: K51.XX, K51.XXX) 2. Had received any dose of biologics for IBD treatment, including adalimumab, infliximab, golimumab, or vedolizumab, from February 2008 to March 2020 (or per local IRB permitted date)	
Criteria for Exclusion of IBD Patients:	

Patients with any suspected diagnosis of CD or UC within one year before the initial date of confirmed IBD diagnosis will be excluded.
Criteria for Evaluation and Analyses: Objective 1: predictors of relapse post biologics discontinuation 1. To determine the percentage of relapse and time-to-relapse after biologics discontinuation due to reimbursement limitation or reasons other than loss of response or adverse event. 2. To determine the potential correlation between the clinical variables and the relapse post biologics discontinuation. Objective 2: comparative effectiveness 1. To compare the incidence rates of patients achieving treatment effectiveness, including clinical response, clinical remission, steroid-free remission, and mucosal healing among patients receiving vedolizumab versus those receiving anti-TNF-α. 2. To determine the potential correlation between the clinical variables and treatment effectiveness. Objective 3: comparative safety To compare the incidence rates of patients experiencing opportunistic infections, hepatic viral infections, gastrointestinal infections, respiratory infections, respiratory failure, or sepsis or septic shock among patients receiving vedolizumab versus those receiving anti-TNF-α.
Statistical Considerations: Descriptive analysis: Chi-square test and Student's t-test Baseline correction: Propensity score matching Incidence of outcomes & predictors outcomes: Kaplan-Meier method and time dependent Cox regression models
Sample Size Justification: According to the epidemiological information and field insights, approximately 724 IBD patients treated with biologics during February 2008 to March 2020 will be included in this study.

N/A=not applicable

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List of Abbreviations and Definition of Terms

5-ASA:	5-Aminosalicylic Acid
ATC:	Anatomical Therapeutic Chemical
BMI:	Body Mass Index
CA:	Competent Authority
CD:	Crohn's Disease
CDAI:	Crohn's Disease Activity Index
CDEIS:	Crohn's Disease Endoscopic Index of Severity
CGRD:	Chang Gung Research Database
CI:	Confidence Interval
CIC:	Catastrophic Illness Certificat
CMUH:	China Medical University Hospital
CMV:	Cytomegalovirus
CRO:	Contract Research Organisation
CRP:	C-Reactive Protein
DVP:	Data Validation Plan
EBV:	Epstein-Barr Virus
EIM:	Extra-Intestinal Manifestation
EMR:	Electronic Medical Record
EOT:	End of Treatment
ER:	Emergency Room
FCP:	Fecal Calprotectin
GCP:	Good Clinical Practice
GI:	Gastrointestinal
GPP:	Good Pharmacoepidemiology Practices
Hb:	Hemoglobin
HCRU:	Healthcare Resource Utilization
IBD:	Inflammatory Bowel Disease
ICD-9-CM:	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM:	International Classification of Diseases, Ten Revision, Clinical Modification
ICD-10-PCS:	International Classification of Diseases, Ten Revision, Procedure Coding System

ICH:	International Council for Harmonisation
ID:	Identity
IEC:	Independent Ethics Committee
IMM:	Immunomodulator
INP:	Inpatient
IRB:	Institutional Review Board
ISPE:	International Society for Pharmacoepidemiology
IV:	Intravenous
MI:	Multiple Imputation
NHI:	National Health Insurance
NHIA:	National Health Insurance Administration
NTUH-*i*MD:	National Taiwan University Hospital-integrated Medical database
OPD:	Outpatient Department
PML:	Progressive Multifocal Leukoencephalopathy
SAP:	Statistical Analysis Plan
SOP:	Standard Operation Procedure
TB:	Tuberculosis
TVGH:	Taichung Veterans General Hospital
UC:	Ulcerative Colitis
WBC:	White Blood Cell

2 Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease of gastrointestinal tract and characterized by recurrent ulceration of the bowels. According to the IBD epidemiological study in Taiwan in 2015, both incidence and prevalence of IBD have increased in Taiwan in recent years [1]. The prevalence of CD is 3-4 cases per 100,000 people and the incidence of CD has an annual increment of 4-5 new cases per 1,000,000 persons [1]. In addition, the prevalence of UC is 12 cases per 100,000 people and the incidence of UC has an annual increment of 9-10 new cases per 1,000,000 persons [1].

Conventional treatments for IBD include 5-aminosalicylic acid (5-ASA drugs), steroids, and immunomodulators (IMMs). With the development of immunology and biotechnology, the invention of biologics has made significant progress on IBD treatment. Biologics are used in autoimmune disease treatment by modifying or inhibitory of inflammatory response in the immune system. In Taiwan, adalimumab is the first National Health Insurance Administration (NHIA) reimbursed anti-TNF-α biologics for IBD treatment since July 2011. After that, other anti-TNF-α biologics including infliximab and golimumab are also reimbursed. Moreover, vedolizumab, an anti-$\alpha_4\beta_7$ integrin biologics, is reimbursed since October 2017.

In Taiwan, biologics are only reimbursed by NHIA to treat moderate and severe IBD for a limited period of use. The mandatory drug holiday is part of the reimbursement policy for biologics used in the treatment of IBD. After the drug holiday, patients will be allowed to apply the subsequent doses of biologics depends on the effectiveness (clinical response and remission) of previous dosing of biologics. Patients could receive a reimbursement cycle up to around one year of biologic treatment and discontinue the use of biologics at the end of reimbursement cycle regardless of clinical presentation. For those who experience relapse after biologics discontinuation, another cycle of treatment could be applied after 6 months of drug holiday (since October 2019, the drug holiday was shortened to 3 months).

Recently, there is still no recommendation for when to discontinue biologic treatment after patients achieving clinical remission. Although the IBD relapse rate after biologics discontinuation and the predictors of IBD relapse have been studied in some retrospective studies, most of them were focused on anti-TNF-α biologics and seldom of them were studied in Taiwan population [2–7]. Therefore, an observational, retrospective study to understand the

outcomes of IBD patients treated with biologics using the clinical data collected form electronic medical record (EMR) database in Taiwan will be performed.

In this study, the relapse rate and the potential predictors of IBD relapse in IBD patients after biologics discontinuation will be evaluated by analysis of retrospective clinical data. In addition, the effectiveness and safety of anti-TNF-α (adalimumab, infliximab, and golimumab) and anti-$\alpha_4\beta_7$ integrin (vedolizumab) will be evaluated in this study.

Through identifying the predictors of relapse after biologics discontinuation, and quantifying the portion of patients who are not suitable for treatment de-escalation at the end of reimbursement cycle based on local real-world data, the predicting models informing treatment de-escalation and re-escalation strategy may be built up, and ultimately maximize the access by turning the reimbursement scheme from current "mandatory drug holiday between each fixed-duration treatment cycle" into "personalized treatment based on the predicting model and patients clinical presentation".

Through quantifying the treatment effectiveness of biologics among patients treated with vedolizumab versus anti-TNF-α, in consideration of disease duration and previous exposure to biologics, the concept of accelerated step up is expected to be raised through the expected better outcomes in bio-naïve (without other biologics experience) patients. Through quantifying the infection risk among patients treated with vedolizumab versus anti-TNF-α, the importance of using a gut-selective biologic (vedolizumab) in the treatment of IBD will be determined for safety concerns.

3 Study Objectives and Outcomes

3.1 Objectives

1. To quantify the relapse rate post mandatory biologic discontinuation due to reimbursement limitation or reasons other than loss of response or adverse event, and identify predictors (at the time of treatment discontinuation and off treatment) of relapse.
2. To quantify the treatment effectiveness of biologics including anti-TNF-α and vedolizumab in IBD patients and identify predictors of response to treatment.
3. To quantify the safety (particularly septic shock, pneumonia & tuberculosis [TB] reactivation) of biologics including anti-TNF-α and vedolizumab in IBD patients.

