Title: Safety and Effectiveness of Vedolizumab IV in Real World Clinical Practice in Taiwan: A Registry-Based Study

Protocol Approve Date: 7 September 2018

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NON-INTERVENTIONAL STUDY

PROTOCOL

Safety and Effectiveness of Vedolizumab IV in Real World Clinical Practice in Taiwan: A Registry-Based Study

Study Number: Vedolizumab-5026

Version Number: 2

Version Date: 7 September 2018

Signature Page

Safety and Effectiveness of Vedolizumab in Real World Clinical Practice in Taiwan: A Registry-Based Study

Vedolizumab-5026 Protocol Version 2, 7 September 2018

Sponsor Signature & Date

PPD

Investigator Signature & Date

PPD

1.0 TABLE OF CONTENTS

LIST OF ANNEXES

2.0 LIST OF ABBREVIATIONS

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
1Q	first quarter
2Q	second quater
3Q	third quarter
4Q	fourth quarter
AE	adverse event
CD	Crohn's disease
CDEIS	Crohn's Disease Endoscopic Index of Severity
C difficile	*Clostridium difficile*
CI	confidence interval
CMV	cytomegalovirus
DILI	drug induced liver injury
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GI	gastrointestinal
HLT	high-level term
IBD	inflammatory bowel disease
IRB	institutional review board
IV	intravenous
JCV	John Cunningham virus
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
PML	progressive multifocal leukoencephalopathy
SAE	serious adverse event
SAP	statistical analysis plan
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SMQ	standardized MedDRA queries
SOC	system organ class
TB	tuberculosis
TDC Europe	Takeda Development Centre Europe Ltd.
TFDA	Taiwan Food and Drug Administration
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
TSIBD	Taiwan Society of Inflammatory Bowel Disease
UC	ulcerative colitis

3.0 MARKETING AUTHORIZATION HOLDER / SPONSOR

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4.0 RESPONSIBLE PARTIES

PPD

5.0 ABSTRACT

Title

Safety and Effectiveness of Vedolizumab IV in Real World Clinical Practice in Taiwan: A Registry-Based Study

Author: PPD

Rationale and Background

Ulcerative colitis (UC) is a chronic, relapsing, remitting inflammatory disease of the colonic mucosa and submucosa. Crohn's disease (CD) is a chronic, relapsing, remitting inflammatory disease that may involve any portion of the gastrointestinal (GI) tract, from mouth to anus, in a transmural fashion from mucosa to serosa. In Taiwan, prevalence of UC and CD from 1998 through 2008 was relatively low at 8/100,000 persons and 2/100,000 persons, respectively, but increasing. In North America, the highest annual prevalence for UC and CD is 249/100,000 persons and 319/100,000 persons respectively. In Europe, the highest annual reported prevalence for UC and CD is 505/100,000 persons and 322/100,000 persons, respectively.

UC and CD are lifelong diseases that cause considerable morbidity in a relatively young patient population. Many patients experience refractory diarrhea and rectal bleeding and require frequent hospitalizations, enteral nutrition, and surgical procedures. Specifically, patients with UC often will have colectomies, while many patients with CD will regularly experience fistulae and GI abscesses and have serial bowel resections. These patients are often unable to function normally in society by virtue of having uncontrolled disease.

Vedolizumab is a gut-selective humanized immunoglobulin G1 monoclonal antibody (mAb) that antagonizes the adhesion of human lymphocyte integrin α4β7 to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), and results in reduced trafficking of leukocytes into GI mucosa and gut-associated lymphoid tissue. By virtue of its gut-selective mechanism of action, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with other current treatments for UC and CD.

This postmarketing study is being undertaken at the request of the Taiwan Food and Drug Administration (TFDA) to provide real-world data on the safety and effectiveness of vedolizumab intravenous (IV) in Taiwanese patients.

Research Question and Objectives

- To assess the safety of vedolizumab IV in patients with UC and CD in Taiwan.
- To assess the effectiveness of vedolizumab IV in patients with UC and CD in Taiwan.

Study Design

This is a prospective longitudinal cohort study that will analyze data from the TSIBD Prospective Inflammatory Bowel Disease (IBD) Registry (hereinafter referred to as the Registry).

The Registry is a national registry of IBD patients that systematically collects longitudinal information on the clinical management, medication use, and clinical outcomes of patients with IBD from participating IBD clinics.

Study Population

The study population is all UC and CD patients in the Registry who receive at least 1 dose of vedolizumab IV during a 2.75-year period (ie, from August 2017 through 17 May 2020).

Study Size

To date, there has been relatively little use of biologic agents for UC and CD in Taiwan.

At least 90 patients are expected to be treated with vedolizumab IV from August 2017 through 17 May 2020. This forecast is dependent on multiple factors, including approval for use in both UC and CD patients with inadequate response, lost response, or intolerance to an immunomodulator or tumor necrosis factor (TNF) blocker, national health insurance reimbursement for the approved uses, and uptake by gastroenterologists.

Data Collection and Follow-Up

The Registry collects baseline information on disease type, locations, activity and severity, previous IBD medications, previous surgery, IBD risk factors, current medications, and blood laboratory values. The Registry is prospectively updated every 3 months by participating IBD clinics with new information on participant's disease type, locations, and severity; in addition, information is recorded on changes to medications, IBD surgery or hospitalizations, and adverse events (AEs).

Variables

The following data will be abstracted from the Registry:

<u>Demographics and risk factors</u>

- Demographic variables: year of birth, sex, date of joining registry, and body mass index.
- Age at UC/CD onset, age at diagnosis, and age at receipt of Catastrophic Illness Card.
- IBD risk factors, including smoking and family history.

<u>Clinical</u>

- Inflammatory (IBD) clinical history and type.
- Disease locations.
- Extra-intestinal manifestations.
- Harvey-Bradshaw Index scores (CD patients only).
- Crohn's Disease Activity Index scores (CD patients only).
- Crohn's Disease Endoscopic Index of Severity (if endoscopy is performed) (CD patients only).

- Simple Clinical Colitis Activity Index (UC patients only).
- Partial or full Mayo scores (UC patients only).
- Biopsy findings (if performed).
- Clinical laboratory values, including fecal calprotectin, C-reactive protein, erythrocyte sedimentation rate, hemoglobin, albumin, platelet count, and *Clostridium difficile* (*C difficile*) (if measured).

IBD medication

- IBD medication history prior to start of vedolizumab IV.
- Start date of vedolizumab IV.
- Concurrent use of other IBD medications: other biologic agents, immunomodulators, 5-aminosalicylate (5-ASA), corticosteroids, antibiotics, and opioid pain medications.
- Date and reasons for vedolizumab IV discontinuation, and type of medication switch.
- Start/stop date of steroid use following initiation of vedolizumab IV.

Healthcare resource use

- IBD surgery.
- IBD hospitalizations.
- IBD emergency room visits.
- Frequency of endoscopy and other IBD procedures.

Safety

- Serious infections.
- Opportunistic infections, including but not limited to:
  - Tuberculosis (TB) infection or reactivation, including extrapulmonary TB.
  - Progressive multifocal leukoencephalopathy (PML).
- Hepatitis viral infection.
- GI infections.
- Respiratory infections.
- Malignancies.
- Infusion-related reactions and hypersensitivity.
- Hepatic injury.
- Serious adverse events (SAEs).

- Pregnancy outcomes.

Patient-reported quality of life assessment

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ) scores.

Data Analyses

The baseline characteristics of patients at the time of initiating vedolizumab IV will be described, including demographic variables, disease characteristics, prior IBD surgery and hospitalizations, prior and concurrent IBD medications, disease risk factors, and year of treatment initiation.

Safety

The safety analyses will present number of patients with an event, person-time at risk, and crude incidence rates. Analyses of incidence rates and time to events will be presented for all patients and separately for UC and CD patients.

Effectiveness

Effectiveness analyses will present change from Baseline in UC and CD disease activity scores, incidence of and time to IBD surgery or hospitalization, steroid tapering, and time to vedolizumab IV treatment change. Effectiveness will also be assessed with respect to change from Baseline in patient's health-related quality-of-life scores.

6.0 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
01	11 July 2017	7.0 Study milestones; 13.0 Plans for disseminating and communicating study results	Amendment, from 5 to 2.75 year study period.	Final report to be submitted to TFDA before license extension application in 2021.
02	7 Sep 2018	Signature page; 4.0 Responsible parties;	Change of department name for PPD	Department name update.
02	7 Sep 2018	5.0 Abstract; 10.5 Study size; 10.9.1 Limited use of vedolizumab	Reduced expected number of enrolled study subject from 350 to 90.	Factors affecting data collection and other operations related issues should be considered.
02	7 Sep 2018	10.2.3 The Registry; 10.9.2 Coverage of the Registry	Removed description related to the coverage rate of the Registry	The coverage rate is dynamic.
02	7 Sep 2018	10.2.2 Inclusion and Exclusion Criteria	Removed requirement for Registry enrolment prior to initiating vedolizumab IV due to individual study site approval at participating hospitals.	Patients may be enrolled into the Registry after the time of first dose of vedolizumab IV because not every site is already initiated at the time of patient's first injection.

7.0 MILESTONES

Study Milestone	Planned date	Actual date	Comments
Product license issue by TFDA	-	17-Nov-2016	
Product availability in Taiwan	Aug-2017	Aug-2017	
First patient in	Aug-2017	Aug-2017	
Protocol amendment	Aug-2018	Aug-2018	Removed requirement for Registry enrolment requirement
Data lock for final analysis	17-May-2020		
Final study report	17-Nov-2020		
Receive & submit reference approval letter for final study report to TFDA	17-May-2021		
Expiration date of Entyvio licenses	17-Nov-2021		

8.0 RATIONALE AND BACKGROUND

8.1 Background

8.1.1 The Inflammatory Bowel Diseases: Ulcerative Colitis and Crohn's Disease

UC is a chronic, relapsing, remitting inflammatory disease of the colonic mucosa and submucosa. CD is a chronic, relapsing, remitting inflammatory disease that may involve any portion of the gastrointestinal (GI) tract, from mouth to anus, in a transmural fashion from mucosa to serosa. In Taiwan, prevalence of UC and CD from 1998 through 2008 was relatively low at 8/100,000 persons and 2/100,000 persons, respectively, but increasing [1]. In North America, the highest annual prevalence for UC and CD is 249/100,000 persons and 319/100,000 persons respectively [2]. In Europe, the highest annual reported prevalence for UC and CD is 505/100,000 persons and 322/100,000 persons, respectively [2].