3.2 Study Outcomes

Objective 1: predictors of relapse post biologics discontinuation

1. To determine the percentage of relapse and time-to-relapse after biologics discontinuation due to reimbursement limitation or reasons other than loss of response or adverse event.
2. To determine the potential correlation between the clinical variables and the relapse post biologics discontinuation.

Objective 2: comparative effectiveness

1. To compare the incidence rates of patients achieving treatment effectiveness, including clinical response, clinical remission, steroid-free remission, and mucosal healing among patients receiving vedolizumab versus those receiving anti-TNF-α.
2. To determine the potential correlation between the clinical variables and treatment effectiveness.

Objective 3: comparative safety

To compare the incidence rates of patients experiencing opportunistic infections, hepatic viral infections, gastrointestinal (GI) infections, respiratory infections, respiratory failure, or sepsis or septic shock among patients receiving vedolizumab versus those receiving anti-TNF-α.

4 Study Administrative Structure

Study Site[&]	Principal Investigator
Chang Gung Research Database Chang Gung Medical Foundation, Linkou	PPD
China Medical University Hospital	
National Taiwan University Hospital	
Taichung Veterans General Hospital	
Study Personnel from QPS-Qualitix	
Data Manager	PPD
Biostatistician	
Medical Writing	

[&]Ranked according the alphabetical order of the first letter in the title

4.1 Sponsor Personnel

PPD

5 Ethics

This is an observational, retrospective study to investigate the effectiveness and safety of biologic therapies in IBD patients in Taiwan. This study will use real world data, i.e. by collecting clinical data from the EMR database of selected medical centers in Taiwan in an anonymous manner. The existence of the study will not have impact on the patients because all data collection will be completed by obtaining the identity (ID) encrypted data from the data center or database of each medical center.

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 [8], International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) guideline [9] and any local regulations.

Takeda Pharmaceuticals Taiwan, Ltd. and the appointed Contract Research Organization (CRO) will ensure that the protocol, any amendments, and proper informed consent waiver for patients will be applied for conducting the proposed study.

Takeda Pharmaceuticals Taiwan, Ltd. and the appointed CRO will be responsible for meeting the International Council for Harmonisation (ICH) requirement for yearly updates to the Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs), if applicable.

5.2 Independent Ethics Committee / Institutional Review Board and Authorities

IEC/ IRB

According to applicable regulations, the appointed CRO will:

- notify or obtain the approval from the relevant IEC / IRB of the protocol and any amendments if applicable
- notify or obtain the waiver for the informed consent process

The appointed CRO 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 appointed CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide Takeda Pharmaceuticals Taiwan, Ltd. with a copy of this list. Copies of the documents will be sent to Takeda Pharmaceuticals Taiwan, Ltd. electronically or by post mail.

The Sponsor or the appointed 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 Responsible with a copy of this list. Copies of the documents will be distributed upon request.

5.3 Authorities

This is an observational, retrospective study utilizing clinical data in the EMR database in 4 medical centers for post-marketing survey, so no commitment to regualtory authority is required.

5.4 Subject Information and Written Informed Consent

This is an observational, retrospective study to collect IBD patients' clinical data from the EMR database in an anonymous manner.

Personal identifiable data will not be collected in this study. A waiver for Subject Consent will be applied to individual IRB or IEC for approval before the initiation of data collection.

6 Study Design and Plan

This study is a 'non-interventional study' as defined in Directive 2001/20/EC and will follow the guidelines for GPP.

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.
- Biologics (including adalimumab, infliximab, golimumab, and vedolizumab) were prescribed in accordance with the terms of the marketing authorization(s).
- The prescription of biologics is clearly separated from the decision to include the subject in the study.

6.1 Study Schedule

Estimated first IRB approval:	Q2, 2020
Planned Start of Study:	Q3, 2020
Planned collection of first data point:	Q3, 2020
Planned End of Study:	Q3, 2021
Planned collection of the last data point:	Q1, 2021
Planned completion of the Study Report:	Q3, 2021

Takeda Pharmaceuticals Taiwan, Ltd. and the appointed CRO will ensure that End-of-Study notification is submitted to individual IEC / IRB for each site, for each country and for the complete study, as locally required.

Based on upcoming knowledge, Takeda Pharmaceuticals Taiwan, Ltd. might choose to terminate the study prematurely. In such case the study sites and individual IECs/IRBs will be informed promptly.

6.2 Study Design

A retrospective cohort study is planned to investigate IBD relapse, effectiveness, and safety of biologic treatments in IBD patients in Taiwan. The relapse rate in IBD patients and predictors of IBD relapse after the discontinuation of biologics will be evaluated. In addition, the effectiveness and potential risk of infection after receiving anti-TNF-α antibodies (including adalimumab, infliximab, or golimumab) or anti-$\alpha_4\beta_7$ integrin antibody

(vedolizumab) will be evaluated.

This study will use real world data, i.e. by collecting clinical data from the EMR database of selected medical centers in Taiwan. The clinical data of IBD patients will be collected with their IDs encrypted from February 1, 2007 to March 31, 2020. All eligible IBD patients from 4 medical centers will be included for data collection and analysis per local IRB regulation. All included IBD patients will be grouped into 2 cohorts for outcome analyses.

The exposure variables of IBD patients treated with biologics will be collected at baseline (within one year before the index date [the date when patient receiving the first dose of biologics]), during biologic treatment (i.e., on treatment, from the index date to the end of treatment [EOT]), and during the follow-up period post EOT. IBD patients' demographics (e.g., age, gender, body mass index [BMI], etc.), clinical characteristics of IBD (e.g., IBD location, disease duration, laboratory results, etc.), healthcare resource utilization records (e.g., surgery records), and medication treatment of IBD will be collected.

The diagnosis records will be collected based on diagnostic code (International Classification of Diseases, Ninth Revision, Clinical Modification 2001 edition [ICD-9-CM] or the International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM], please refers to Table A1 in the Appendices). The IBD-related surgery or inspection records and respiratory failure related procedure records will be collected from EMR database based on the IBD related surgeries or endoscopy inspections codes and respiratory failure related procedures codes (ICD-9-CM Procedure Code or the International Classification of Diseases, Ten Revision, Procedure Coding System [ICD-10-PCS], please refers to Table A2 and A3 in the Appendices). The medication records will be collected from EMR database based on the Anatomical Therapeutic Chemical (ATC) drug codes (please refers to Table A4 in the Appendices).

6.3 Data Sources

In this study, the clinical data will be collected from EMR database in 4 medical centers as listed below.

Table 1 Electronic Medical Record Database from 4 Medical Centers

EMR Database	Available Clinical Data
Chang Gung Research Database (CGRD)	It comprises seven medical institutes located from the northeast to southern regions in Taiwan. The volume of clinical and scientific studies based on the CGRD is reported to be of high quality. • Administration

EMR Database	Available Clinical Data
	• Demography • Diagnosis • Medical and surgical procedures • Prescriptions • Laboratory measurements • Healthcare resource utilization (HCRU, including outpatient department (OPD), emergency room (ER) visit, and hospitalization) record • Nursing record • Payment and National Health Insurance (NHI) medical claims
China Medical University Hospital (CMUH)-Clinical Research Database	The clinical data from CMUH-Clinical Research Database will not be released to external stakeholder. Thus, requested data will be integrated and analyzed by CMUH Big Data Center according to the study protocol and statistical analysis plan (SAP). Then the results will be provided to Takeda.
National Taiwan University Hospital-integrated Medical database (NTUH-*i*MD)	It contains all records of inpatient (INP) and outpatient visits to the NTUH since 2006, including data not covered by NHI. • Demography • HCRU record • Diagnosis • Medical and surgical procedures • Prescriptions • Laboratory measurements • Examination report • Nursing record • Payment and NHI medical claims
Taichung Veterans General Hospital (TVGH)-Research Database	• Demography • Prescriptions • Catastrophic illness status • HCRU record • Diagnosis • Laboratory measurements • Payment and NHI medical claims

Anonymous clinical data of IBD patients that are not structured as in electronic format or not electronically archived (e.g. endoscope examination report, OPD SOAP, etc.) will be applied additionally by performing internal data review and recording by investigators within individual clinical site with local IRB/IEC approval.

6.4 Study Population

Newly diagnosed IBD patients treated with biologics including vedolizumab, adalimumab, infliximab, or golimumab during February 2008 to March 2020 will be included.

6.4.1 Inclusion Criteria

Patients' eligibility will be confirmed according to all the following criteria prior to entry into the study.

1. Patient aged ≥ 20 years old when IBD (CD or UC) was first diagnosed during February 2008 to March 2020 (or per local IRB permitted date).
   - CD (ICD-9-CM: 555.X or ICD-10-CM: K50.XX, K50.XXX)
   - UC (ICD-9-CM: 556.X or ICD-10-CM: K51.XX, K51.XXX)
2. Had received any dose of biologics for IBD treatment, including vedolizumab adalimumab, infliximab or golimumab, from February 2008 to March 2020 (or per local IRB permitted date)

6.4.2 Exclusion Criteria

Patients with any suspected diagnosis of CD or UC within one year before the initial date of confirmed IBD diagnosis will be excluded.

6.4.3 Study Cohorts

The patients with at least 1 year follow-up history and without biologics treatment before the initial confirmed diagnosis of IBD and their first confirmed diagnoses of IBD were after February 2008 will be classified into the following study groups based on the criteria as listed below:

1. Biologics discontinuation cohort (cohort 1)
   IBD patient will be assigned into the cohort 1, if he/she
   (1) had received biologic treatments for at least 6 months after the initial confirmed diagnosis of IBD, and
   (2) with at least 3 months follow-up period after biologics discontinuation
2. Biologics treated cohort (cohort 2)
   IBD patient will be assigned into the cohort 2, if he/she had any dose of biologic for IBD treatment after the initial confirmed diagnosis of IBD

6.5 Definition of Exposure

6.5.1 Study Drugs

Biologics for IBD treatment include adalimumab, infliximab, golimumab, and vedolizumab

6.5.2 Identification of Each Biologic Treatment Cycle

To investigate the potential impact of discontinuing biologic treatment cycles on the biologic effectiveness and potential IBD relapse, each treatment cycle in individual IBD patient will be identified.

The date when the first dose of the biologic was prescribed in each treatment cycle will be defined as the index date of each treatment cycle in individual IBD patient. The baseline of the first cycle is defined as one year before the index date. After receiving the same biologic treatments for at least 6 months, the end of treatment (EOT) will be defined as the last date of the continuous biologic treatment in each biologic treatment cycle (≥ 6 months).

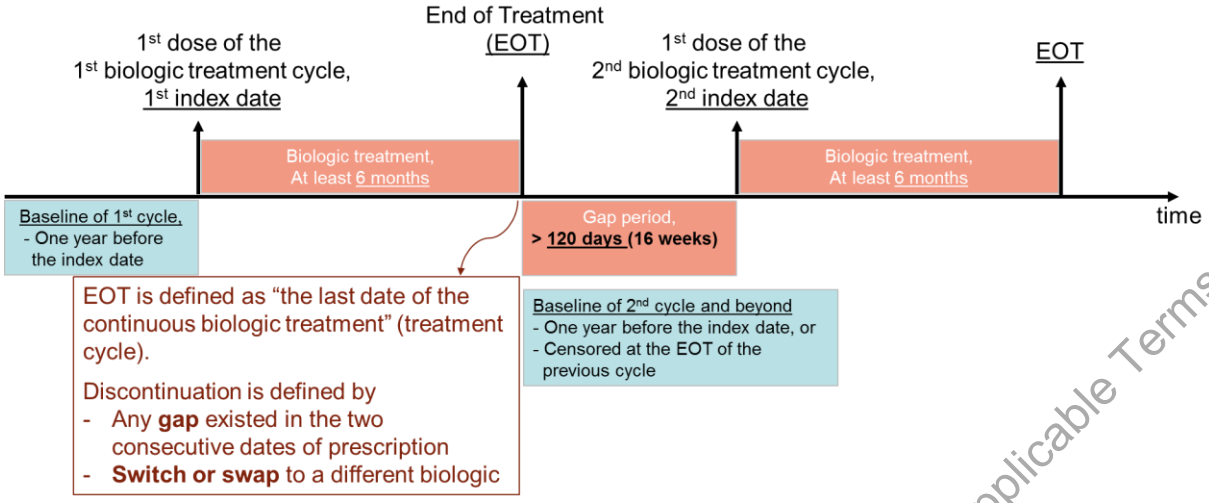
The EOT in each patient will be followed by discontinuation gap of biologic treatment with the minimal 120 days (approximately 16 weeks) without any biologic treatment between EOT and the next index date of the subsequent biologic treatment cycle (either with the same of biologic treatment or a different biologic treatment).

Multiple biologic treatment cycles can then repeat during the study period until the end of study follow-up. Detailed identification of each biologic treatment cycle please refers to Figure 1.

Each biologic treatment cycle with its index date and its EOT will be treated as the unit to assess the study outcome based on the corresponding study cohort and follow-up period for outcome assessment. The patient and disease characteristics within one year before the index date, during the biologic treatment period, and at EOT of each biologic treatment cycle will be considered and justified for data analysis.

For patients with more than one cycle of biologic treatment, starting from the 2nd cycle and beyond, the baseline period would be left censored at the EOT of the previous biologic treatment cycle or one year before the index date, whichever is the shorter period.

Figure 1 Diagram for Identification of Each Biological Treatment Cycle



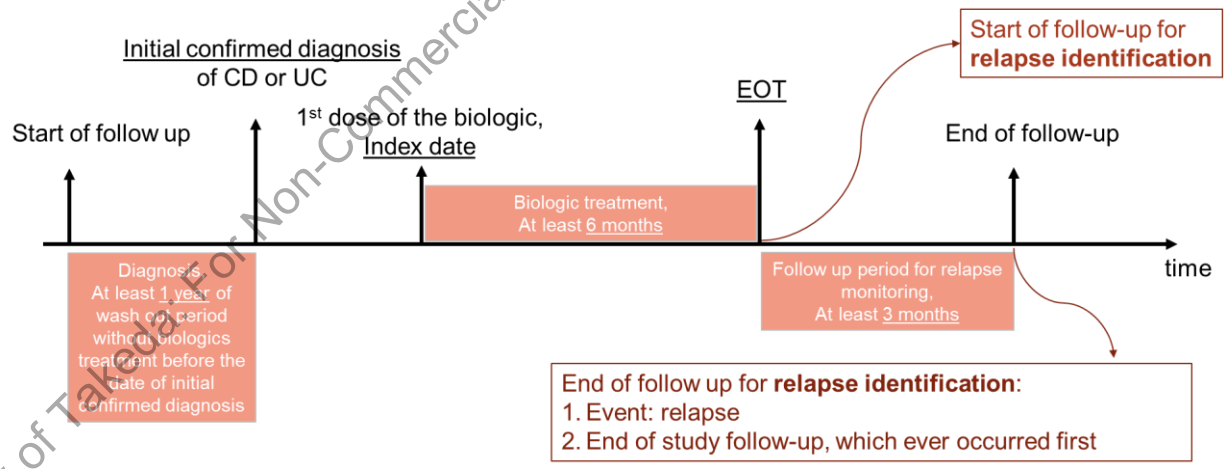
6.6 Outcome Variables (Dependent Variables)

6.6.1 Objective 1: Predictors of Relapse post Biologics Discontinuation

6.6.1.1 Relapse

To determine the incidence of relapse, IBD patients in cohort 1 will be followed from EOT until any of the following conditions that occurs first: (1) IBD relapse or (2) the end of study follow-up (the last date of data collection period). Please see Figure 2 for details.