UC and CD are lifelong diseases that cause considerable morbidity in a relatively young patient population. Many patients experience refractory diarrhea and rectal bleeding and require frequent hospitalizations, enteral nutrition, and surgical procedures. Specifically, patients with UC often will have colectomies, while many patients with CD will regularly experience fistulae and GI abscesses and have serial bowel resections. These patients are often unable to function normally in society by virtue of having uncontrolled disease.

Current treatments have been effective for many patients with UC and CD but have numerous limitations for patients with moderate to severe disease. The limitations of current therapies for UC and CD indicate that there is a significant unmet medical need for safer and more effective therapies. Pharmacologic treatments for UC and CD include 5-ASAs, corticosteroids, and immunomodulators (thiopurines such as azathioprine and 6-mercaptopurine [6-MP], along with methotrexate). The biologic agent adalimumab (HUMIRA) is a monoclonal antibody (mAb) directed against tumor necrosis factor alpha (TNF-α) and has been approved for UC and CD in Taiwan, and other biologic agents and biosimilars may be approved in the future in Taiwan for UC and CD. These agents have substantially improved the care of patients with UC or CD in other countries, decreasing the need for hospitalizations and surgeries [3]. Although TNF-α antagonists represent an important addition to the pharmacologic armamentarium, they are effective in only a subset of patients, with roughly two-thirds of patients in controlled trials failing treatment at the end of the first year of therapy [4-6].

8.1.2 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 or CD.

Vedolizumab IV is approved in Taiwan for use in both UC and CD patients with inadequate response, lost response, or who were intolerant to an immunomodulator or TNF blocker. Detailed information regarding the safety and efficacy of vedolizumab IV is found in the most current version of the Taiwan prescribing information.

8.2 Study Rationale

This post marketing study is being undertaken at the request of the TFDA to provide real-world data on the safety and effectiveness of vedolizumab IV in Taiwanese patients.

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

9.0 RESEARCH QUESTION AND OBJECTIVES

9.1 Objectives

- To assess the safety of vedolizumab IV in patients with UC and CD in Taiwan.
- To assess the effectiveness of vedolizumab IV in patients with UC and CD in Taiwan.

10.0 RESEARCH METHODS

10.1 Study Design

This is a prospective longitudinal cohort study that will analyze data from the TSIBD Prospective IBD Registry (hereinafter referred to as the Registry).

The Registry is a national registry of IBD patients that systematically collects longitudinal information on the clinical management, medication use, adverse events, and clinical outcomes of patients with IBD at participating IBD clinics across Taiwan.

10.2 Setting

10.2.1 Study Population

The study population is all UC and CD patients in the Registry who receive at least 1 dose of vedolizumab IV during a 2.75-year period (ie, from August 2017 through 17 May 2020).

10.2.2 Inclusion and Exclusion Criteria

The following inclusion criteria will be used to identify patients treated with vedolizumab IV in the Registry:

- Patient initiated vedolizumab IV treatment from August 2017 through 17 May 2020.
- Patient was enrolled in the Registry.
- Patient was at least 18 years of age at time of initiating vedolizumab IV.
- IBD clinic and local institutional review board (IRB) (where required) agrees to use of their data from the Registry in this analysis (see Section 11.3).

The following exclusion criteria will be applied:

- Patient was enrolled in an IBD clinical trial at time of using vedolizumab IV.

10.2.3 The Registry

The Registry was established by the TSIBD to provide research quality data on the clinical management and clinical outcomes of patients with IBD in Taiwan. The Registry includes patients on conventional therapy and patients on biologic agents.

The Registry is observational. All decisions on clinical management and drug therapy are independent of the patient's participation in the Registry, and provided as part of routine clinical care. The Registry asks participating gastroenterologists to provide information on the routine clinical management of their IBD patients, and does not require any additional tests or procedures be undertaken for the Registry.

10.3 Variables

The data in the following subsections will be abstracted from the Registry.

10.3.1 Demographics and Risk Factors

- Year of birth.
- Sex.
- Age at UC/CD onset.
- Age at UC/CD diagnosis.
- Age at receipt of Catastrophic Illness Card.
- Date of joining Registry.
- Body mass index.
- IBD risk factors, including smoking and family history.

10.3.2 Clinical

- IBD clinical history.
- IBD type (UC or CD).
- Disease locations.
- Extra intestinal manifestations.
- Harvey-Bradshaw Index (CD patients only) (Annex 1).
- Crohn's Disease Activity Index (CD patients only) [7] (Annex 2).
- Crohn's Disease Endoscopic Index of Severity, if endoscopy is performed (CD patients only) (Annex 3).
- Simple Clinical Colitis Activity Index (UC patients only) (Annex 4).
- Partial or full Mayo score (UC patients only) [8] (Annex 5).
- Biopsy findings (if performed).
- Clinical laboratory values, including fecal calprotectin, C-reactive protein, erythrocyte sedimentation rate, hemoglobin, albumin, platelet count, and *C difficile* (if measured).