Figure 2 Diagram for Cohort 1 Identification and the Time Period for Follow-up



The event of relapse will be identified by any of the following conditions:

(1) Re-treatment with biologics

I. Re-treatment with the same biologic

II. Switch or swap to a different biologic

(2) Steroid use

(3) IBD-related hospitalization

(4) IBD-related ER visits

(5) IBD-related surgery

I. Perianal disease

II. Bowel resection

(6) Increase in disease index

If multiple events are identified in an individual patient after the EOT, the first date with identified relapse event will be used as the event date. Outcome variables indicating IBD relapse are summarized in Table 2.

Table 2 Outcome Variables Indicating IBD Relapse

Indicators of relapse	**Variable for IBD relapse** Duration: After the EOT before the end of study follow-up
Re-treatment with biologics	Any biologics received after the EOT, including: • Biologics which were the same as prescribed in the previous treatment cycle • Switch or swap to a different biologic treatment
Steroid use	Anyone in the following while the specialty of prescribing physicians is limited to gastroenterology, colon rectal surgery, and rheumatology: • For patients who were on steroid at EOT: dose increase of steroids > 10 mg within any 2-week period • For patients who were steroid-free at EOT: any dose increase of steroids within any 2-week period • Intravenous (IV) steroids use
IBD-related hospitalization	IBD-related hospitalization record (identified by IBD diagnosis code, please refer to Table A1 in the Appendices)
IBD-related ER visits	IBD-related ER visit (identified by IBD diagnosis code, please refer to Table A1)
IBD-related surgery	IBD-related surgeries record (identified by any of procedure for bowel resection or perianal disease listed in Table 3)
Increase in disease index	Anyone in the following: • Crohn's disease activity index (CDAI) > 150 or Mayo score ≥ 3 • Laboratory results (fecal calprotectin [FCP] ≥ 250 μg/g) • Clinical findings in endoscope image (include intestinal ulcers, cobblestone appearance, or spontaneous bleeding)
Note: The occurrence of any of the above records will be regarded as an IBD relapse.	

Table 3 List of Surgery for Bowel Resection and Perianal Disease

IBD-related surgery	**Procedure**
Bowel Resection	Total colectomy Left/right hemicolectomy

IBD-related surgery	Procedure
	Partial colectomy Segmental resection of small bowel Stoma Fistula closure Enterocutaneous fistula closure Entero-enteric fistula closure Other fistula closure Total colostomy with ileostomy Left/right hemicolectomy with stoma Segmental resection of small bowel with stoma Stoma closure Fistulectomy
Perianal Disease	Fistulotomy Fistulectomy Incision and drainage Seton tie

6.6.1.2 Covariates for IBD Relapse

We will control potential confounders in the analysis of IBD relapse. Potential confounders for IBD relapse are summarized at Table 4.

Table 4 Potential Confounders for IBD Relapse

Time of data acquisition	Type of confounder	Confounder
Baseline	Demographic	Age
		Gender
		BMI
		Smoking history
		Alcohol history
	Disease	Disease duration
		Disease location
		Disease behavior (CD only)
		Disease index - CDAI (CD only)
		Disease index - Crohn's disease endoscopic index of severity (CDEIS) (CD only)
		Disease index - Mayo Score (UC only)
		Extra-intestinal manifestation (EIM)
	Use of IBD-related treatment	5-ASAs
		Steroids
		IMMs
		Biologics
	Use of symptom control treatment	Analgesics
		Anti-diarrhea

Time of data acquisition	Type of confounder	Confounder
	Lab	C-reactive protein (CRP)
		Albumin
		Hemoglobin (Hb)
		White blood cell (WBC)
		FCP
	Complication	IBD related surgery - perianal disease
		IBD related surgery - bowel resection
		IBD related ER visit
		IBD related hospitalization
On treatment	Disease	Disease location
		Disease behavior (CD only)
		Disease index - CDAI (CD only)
		Disease index - CDEIS (CD only)
		Disease index - Mayo Score (UC only)
		EIM
	Use of IBD-related treatment	5-ASAs
		Steroids
		IMMs
		Biologics
	Use of symptom control treatment	Analgesics
		Anti-diarrhea
	Lab	CRP
		Albumin
		Hb
		WBC
		FCP
	Complication	IBD related surgery - perianal disease
		IBD related surgery - bowel resection
		IBD related ER visit
		IBD related hospitalization
	Effectiveness onset	Time to steroid free
		Time to mucosal healing
EOT	Demographic	Smoking history
		Alcohol history
	Disease	Disease location
		Disease behavior (CD only)
		Disease index - CDAI (CD only)
		Disease index - CDEIS (CD only)
		Disease index - Mayo Score (UC only)
		EIM

Time of data acquisition	Type of confounder	Confounder
	Treatment	Biologic treatment duration
	Lab	CRP
		Albumin
		Hb
		WBC
		FCP
Off-treatment (from EOT until the occurrence of relapse or the end of study follow-up)	Demographic	Smoking history
		Alcohol history
	Disease	Disease location
		Disease behavior (CD only)
		Disease index - CDAI (CD only)
		Disease index - CDEIS (CD only)
		Disease index - Mayo Score (UC only)
		EIM
	Lab	CRP
		Albumin
		Hb
		WBC
		FCP

Proposed confounders will be analyzed as potential predictors for IBD relapse using regression model that will be defined in SAP.

6.6.1.3 Subgroup Analysis for IBD Relapse

The incidence of relapse and the predictors of relapse assessed in cohort 1 will be further analyzed in the following 3 subgroups.

(1) Patients with catastrophic illness certificate (CIC) for CD or UC

(2) Patients with steroid-free remission or with ≤ 10 mg/day prednisolone equivalent dose at EOT

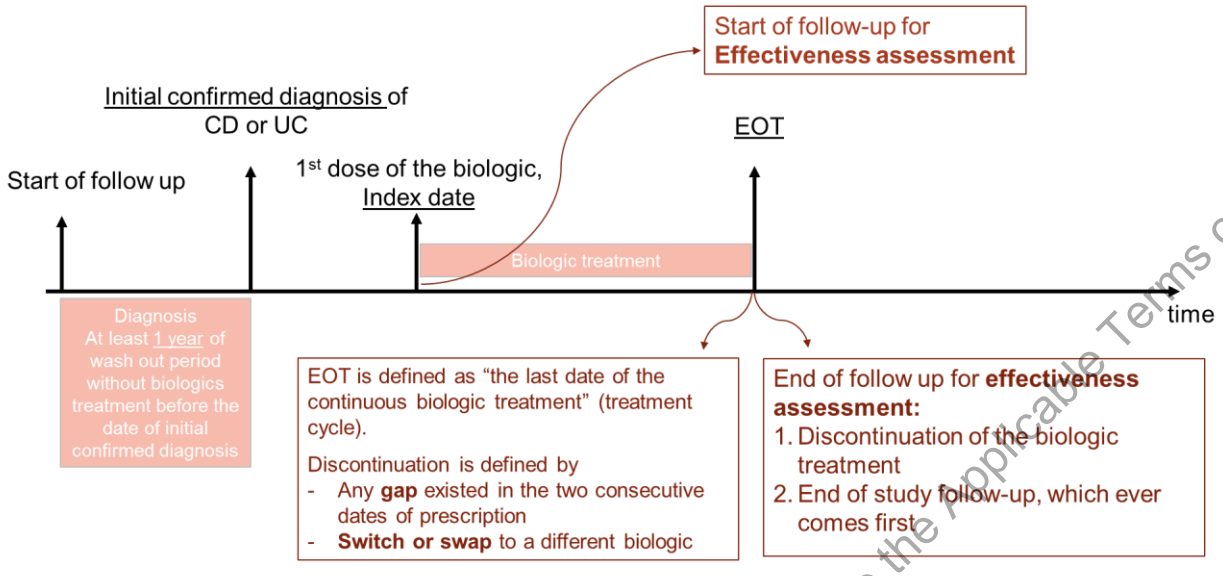
(3) Patients with the first index date later than September 1st 2016

6.6.2 Objective 2: Comparative Effectiveness

6.6.2.1 Biologic Effectiveness

The effectiveness of different biologic treatments will be assessed in cohort 2 every 3 months from the index date until any of the following conditions that occurs first: (1) EOT, or (2) the end of study follow-up (the last date of data collection period). Please see Figure 3 for details.

Figure 3 Diagram for the Time Period for Follow-up in Comparative Effectiveness Analysis



The effectiveness of biologic treatment is defined by any of the following observations during the study period:

(1) Clinical response

(2) Clinical remission

(3) Steroid-free remission

(4) Mucosal healing.

Outcome variables indicating the effectiveness of biologic treatment are summarized in Table 5.

Table 5 Outcome Variables Indicating Biologic Treatment Effectiveness

Indicators of Effectiveness	IBD Type	Outcome Variables for Effectiveness	Time of Assessment
Clinical Response	CD	Disease index reduction (CDAI ≥ 70 points reduction from the index date)	Every 3 months (±1 month) after the index date until the EOT or the end of follow-up, whichever comes first, in each biologic treatment cycle
	UC (to meet any of the incidence in the right)	Disease index reduction (Mayo score ≥ 3 points reduction and ≥ 30% decrease from the index date) with an accompanying rectal bleeding subscore ≥ 1 points reduction or with absolute rectal bleeding subscore ≤ 1	
		Disease index reduction (partial Mayo score ≥ 2 points reduction)	
Clinical Remission	CD	Disease index (CDAI ≤ 150)	
	UC (to meet any of the incidence in the right)	Disease index (Mayo score ≤ 2 and no individual subscore > 1)	
		Disease index (partial Mayo score ≤ 1)	

Indicators of Effectiveness	IBD Type	Outcome Variables for Effectiveness	Time of Assessment
Steroid-free Remission	CD and UC (to meet all of the incidence in the right)	Clinical remission achieved (please refer to above)	
		Absence of steroid treatment (within 1 week before and after the date of potential clinical remission achieved) among patients on steroids at baseline (the index date)	
Mucosal Healing	CD and UC (to meet any of the incidence in the right)	Absence of any symptom finding of ulcer or spontaneous bleeding on endoscopic assessment	
		CDEIS < 4 for CD patients or Mayo endoscopic subscore ≤ 1 for UC patients	
Note: Any of the above variables with the closest date to the assessment date during the follow-up period will be identified as the event of effectiveness.			

6.6.2.2 Covariates for Biologic Effectiveness

Similar as in 6.6.1.2, we will control potential confounders in the analysis of biologic effectiveness. Potential confounders for biologic effectiveness are summarized in Table 6.

Table 6 Potential Confounders for Biologic Effectiveness

Time of Data Acquisition	Type of Confounder	Confounder
Baseline	Demographic	Age
		Gender
		BMI
		Smoking history
		Alcohol history
	Disease	Disease duration
		Disease location
		Disease behavior (CD only)
		Disease index - CDAI (CD only)
		Disease index - CDEIS (CD only)
		Disease index - Mayo Score (UC only)
		EIM
	Use of IBD-related treatment	5-ASAs
		Steroids
		IMMs
		Biologics
	Use of symptom control treatment	Analgesics
		Anti-diarrhea
	Lab	CRP
		Albumin

Time of Data Acquisition	Type of Confounder	Confounder
		Hb
		WBC
		FCP
	Complication	IBD related surgery - perianal disease
		IBD related surgery - bowel resection
		IBD related ER visit
		IBD related hospitalization
On treatment	Disease	Disease location
		Disease behavior (CD only)
		Disease index - CDAI (CD only)
		Disease index - CDEIS (CD only)
		Disease index - Mayo Score (UC only)
		EIM
	IBD-related treatment	5-ASAs
		Steroids
		IMMs
	Use of symptom control treatment	Analgesics
		Anti-diarrhea
	Lab	CRP
		Albumin
		Hb
		WBC
		FCP
	Complication	IBD related surgery - perianal disease
		IBD related surgery - bowel resection
		IBD related ER visit
		IBD related hospitalization

The proposed confounders will be analyzed as potential predictors for biologic effectiveness using regression model that will be defined in SAP.

6.6.2.3 Subgroup Analysis for Biologic Effectiveness

The effectiveness of IBD patients treated with vedolizumab or anti-TNF-α will be analyzed, and the predictors of biologic treatment effectiveness will be further analyzed in the following 2 subgroups.

(1) Patients with CIC for CD or UC

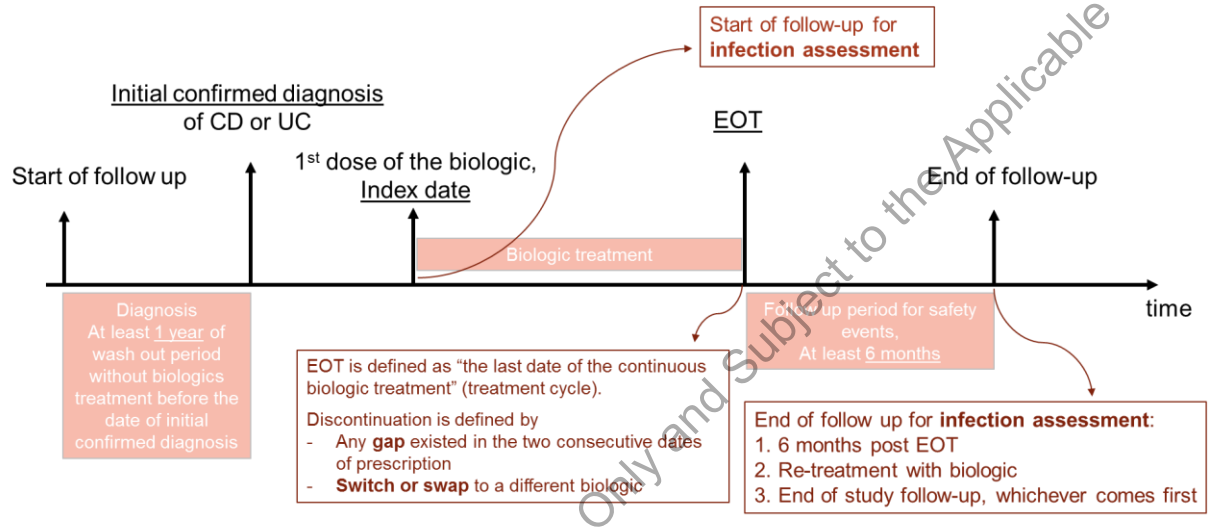
(2) Patients with the first index date later than September 1st 2016

6.6.3 Objective 3: Comparative Safety

6.6.3.1 Biologic Safety

The safety of different biologic treatments will be assessed in cohort 2 from the index date until one of the following conditions that occurs first: (1) 6 months post EOT; (2) re-treatment with biologics, or (3) the end of study follow-up (the last date of data collection period). Please see Figure 4 for details.