10.3.3 IBD Medication

- IBD medication history prior to start of vedolizumab IV.
- Start date of vedolizumab IV.
- Concurrent use of other IBD medications at time of starting vedolizumab IV:
  - Other biologic agents.
  - Immunomodulators.

- 5-ASA.
- Corticosteroids.
- Antibiotics.
- Opioid pain medications.
- Others

- Date and reasons for vedolizumab IV discontinuation, and type of medication switch.
- Dates start/stop steroids after start of vedolizumab IV.

10.3.4 Healthcare Resource Use

- IBD surgery.
- IBD hospitalizations.
- IBD emergency room visits.
- Endoscopy and other IBD procedures.

10.3.5 AEs

All AEs occurring on or after start of vedolizumab IV therapy will be abstracted and categorized as defined below.

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

10.3.5.1 Serious Infections

Serious infection is defined as any event coded to MedDRA terms within the MedDRA system organ class (SOC) of Infections and Infestations that meets the seriousness definition (Section 12.1.2).

10.3.5.2 Opportunistic Infection

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, oesophagitis, 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 Karposi 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 extra pulmonary 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 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 [9]. Possible cases of PML not meeting these criteria shall be included in the study report but not in the main analyses.
- *Salmonella septicaemia*, recurrent. This is defined as events coded to the MedDRA terms Salmonella sepsis or Salmonella septicaemia.
- *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.

10.3.5.3 Hepatic viral infection

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, subanalyses of specific types of infection (hepatitis B and hepatitis C) will be undertaken.

10.3.5.4 Gastrointestinal infections

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

10.3.5.5 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.

10.3.5.6 Malignancies

This is defined as all malignant and benign neoplasms within the MedDRA Malignant tumors substandardized MedDRA queries (SMQ). This SMQ includes all malignancies and carcinomas in situ.

10.3.5.7 Infusion-Related Reactions and Hypersensitivity

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

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

10.3.5.8 Hepatic Injury

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

- Cholestasis and jaundice of hepatic origin SMQ.
- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ.
- Hepatitis noninfectious SMQ.
- Liver related investigations signs and symptoms (Narrow SMQ).

- Liver infections SMQ.

Abnormal liver function is defined as levels >2 × Upper Limit of Normal.

10.3.5.9 SAEs

All adverse events that meet the seriousness criteria (Section 12.1.2).

10.3.5.10 Pregnancy Outcome

Pregnancy outcomes including spontaneous abortion, induced abortion, still birth, live birth, and any adverse birth outcomes.

10.3.6 Patient-reported quality of life assessment

SIBDQ scores (Annex 6).

10.4 Data Sources

The data source for the analysis is the data contained in the Registry.

10.5 Study Size

To date, there has been relatively little use of biologic agents for IBD in Taiwan.

At least 90 patients are expected to be treated with vedolizumab IV from August 2017 through 17 May 2020 and included in the analysis. This forecast is dependent on multiple factors, including approval for use in both UC and CD patients with inadequate response, lost response or were intolerant to an immunomodulator or TNF blocker, insurance reimbursement for the approved uses, and uptake of this new biologic agent by gastroenterologists. In addition, it assumes the TSIBD successfully expands the coverage of its Registry to include as many as possible of the vedolizumab treated patients. Finally, it is also assumed that all IBD centers agree to their data in the Registry being included in the study, as required by the governance of the Registry.

10.6 Data Management

An anonymized dataset (with all patient and clinic identifier removed) will be provided by the TSIBD for the study analyses. The data set will be held on a secure server with password protected access limited to the study researchers. The registry contains verbatim (as reported) text on adverse events. Each adverse event term will be coded using the MedDRA dictionary version in effect at time of data lock.

10.7 Data Analysis

All planned analyses will be documented in the statistical analysis plan (SAP). The analytical dataset will be comprised of all patients in the Registry who receive at least 1 dose of vedolizumab IV from August 2017 through 17 May 2020. Longitudinal data on each patient will

be abstracted from the registry and form the analytical dataset. There will not be imputation of missing data.

Baseline will be defined as date of first vedolizumab IV dose.

10.7.1 Patient Follow-up

A patient's follow-up for the vedolizumab IV analysis will be censored at the earliest of any of the following:

- Patient lost to follow-up.
- Patient withdrawal from the Registry.
- Patient death.
- End of study period.

10.7.2 Baseline Characteristics and Drug Utilization Pattern

The baseline characteristics of patients at time of initiating vedolizumab IV will be described in relation to demographic variables, disease characteristics, prior IBD surgery and hospitalizations, prior and concurrent IBD medications, disease risk factors and year of treatment initiation. Longitudinal data will be analyzed to describe vedolizumab IV discontinuation, reasons for discontinuation, and switching patterns. Covariates will have a 'missing' category for patients with missing data, and will be included in the analyses. Descriptive statistics will include the number of observations (n), mean, SD, median, minimum, and maximum for continuous variables, and frequency (n and percent) for categorical variables.