Figure 4 Diagram for the Time Period for Follow-up in Comparative Safety Analysis



The safety events possibly related to biologic treatment include:

(1) Opportunistic infections

(2) Hepatic viral infections

(3) GI infections

(4) Respiratory infections

(5) Respiratory failure

(6) Septic shock

The severity of identified safety events will be analyzed by the types of hospital visit (i.e. moderate event in OPD visit record; severe event in INP visit record).

The definition of these safety events is described in Table 7. The identification criteria for opportunistic infection are summarized in Table 8.

Table 7 Outcome Variables Indicating Safety Events

Outcome Variables for Infection Duration: After the index date until 6 months post EOT, re-treatment with biologics, or the end of study follow-up, whichever comes first	
Opportunistic infections	• Candidiasis of bronchi, trachea, esophagus, or lungs • Coccidioidomycosis • Cryptococcosis • Cryptosporidiosis • Cytomegalovirus (CMV) disease • Epstein-Barr virus (EBV) infection • Encephalopathy related infections, including: Herpes simplex virus, varicella-zoster virus, EBV, or CMV • Herpes simplex • Histoplasmosis • Isosporiasis • Kaposi's sarcoma • Mycobacterium avium complex • TB • Pneumocystis carinii pneumonia • Pneumonia, recurrent • Legionella pneumophila • Progressive multifocal leukoencephalopathy (PML) • Salmonella septicaemia, recurrent • Toxoplasmosis of brain • Clostridium difficile infection
Hepatic viral infections	• Hepatitis B reactivation • Hepatitis C reactivation
GI infections	• Viral or bacterial infections that cause gastroenteritis: - Virus: ✓ rotavirus, ✓ small round viruses, ✓ CMV - Bacteria: ✓ *Bacillus cereus*, ✓ *Campylobacter spp.*, ✓ *Clostridium perfringens*, ✓ *Clostridium difficile*, ✓ *Escherichia coli*, ✓ *Salmonella spp.*, ✓ *Shigella*, ✓ *Vibrio cholerae, Vibrio parahaemolyticus*, ✓ *Yersinia enterocolitica*
Respiratory infections	• Respiratory tract infection, including, common cold sinusitis, pharyngitis, epiglottitis, and laryngotracheitis, bronchitis, bronchiolitis, or pneumonia: - Virus: ✓ adenoviruses, ✓ coronaviruses,

Outcome Variables for Infection Duration: After the index date until 6 months post EOT, re-treatment with biologics, or the end of study follow-up, whichever comes first	
	✓ coxsackieviruses, ✓ cytomegalovirus, ✓ EBV, ✓ hantavirus, ✓ herpes simplex virus, ✓ influenza virus, measles virus, ✓ parainfluenza viruses, ✓ respiratory syncytial virus, ✓ rhinoviruses, ✓ varicella-zoster virus - Bacteria: ✓ *Acinetobacter baumannii,* ✓ *Chlamydia spp,* ✓ *Corynebacterium diphtheriae,* ✓ *Coxiella burnetii,* ✓ *Escherichia coli,* ✓ Group A β-hemolytic streptococcus, *Streptococcus pneumoniae,* or *Streptococcus pyogenes,* ✓ *Haemophilus influenzae,* ✓ *Klebsiella pneumoniae,* ✓ *Legionella spp.,* ✓ *Mycoplasma spp.,* ✓ *Mycobacterium tuberculosis,* ✓ *Neisseria gonorrhoeae,* ✓ *Pseudomonas aeruginosa* - Fungus: ✓ *Aspergillus spp.,* ✓ *Blastomyces dermatitidis,* ✓ *Candida albicans,* ✓ *Coccidioides immitis,* ✓ *Filobasidiella [Cryptococcus] neoformans,* ✓ *Histoplasma capsulatum,* ✓ *Paracoccidioides brasiliensis*
Respiratory failure	Identified by ICD diagnosis codes (please refer to Table A1 in the Appendices) and respiratory failure-related procedure codes (please refer to Table A3 in the Appendices)
Septic shock	Identified by ICD diagnosis code, please refer to Table A1 in the Appendices
Note: 1. The bacterium infectious event will be identified by diagnosis code combined with the data of microbial culture if available, the antibiotics prescription record (for Clostridium difficile infection), or confirmation by investigator's medical chart review. 2. The virus infectious event will be identified by the diagnosis code combined with confirmed antivirals prescription record that will be confirmed by investigator's medical chart review. 3. The recurrent infection is defined as two or more infections identified until the end of follow-up after the	

Outcome Variables for Infection Duration: After the index date until 6 months post EOT, re-treatment with biologics, or the end of study follow-up, whichever comes first
index date.

Table 8 Criteria for Identification of Opportunistic Infection

Infection Diagnosis Combined with Microbial Culture	
Bacterial or Fungal Infection	**Strain**
Candidiasis	*Candida albicans* *Candida glabrata* *Candida rugosa* *Candida parapsilosis* *Candida tropicalis* *Candida dubliniensis* *Candida auris* *Candida krusei*
Coccidioidomycosis	*Coccidioides immitis* *Coccidioides posadasii*
Cryptococcosis	*Cryptococcus neoformans* *Cryptococcus gattii*
Cryptosporidiosis	*Cryptosporidium*
Histoplasmosis	*Histoplasma capsulatum*
Isosporiasis	*Isospora belli* (*Cystoisospora belli*)
Legionella pneumophila	*Legionella pneumophila*
Mycobacterium avium complex;	*Mycobacterium intracellulare* *Mycobacterium avium*
Pneumocystis carinii pneumonia	*Pneumocystis carinii* (*Pneumocystis jirovecii*)
Salmonella septicaemia	*Salmonella bongori* *Salmonella enterica*
Toxoplasmosis	*Toxoplasma gondii*
TB	*Mycobacterium tuberculosis*
Pneumonia, recurrent	- Virus: ✓ *adenoviruses,* ✓ *cytomegalovirus,* ✓ *hantavirus,* ✓ *herpes simplex virus,* ✓ *influenza viruses,* ✓ *measles virus (measles morbillivirus),* ✓ *parainfluenza viruses,* ✓ *respiratory syncytial virus,* ✓ *varicella-zoster virus* - Bacteria : ✓ *Chlamydia spp.,* ✓ *Coxiella burnetii,* ✓ *Escherichia coli,* ✓ *Haemophilus influenzae,*

Infection Diagnosis Combined with Microbial Culture	
Bacterial or Fungal Infection	**Strain**
	✓ *Klebsiella pneumoniae,* ✓ *Legionella spp.,* ✓ *Mycoplasma spp.,* ✓ *Mycobacterium tuberculosis,* ✓ *Pseudomonas aeruginosa,* ✓ *Staphylococcus aureus, Streptococcus pneumoniae*, or *Streptococcus pyogene* - Fungus: ✓ *Aspergillus spp.,* ✓ *Blastomyces dermatitidis,* ✓ *Candida albicans,* ✓ *Coccidioides immitis,* ✓ *Filobasidiella [Cryptococcus] neoformans,* ✓ *Histoplasma capsulatum,* ✓ *Paracoccidioides brasiliensis*
Infection Diagnosis Combined with Treatment	
Infection	**Treatment**
CMV disease	ganciclovir or valganciclovir
EBV infection	ganciclovir or valganciclovir
Varicella-zoster virus	acyclovir, famciclovir, or valacyclovir
Herpes simplex	acyclovir, famciclovir, or valacyclovir
Kaposi's sarcoma	doxorubicine or daunorubicin
Clostridium difficile infection	metronidazole, vancomycin, or fidaxomicin

6.6.3.2 Covariates for Safety

Same as in 6.6.2.2, the same set of potential confounders will be controlled in the analysis of biologic safety that will be defined in SAP.