10.7.3 Safety Analyses

For each safety endpoint, a descriptive analysis of event characteristics will be presented together with a summary of distribution by demographic and other baseline characteristics. Data will be presented as number of patients with an event, person-years at risk, and a crude and age-sex-standardized incidence rate with 95% confidence intervals (CIs) for all patients, and separately for UC and CD patients. Time to event from first dose of vedolizumab will be displayed using Kaplan-Meier curves. The analyses will separately present all events, and events coded as related to vedolizumab IV.

Each safety analysis will be presented (1) based on events occurring between first and lost dose of vedolizumab and (2) based on events occurring between first dose of vedolizumab and end of study follow-up, unless specified otherwise below. This second analysis will allow for delayed effects that occur after last dose, but may include events attributable to subsequent therapies.

<u>Infections</u>

The analysis of infections will be based on the first event for each type of infection.

<u>Tuberculosis</u>

Analyses will include all active TB, and if numbers are sufficient, separate analyses will be provided for pulmonary, extra-pulmonary and disseminated TB. Latent TB infection will be included in the study report but not in the main analyses, as such infections are likely to predate use of vedolizumab IV. Data shall also be presented by geographic region if sufficient numbers of events occur.

Viral Hepatitis

Analyses will separately present hepatitis B and C infections, and data shall also be presented by geographic region if sufficient numbers of events occur.

Malignancies

Analyses will include malignant neoplasms and carcinomas in situ. Analyses will examine all malignancies pooled, then separately for each of the most common malignancies, if sufficient events occur. Malignancies that occur within 6 months after initiating vedolizumab IV will be included in the study report but not in the main analyses to minimize the likelihood of including pre-existing malignancies. Person-time at risk for calculation of incidence rates for malignancies will thus start 6 months after initiation of vedolizumab IV.

Infusion-Related Reaction and Hypersensitivity

A 1-day risk window after each infusion will be used as the risk window for infusion-related reactions and hypersensitivity. Each 1-day window will be used to determine cumulative incidence.

Hepatic injury

Analyses will be presented for all hepatic events and separately for each type of hepatic events, stratified by all events and those coded as related to vedolizumab IV.

Other AEs

Other SAEs, adverse reactions, and pregnancies and pregnancy outcomes will be summarized using descriptive statistics.

10.7.4 Effectiveness analyses

Effectiveness analyses will present change from Baseline in UC and CD disease activity scores, incidence of and time to IBD surgery or hospitalization, steroid tapering, and time to vedolizumab IV treatment change. Effectiveness will also be assessed with respect to change from Baseline in patient's health-related quality of life scores.

10.7.5 Effect Modifiers

Baseline disease severity, as evidenced by disease activity scores, as well as prior hospitalizations for disease exacerbation and prior disease-related surgeries, prior treatment with TNF-α antagonists, prior UC or CD drug failures, and duration of disease at the time of initiating vedolizumab are likely to be associated with risk for some AEs and with measures of effectiveness.

As risk of outcomes such as infections appears to increase with prior use of some IBD therapies [10,11], stratified analyses will be presented to quantify risk for endpoints with sufficient number of events.

10.8 Quality Control

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

10.9 Limitations of the Research Methods

The study is of sound design and should provide quality data on the safety and effectiveness profile of vedolizumab in Taiwan. As with all registry studies, the following subsection describe the limitations to be considered when the results are interpreted.

10.9.1 Limited use of vedolizumab

It is anticipated that only 90 patients will be treated with vedolizumab IV in Taiwan during the 2.75-year study period. Because of this small study population, the incidence rates for some safety endpoints may be based on few events and thus have wide 95% CIs. In addition, for endpoints with few events it may not be possible to undertake the planned stratified analyses.

10.9.2 Coverage of the Registry

While the TSIBD is working to expand the coverage of the Registry toward all IBD clinics, it is unlikely the Registry will include exactly 100% of all biologic users, as some centers and patients may decline to participate. As vedolizumab is only available by infusion, it is thought there will be limited use outside the major centers participating in the Registry.

10.9.3 Comparator

The use of biologic agents for the treatment of IBD in Taiwan is limited. Thus, there is no similar treatment group that could provide appropriate comparator data.

10.9.4 Channeling

As vedolizumab IV is a new and first-in-class treatment for IBD, it is possible that patients receiving vedolizumab IV in the early years of this study will be more severe disease or in greater need of a new therapy than those seen in subsequent years. This channeling of such patients into vedolizumab IV therapy may yield a safety and effectiveness profile different to that observed in later years. As part of the analyses, the calendar year of vedolizumab initiation will be examined to assess if there has been a shift during the 2.75-year study period in the characteristics of patients being treated with vedolizumab IV.

11.0 PROTECTION OF HUMAN PATIENTS

11.1 Risk to Patients

This study involves statistical analysis of data held in the Registry. There is negligible risk to patients in this study.

The conduct of the Registry and protection of patients by the Registry is separately covered by the Registry's protocol and IRB approvals.