6.6.3.3 Subgroup Analysis for Safety

The safety events assessed in cohort 2 will be further analyzed in the following 2 subgroups.

(1) Patients with CIC for CD or UC

(2) Patients with the first index date later than September 1st, 2016

6.7 Data Validation and Analysis

6.7.1 Data Validation

6.7.1.1 General Validation Methods

The variables will be validated by comparing with the clinical records in different EMR datasets. Details of performing data validation will be provided in the data validation plan.

- The date of diagnosis record will be validated by comparing with the date of record in HCRU dataset.
- The HCRU record will be validated by cross-check with the subsequent IBD-related medication treatment or surgery procedure record.
- The prescription record for biologic treatments will be validated by only collecting the biologics prescription order issued by physician/specialist in gastroenterology, colon rectal surgery, or rheumatology.

The date of lab record will not be validated because the lab data are regarded as authentic source in EMR database.

6.7.1.2 Objective 1: Relapse Events

The identified relapse events will be validated using the following criteria.

Validation Criteria

- Re-treatment with biologics and steroid use:

  The prescription record of biologic re-treatment is validated by limiting the biologics prescription from prescribing specialist in gastroenterology, colon rectal surgery, or rheumatology with the physician code of prescribing physician. If the identified prescription record is prescribed by physician/specialist in gastroenterology, colon rectal surgery, or rheumatology, this re-treatment or steroid use is validated as the relapse event.

- IBD-related hospitalization/ER visits/ surgery:

  The date of identified ER visit or hospitalization record will be cross checked with the date of IBD-related surgery or intervention record by medical chart review. If the date of IBD-related surgery or intervention record is within the subsequent 2 weeks of identified HCRU record, such identified HCRU record is validated as the IBD relapse event.

- Increase in disease index:

  The identified disease date with flare-up will be cross checked with the prescription record of analgesics or anti-diarrhea. If the interval between the date of identified disease flare-up and the date of analgesics or anti-diarrhea prescription is within 2-week, this flare-up event is validated as the relapse event.

6.7.1.3 Objective 2: Biologic Effectiveness

The biologic effectiveness will be validated by using the following criteria.

Validation Criteria

(1) Clinical response

The date with clinical response will be cross checked with the date of anti-diarrheal prescription record and the EIMs diagnosis record or confirmed by medical chart review by investigator or his/her designated site personnel.

For CD patients:

- If any of the below events and the clinical response are observed within 2-week, the observed clinical response is validated.
  - The reduced dose or the absence of anti-diarrheals prescription record
  - Absence of EIMs diagnosis record
  - Confirmed by investigator's medical chart review

For UC patients:

- If the reduced dose or the absence of anti-diarrheals prescription record and the clinical response are observed within 2-week, the clinical response event is validated.

(2) Clinical remission

The event of clinical remission will be validated by cross check with the date of anti-diarrheals or steroid prescription records, the EIMs or GI complication diagnosis records, or the IBD-related surgery record, or confirmed by investigator's medical chart review. If any of the below events and the clinical remission are observed within subsequent 2-week, the clinical remission event is validated.

- The reduced dose or the absence of anti-diarrheals prescription record
- The tapering dose of steroid use
- The absence of EIMs diagnosis record
- The absence of IBD-related surgery record or GI complication record

Alternatively, the clinical remission can be validated by investigator's medical chart review.

(3) Steroid-free remission

The event of steroid-free remission will be validated using the same method (except for the tapering dose of steroid use) as above validation method for clinical remission.

(4) Mucosal healing

The achievement of mucosal healing will be validated by cross-check with the date of GI bleeding diagnosis records, or confirmed by investigator's medical chart review. If the GI bleeding diagnosis record is not observed within subsequent 2-week after the identified mucosal healing event, then this healing event is validated.

Alternatively, the achievement of mucosal healing can be validated by investigator's medical chart review.

6.7.1.4 Objective 3: Biologic Safety Events

The identified infectious event will not be validated because the identification criteria for the infectious event are using diagnosis records combined with microbial test results or prescription records, which are regarded as the authentic source in the EMR database.

6.7.2 General Consideration for Data Analysis

All demographic covariates will be summarized by the types of disease (CD or UC) and by the types of biologics (anti-TNF-α or anti-$\alpha_4\beta_7$ integrin) descriptively.

Categorical variables will be presented as counts and percentage and will be analyzed by Chi-square test.

Continuous variables will be presented as number of observation (n), mean and median, standard deviation, minimum and maximum and will be analyzed by Student's t-test.

The predictors will be analyzed using time dependent Cox regression model. All statistical significance will be set at p <0.05 unless otherwise specified.

Handling of missing data:

(1) Random missing: The multiple imputation (MI) method will be adopted for handling the missing data.

(2) If the data of interest is not available from EMR database in one of the medical centers, subgroup analysis will be performed by the patients with available data in other medical centers.

Data censoring rule: The data of the individual IBD patient will be censored at the end of follow-up (the last date of data collection period) when no outcome event can be identified after receiving biologics.

6.7.3 Data Analysis

6.7.3.1 Objective 1: Predictors of Relapse post Biologics Discontinuation

The time-to-IBD relapse, percentage of IBD relapse, and predictors of IBD relapse will be analyzed in cohort 1.

6.7.3.1.1 Analysis for Relapse

The percentage of patients with IBD relapse will be determined and the result will be presented by the number of biologic treatment cycles (i.e. total number of treatment cycles in

individual patient's biologic treatment history and the total number of treatment cycles in the overall population).

The time-to-IBD relapse is defined as the time interval from EOT to the first IBD relapse. The time-to-IBD relapse will be analyzed using Kaplan–Meier method and the time to event curve will be presented by Kaplan–Meier plot.

The total number of patient, the total IBD relapse event number, and the median of IBD relapse time will be tabulated.

6.7.3.1.2Predictor of IBD Relapse

To identify the potential bias in baseline/demographic variables between IBD patients (i.e. CD versus UC), univariate comparative analysis using T-test or Chi-square test depending on the types of variables will be performed in pair to identify the bias prior to predictor analyses. The variables with α-values < 0.1 using the above univariate analysis will be considered as significant and may be further analyzed using the multivariate analysis.

The potential confounders that may predict IBD relapse (summarized in Table 4) will be included in the multivariate analysis. The predictors of IBD relapse will be analyzed using time dependent Cox regression models by the time of data acquisition: (1) the time period from baseline to EOT (inclusive) and (2) off-treatment period (from EOT until the occurrence of relapse or the end of study follow-up).

6.7.3.2 Objective 2: Comparative Effectiveness

The effectiveness outcomes will be analyzed in cohort 2 and presented by each treatment cycle between different biologic treatments.