11.2 Anonymized Data

The data to be provided from the Registry will be anonymized with all personal and clinic identifiers removed.

11.3 IRB Approval

This study protocol for statistical analyses and any substantial amendments shall be submitted by the TSIBD and/or its local participating centers to local IRBs, as required by local regulations.

The conduct of the Registry is covered by a separate protocol and IRB approvals.

11.4 Adherence to the Protocol

This study is limited to statistical analyses and does not require any additional clinical procedures or tests, or direct contact with patients, and is totally independent of all decisions on clinical management of patients included in the Registry. Protocol violations in this study is unlikely and of minimal risk to study participants in the Registry.

11.5 Protocol Amendment

Any significant amendment to the protocol will be created by the sponsor in collaboration with TSIBD, and subsequently submitted by the site to the IRB and TFDA for approval. If the protocol amendment substantially alters the study design or increases the potential risk or discomfort to the patients, written consent for continued participation in the study will be obtained.

11.6 Confidentiality

The information in study documents from the Sponsor may include trade secrets and commercial information that are confidential and may not be disclosed, unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

The dataset abstracted from the Registry will not contain any named patient data. The anonymized individual patient medical information in the dataset shall be treated as confidential, and disclosure to third parties is prohibited, except where required by the TFDA.

Data generated as a result of this study will be available for inspection on request of the sponsor's representative, the IRB, or TFDA. An interim data report will be submitted to TFDA as part of the first marketing renewal. The final data report will be submitted to TFDA upon the study completion.

12.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

12.1 Definitions

12.1.1 AEs

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or 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.

12.1.2 SAEs

An SAE is an AE that meets any of the following criteria:

- Is fatal or life threatening, ie, in the view of the physician, places the patient at immediate risk of death from the reaction as it occurred. An event would not be classified as life threatening solely because, had it occurred in a more serious form, it might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis can be fatal.
- Results in persistent or significant disability or incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Requires in-patient hospitalization or prolongation of an existing hospitalization.
- Is a congenital anomaly/birth defect.
- Malignancy.
- Any other important medical event that may not result in death, be life-threatening or require hospitalization, but based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Hospitalization for underlying UC or CD will constitute an SAE. Hospitalization for an elective or planned procedure to treat a pre-existing condition is not considered an SAE, unless it results in one of the other outcomes listed above.

12.2 Collection and Notification of AEs to Sponsor

All AEs/SAEs will be systematically abstracted from the Registry at the time of the interim analyses and final analyses and included in the interim and final study reports. The notification of individual AEs in the abstracted Registry information to the Sponsor for expedited reporting purposes is not required as this study is limited to the secondary use and analysis of previously collected data held in the Registry.

12.3 Reporting of AEs to Regulatory Authorities

The Sponsor is responsible for reporting of adverse events to regulatory agencies, where required by Taiwanese regulations. The TSIBD is responsible for ensuring that all commitments are fulfilled to the IRB that approved the study protocol.

13.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The sponsor, in collaboration with the TSIBD, will prepare progress reports for the TFDA. In addition, these data may be summarized periodically for presentation at professional conferences and sessions, as appropriate.

The final study report will be submitted to the TFDA within 6 months of final data lock (17 November 2020). It is planned to submit these data for publication in international medical journals and to present at medical conferences.

Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines [12] will be followed, and this study, including full protocol, will be publically disclosed on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register of post approval studies (encepp.eu/encepp/studiesDatabase.jsp).

14.0 REFERENCES

1. Wei SC, Lin MH, Tung CC, Weng MT, Kuo JS, Shieh MJ, et al. A nationwide population-based study of the inflammatory bowel diseases between 1998 and 2008 in Taiwan. BMC Gastroenterol 2013;13:166.
2. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142(1):46-54 e42; quiz e30.
3. Sandborn WJ. Current directions in IBD therapy: what goals are feasible with biological modifiers? Gastroenterology 2008;135(5):1442-7.
4. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359(9317):1541-9.
5. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353(23):2462-76.
6. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132(1):52-65.
7. Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70(3):439-44.
8. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis 2008;14(12):1660-6.
9. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology 2013;80(15):1430-8.
10. Berger JR, Houff SA, Major EO. Monoclonal antibodies and progressive multifocal leukoencephalopathy. MAbs 2009;1(6):583-9.
11. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREATTM registry. American Journal of Gastroenterology 2012;107(9):1409-22.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61(4):344-9.
13. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;315(8167):514.

Annex 1 Harvey-Bradshaw Index for CD

Component	Score
General Well-Being	
Very well	0
Slightly below average	1
Poor	2
Very poor	3
Terrible	4
Abdominal Pain	
None	0
Mild	1
Moderate	2
Severe	3
Number of Liquid Stools per Day	(#)
Abdominal Mass	
None	0
Dubious	1
Definite	2
Tender	3
Complications	
Arthralgia	1
Uveitis	1
Erythema nodosum	1
Aphthous ulcers	1
Pyoderma gangrenosum	1
Anal fissures	1
New fistula	1
Abscess	1
Total	**(sum)**

Scoring	
<5	Remission
5-7	Mild disease
8-16	Moderate disease
>16	Severe disease

Source: [13].

Annex 2 Crohn's Disease Activity Index and Weight Table

Category	Count	Initial Total	Multiplication Factor	Total
Number of liquid or very soft stools	7-day total number of liquid or very soft stools (reported on the 7 days immediately prior to the study visit)		x 2	
Abdominal pain	7-day total of daily abdominal pain scores on a 3-point scale: 0=none, 1=mild, 2=moderate, 3=severe (reported on the 7 days immediately prior to the study visit)		x 5	
General well being	7-day total of daily general well-being scores on a 4-point scale: 0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible (reported on the 7 days immediately prior to the study visit)		x 7	
Extra-intestinal manifestations of Crohn's Disease	Total number of checked boxes (check all that apply): ☐ Arthritis/arthralgia ☐ Iritis/uveitis ☐ Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis ☐ Anal fissure, fistula, or abscess ☐ Other fistula ☐ Fever over 37.8°C during past week		x 20	
Lomotil/Imodium/opiates for diarrhea	Yes = 1 No = 0		x 30	
Abdominal mass	None = 0 Questionable = 2 Definite = 5		x 10	
Hematocrit (%) (a)	Males: subtract value from 47 Females: subtract value from 42		x 6	
Body Weight (b)	(1 – [Body weight/ Standard Weight]) × 100		x 1	
Final Score			Add totals:	

Source: Adapted from: Best WR, Becktel JM, Singleton JW, Kern F, Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70(3):439-44.
(a) If hematocrit subtotal <0, enter 0. (b) If body weight subtotal <-10, enter -10.

Table for Determining Standard Body Weight (Crohn's Disease Activity Index Variable)

WOMEN	
Height in cm *without shoes*	**Standard Weight in Kg**
148	53.1
149	53.6
150	54.1
151	54.5
152	55.0
153	55.4
154	55.9
155	56.4
156	57.0
157	57.5
158	58.1
159	58.6
160	59.1
161	59.6
162	60.2
163	60.7
164	61.3
165	61.9
166	62.4
167	62.9
168	63.4
169	63.9
170	64.5
171	65.0
172	65.5
173	66.0
174	66.6
175	67.2
176	67.7
177	68.3
178	68.8
179	69.3
180	69.8
181	70.3
182	70.9
183	71.5
184	72.1
185	72.7
186	73.4

MEN	
Height in cm *without shoes*	**Standard Weight in Kg**
158	62.6
159	62.9
160	63.3
161	63.7
162	64.1
163	64.6
164	65.0
165	65.5
166	66.0
167	66.6
168	67.1
169	67.6
170	68.1
171	68.7
172	69.2
173	69.7
174	70.3
175	70.8
176	71.3
177	71.9
178	72.4
179	73.0
180	73.6
181	74.3
182	74.8
183	75.5
184	76.2
185	76.9
186	77.6
187	78.2
188	78.8
189	79.6
190	80.4
191	81.0
192	81.6
193	82.2
194	82.8
195	83.4
196	84.0

Modified for height without shoes from the 1983 Metropolitan Life Insurance Ideal Weights for Height tables.

Annex 3 Crohn's Disease Endoscopic Index of Severity

CDEIS

	Deep ulcerations *12 points*	Superficial ulcerations *6 points*	Surface of ulcerations *(0-10 *)*	Surface of lesions *(0-10 *)*
Ileum	0 or 12	0 or 6	0–10	0–10
Right colon	0 or 12	0 or 6	0–10	0–10
Transverse	0 or 12	0 or 6	0–10	0–10
Left colon	0 or 12	0 or 6	0–10	0–10
Rectum	0 or 12	0 or 6	0–10	0–10

TOTAL (sum of all cases)	N
TOTAL/number of explored segments	N/1–5
+ 3 if ulcerated stenosis	0–3
+ 3 if non-ulcerated stenosis	0–3
CDEIS:	**0 to 44**

*0-10 cm refers to a visual analogue scale

Mary JY, *et al. Gut* 1989;30:983–9

CDEIS= Crohn's Disease Endoscopic Index of Severity.

Annex 4 Simple Clinical Colitis Activity Index

Variable	Description	Scoring	
1	Bowel frequency (day)	n (1 per occurrence)	
		0 – 3	(score 0)
		4 – 6	(score 1)
		7 – 9	(score 2)
		> 9	(score 3)
2	Bowel frequency (night)	0	(score 0)
		1 – 3	(score 1)
		4 – 6	(score 2)
3	Urgency of defecation	None	(score 0)
		Hurry	(score 1)
		Immediately (toilet nearby)	(score 2)
		Incontinence	(score 3)
4	Blood in stool	None	(score 0)
		Trace	(score 1)
		Occasionally frank (<50% of defecation)	(score 2)
		Usually frank (>50% of defecation)	(score 3)
5	General well-being (0 – 10)	≥ 7 = very well	(score 0)
		6 = slightly below par	(score 1)
		5 = poor	(score 2)
		4 = very poor	(score 3)
		< 4 = terrible	(score 4)
6	Extracolonic features	1 per manifestation:	
		Arthritis	Yes = 1 No = 0
		Uveitis	Yes = 1 No = 0
		Erythema nodosum	Yes = 1 No = 0
		Pyoderma gangrenosum	Yes = 1 No = 0

Annex 5 Mayo Score

Component	Score
Stool Frequency	
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
Rectal Bleeding	
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
Physician Rating of Disease Activity	
Normal	0
Mild	1
Moderate	2
Severe	3
Partial Mayo Score	**(sum)**

Baseline Visit

If patient had an endoscopy within the past 3 months, complete endoscopic findings

Follow-up visits

If patient had an endoscopy within the past 1 month, complete endoscopic findings.