To minimize the impact of potential bias from the baseline/demographic variables, baseline matching will be performed using propensity score matching by each treatment cycle and different types of biologic treatments before performing the comparative analysis for effectiveness outcome.

6.7.3.2.1 Analysis for Biologics Effectiveness

The analysis will be presented by the types of biologics (anti-TNF-α or anti-$\alpha_4\beta_7$ integrin). The incidence rates of IBD patients with clinical response, clinical remission, steroid-free remission, and mucosal healing will be analyzed every 3 months (±1 month) after baseline matching. The difference in effectiveness between IBD patients receiving different types of biologic treatment will be compared using Chi-square test.

6.7.3.2.2 Predictors of Effectiveness

The potential confounders that may predict biologics effectiveness (summarized in Table 6) will be included in the multivariate analysis. The predictors of effectiveness outcome will be analyzed using time dependent Cox regression models after baseline matching.

6.7.3.3 Objective 3: Comparative Safety

The safety outcomes will be analyzed in cohort 2.

The potential bias in baseline/demographic variables that may interfere with the comparative safety outcome analysis will be corrected by baseline matching as described in 6.7.3.2.

6.7.3.3.1 Analysis for Safety

The analysis of safety outcome will be presented by the types of biologics (anti-TNF-α or anti-$\alpha_4\beta_7$ integrin), the type of identified event (i.e. opportunistic infections, hepatic viral infections, GI infections, respiratory infections, respiratory failure, or septic shock), and the types of hospital visit (OPD visit or hospitalization).

The incidence rates of IBD patients with identified safety events during the follow-up period will be analyzed after baseline matching. The results will be presented as number of events per patient-time.

6.8 Limitations of Study Methods

This study will collect clinical variables from the EMR database in selected medical centers for analyzing the clinical outcomes and safety of biologics treatments in IBD patients anonymously. All patients' data will be analyzed by the incidence of clinical outcomes based on the assumptions according to the clinical practice guideline or the reimbursement rule of NHIA. Because all the data will be collected retrospectively and through multiple databases, biases may be generated during the data collection process.

Compared to the prospective study, the bias in the retrospective study may be generated due to the deficiency of validation by periodic monitoring or missing data. The authenticity of the collected variables may also be an issue. Thus, to resolve the above potential biases in this study, outcome variables will be validated by data validation plan (DVP) through data cross-comparison between different datasets. In addition, some crucial data (e.g. endoscope examination report, OPD SOAP, etc.) may not be available due to the unstructured data format in the EMR database. Also, the essential unstructured clinical information will be confirmed by investigator's medical chart review on site per local IEC / IRB approval and data imputation will be performed on randomly missing data by using the MI method. If

certain clinical data are not available from the EMR database in one of the medical centers, subgroup analysis may be performed accordingly. Moreover, the data format or organization method may vary between different medical centers. Therefore, the collected data from different medical centers will be integrated through the data mining process to assure standardized data formats are presented before performing data analysis.

7 Safety Reporting

7.1Adverse Event

An adverse event (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

Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing 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
- An 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.)

Adverse Drug Reactions

An adverse drug reaction (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.

Product Quality Issues

A Product Quality Issue (PQI) 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.

Special Situation Reports

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
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product

A SSR should be reported even if there is no associated AE.

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

- SAEs, AEs, ADRs, SSRs and PQIs in the healthcare record or other applicable source data that are part of the study objectives or endpoints.

  Events/issues which are part of the study objectives or endpoints will be systematically identified and collected from healthcare 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 Pharmacovigilance.
- SAEs, AEs, SSRs and PQIs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints.

  Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

8 Data Quality Control and Assurance

8.1 Quality Control

To assure the quality of data collection, including the data format standardization and the accuracy of collected data, data mining process and data validation plan will be developed before data analysis. The data/clinical variables collected from different medical centers will be unified in format before data pooling and analyses. Data imputation will be performed for random missing data by adopting MI method.

Data quality will be assured by general validation method. The clinical variables will be validated by comparing with the clinical records in different EMR datasets or by investigator's medical chart review with permit from local IRB/IEC.

8.2 Audit from Quality Assurance Unit

Not applicable.

8.3 Inspection by IRB/IEC or Competent Authority

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

8.4 Data Management

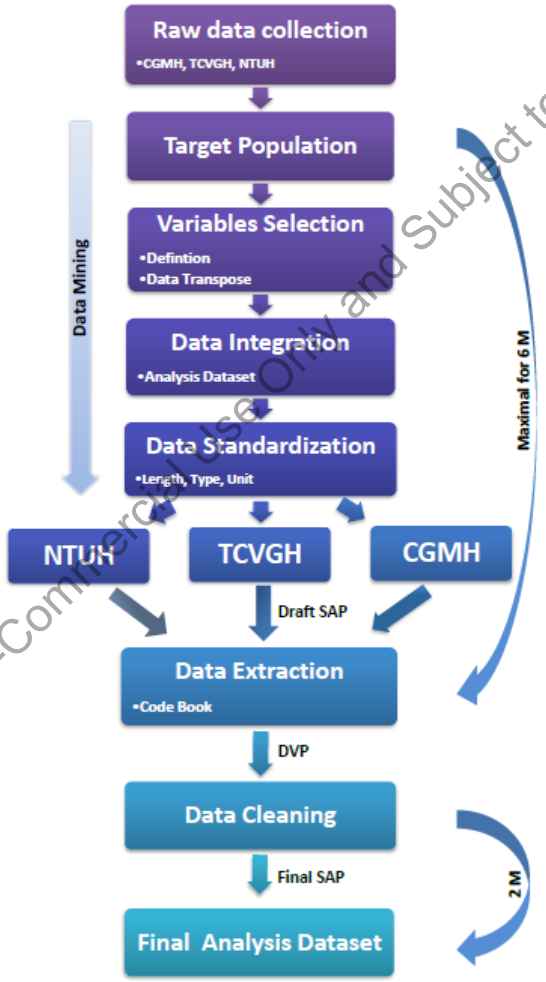
All data collected from the EMR database or obtained from internal medical chart review if with local IEC/IRB approval will be exported anonymously and with encryption manner to the appointed CRO for data analysis. During the study, the data will be stored, archived, backed up in the appointed CRO according to the related Standard Operation Procedure (SOP)

to ensure data confidentiality and safety. If the data corruption occurred, the data will be returned to the latest backup data by the appointed CRO according to the SOP. All the processes will only be accessed by the study related personnel with Takeda's written approval. After the study conducting, all the analytical dataset will be returned from CRO to Takeda Pharmaceuticals Taiwan, Ltd.

8.4.1 Data Collection Tools and Flow

The data collection process will be conducted according to the flow chart as shown in below figure.

Figure 5 Flow Chart of Data Management



Note: The CMUH-clinical research database is not depicted in the flow chart because the data from CMUH may be collected, integrated, and analyzed by CMUH Big Data Center per local policy and in compliance with the study protocol and SAP. The results may be provided to Takeda Pharmaceuticals Taiwan, Ltd.

9 Study Sample Size

According to the epidemiological information and field insights, approximately 724 IBD patients treated with biologics during February 2008 to March 2020 will be included in this study.

10 Reports

A non-interventional study report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalized.

11 Publication, Disclosure, and Clinical Trial Registration Policy

Takeda aims to have the results of this study published and has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

12 Archiving of Study Documentation

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

- Written agreement between the Takeda Pharmaceuticals Taiwan, Ltd. or Takeda's CRO and the four medical centers.
- The study protocol and any amendments
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible
- Written IEC / IRB approval / vote according to local regulations
- The progress reports

After final database lock the Site Responsible should store study documentation as required by any local regulations and/or hospital requirement.

13 References

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