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
Full Mayo Score	**(sum)**

Source: [8].

Annex 6 Short Inflammatory Bowel Disease Questionnaire

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

On this questionnaire there are 10 questions. Each question has a graded response from 1 through 7. Please read each question carefully and answer the number that best describes how you have been feeling **in the past 2 weeks**.

If you are having trouble understanding a question, STOP for a moment! Think about what the question means to you. How is this activity affected by your bowel problem? Then answer the question as best you can.

This questionnaire takes only a few minutes to complete.

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking 1 option from:

    1 All of the time
    2 Most of the time
    3 A good bit of the time
    4 Some of the time
    5 A little of the time
    6 Hardly any of the time
    7 None of the time

2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from:

    1 All of the time
    2 Most of the time
    3 A good bit of the time
    4 Some of the time
    5 A little of the time
    6 Hardly any of the time
    7 None of the time

3. How much difficulty have you had, as a result of your bowel problem, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:

    1 A great deal of difficulty; activities made impossible
    2 A lot of difficulty
    3 A fair bit of difficulty
    4 Some difficulty
    5 A little difficulty
    6 Hardly any difficulty
    7 No difficulty; the bowel problems did not limit sports or leisure activities

4. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:

    1 All of the time
    2 Most of the time
    3 A good bit of the time
    4 Some of the time
    5 A little of the time
    6 Hardly any of the time
    7 None of the time

5. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from:

    1 All of the time
    2 Most of the time
    3 A good bit of the time
    4 Some of the time
    5 A little of the time
    6 Hardly any of the time
    7 None of the time

6. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from:

    1 A major problem
    2 A big problem

3 A significant problem

4 Some trouble

5 A little trouble

6 Hardly any trouble

7 No trouble

7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be? Please choose an option from:

1 A major problem

2 A big problem

3 A significant problem

4 Some trouble

5 A little trouble

6 Hardly any trouble

7 No trouble

8. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from:

1 None of the time

2 A little of the time

3 Some of the time

4 A good bit of the time

5 Most of the time

6 Almost all of the time

7 All of the time

9. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:

1 All of the time

2 Most of the time

3 A good bit of the time

4 Some of the time

5 A little of the time

6 Hardly any of the time

7 None of the time

10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from:

1 All of the time

2 Most of the time

3 A good bit of the time

4 Some of the time

5 A little of the time

6 Hardly any of the time

7 None of the time

Annex 7 ENCePP Checklist

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Study title:
Safety and Effectiveness of Vedolizumab IV in Real World Clinical Practice in Taiwan: A Registry-Based Study

Study protocol number:
Vedolizumab-5016

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	13
1.1.2 End of data collection[2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☒	☐	☐	13
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☐	☐	☒	13
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	15
2.1.2 The objective(s) of the study?	☒	☐	☐	16
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	17
2.1.4 Which formal hypothesis (-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (eg, cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	17
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17
3.3 Does the protocol describe the measure(s) of effect? (eg, relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	22

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	17
4.2.2 Age and sex?	☒	☐	☐	17
4.2.3 Country of origin?	☒	☐	☐	17
4.2.4 Disease/indication?	☒	☐	☐	17
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	17

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (eg, operational details for defining and categorising exposure)	☒	☐	☐	22
5.2 Does the protocol discuss the validity of exposure measurement? (eg, precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	23
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☒	☐	☐	23
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	23
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	23

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	22
6.2 Does the protocol discuss the validity of endpoint measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	22

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (eg, collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	25
7.2 Does the protocol address known effect modifiers? (eg, collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	25

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	22
8.1.2 Endpoints? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	18
8.1.3 Covariates?	☒	☐	☐	18
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	18
8.2.2 Endpoints? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	17
8.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	18
8.3 Is a coding system described for:				
8.3.1 Diseases? (eg, International Classification of Diseases (ICD)-10)	☐	☐	☒	
8.3.2 Endpoints? (eg, Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	19
8.3.3 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
8.4 Is the linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	22

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	22
10.2 Is the choice of statistical techniques described?	☒	☐	☐	22
10.3 Are descriptive analyses included?	☒	☐	☐	22
10.4 Are stratified analyses included?	☒	☐	☐	24
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	25
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	25

Comments:

Safety study; subgroup analyses as needed.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	23
11.2 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	22
11.3 Are methods of quality assurance described?	☒	☐	☐	24
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☒	
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	
12.1.2 Information biases? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	25
12.2 Does the protocol discuss study feasibility? (eg, sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	25

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	26
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	26

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	26

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	29
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	29