Title: Entyvio (vedolizumab) long-term safety study: An international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's Disease.

Protocol Approve Date: 30 October 2017

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

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Protocol

Study No:	MLN-0002_401
Product:	Vedolizumab
Study Title:	Entyvio (vedolizumab) long-term safety study: An international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's Disease.
Short Title:	Entyvio PASS Study
Protocol Version:	Version 3.1: 30 October 2017
Sponsor:	
Europe:	Takeda Development Centre Europe
N. America:	Takeda Development Center Americas
Ethics Statement:	This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature Page

Entyvio (vedolizumab) long-term safety study:
An international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's Disease.

[Entyvio PASS Study]

MLN-0002_401 Protocol Version 3.1, 30 October 2017

Sponsor	Signature & Date
PPD	

Investigator	Signature & Date
Name:	
Address:	____/_____/_____

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LIST OF APPENDICES

1. ABSTRACT

1.1 Title

Entyvio (vedolizumab) long-term safety study: An international observational prospective cohort study comparing vedolizumab to other biologic agents in patients with ulcerative colitis or Crohn's Disease.

Short Title: Entyvio PASS Study

1.2 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. The highest reported annual prevalence of UC and CD in North America is 249/100, 000 persons and 319/100,000 persons, respectively. However, in Europe, the highest annual reported prevalence of 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.

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. Many patients with IBD will continue to experience refractory diarrhea and rectal bleeding and require frequent hospitalizations, enteral nutrition, and surgical procedures. Specifically, patients with UC often will have colectomies, while 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. Therefore, there is a pressing need for a therapy that functions via a mechanism of action distinct from that of existing agents. Vedolizumab is a gut-selective, anti-inflammatory agent that was developed to fulfill this important unmet medical need.

Vedolizumab is a humanized immunoglobulin G1 monoclonal antibody (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 hence impairing the migration of leukocytes into GI mucosa. Therefore, 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 and CD.

This study is an observational study to assess the safety of vedolizumab versus other biologic agents in the real world setting. The participating physicians will be representative of the gastroenterologists who prescribe vedolizumab, or other biologic agents, per the local prescribing information in the participating countries.

The patients enrolled in this study will similarly correspond to the target population of patients with UC or CD, who are initiating vedolizumab, or similar patients who are initiating other biologic agents in the participating countries. This protocol has been designed to accommodate the use of products according to approved product labels in all participating countries.

1.3 Research Question and Objectives

Primary Objective

- To assess the long-term safety of vedolizumab versus other biologic agents in patients with UC or CD.

Secondary Objectives

- To describe changes in UC/CD disease activity, using disease activity scores, health resources used, and patient reported quality of life assessments, during the course of the study.

1.4 Study Design

Design

This is a prospective, observational, multi-center, cohort study designed primarily to assess the long-term safety of vedolizumab versus other biologic agents in patients with UC or CD. The study has two cohorts: a vedolizumab cohort and an other biologic agents cohort.

The study is non-interventional. All decisions on clinical management are made by the investigator as part of routine standard of care, and independent of participation in the study. The study design allows the investigator to modify or change patients' treatment at any time during the study period without having to withdraw the patients from the study.

Cohort Entry Criteria

Patients with UC or CD who are initiating vedolizumab therapy will be recruited into the vedolizumab cohort. Patients may have prior exposure to biologics or be naïve to biologics. Patient may not have prior exposure to vedolizumab at study entry.

Patients with UC or CD who initiate therapy with another biologic agent indicated for UC or CD will be recruited into the other biologic agents cohort. Patients may have prior exposure to biologic agents or be naïve to biologics. Patient may not have prior exposure to vedolizumab at study entry.

This study is designed to permit interested physician within participating countries to participate as investigators, and all interested eligible patients within investigator sites to participate as subjects.

Data Collection and Follow-up

Study assessments will be collected at baseline and at least every 6 months by their treating physician, as part of routine care. Adverse Events of Special Interest, other SAEs, and adverse reactions will be recorded at all visits.

Safety will be evaluated through:

- **Adverse Events of Special Interest:**
    - Serious infections (infections that are SAEs, and opportunistic infections such as progressive multifocal leukoencephalopathy (PML))
    - Gastrointestinal infections
    - Lower and upper respiratory infections
    - Other clinically significant infections (infections that are not SAEs, are classified as moderate or severe, and require anti-infective treatment)
    - Malignancies
    - Infusion-related reactions and hypersensitivity
    - Hepatic injury
- All other SAEs
- Adverse reactions
- Pregnancy outcomes

Data on UC/CD disease activity, medication use, health resource use, and Quality of Life will also be collected.

The sponsor will ensure the routine reporting of aggregate and individual safety information in study progress reports as required by local competent authorities.

The cohort follow-up period will run for 7 years.

1.5 Population

- Male and female patients with UC or CD, aged ≥18 years in North America, Europe and Israel.
- Initiating vedolizumab or another biologic agent for UC or CD
- Signed informed consent and medical records release by the patient or a legally acceptable representative.

1.6 Variables

Safety

- Adverse Events of Special Interest:
    - Serious infections (infections that are SAEs, and opportunistic infections such as PML)
    - Gastrointestinal infections
    - Lower and upper respiratory infections
    - Other clinically significant infections, not SAEs, that are classified as moderate or severe and require anti-infective treatment
    - Malignancies
    - Infusion-related reactions and hypersensitivity
    - Hepatic injury
- All other SAEs
- Adverse reactions
- Pregnancy outcomes

Disease Activity

- UC and CD activity assessment:
    - Partial or full Mayo score for patients with UC
    - Harvey-Bradshaw Index score for patients with CD
    - Fecal calprotectin (if measured)
    - C-reactive protein (if measured)
    - Presence/site of extra-intestinal manifestations
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)

Patient reported Quality of Life assessments:

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
- 12-Item Short Form Health Survey (SF-12)

1.7 Data Sources

Baseline Data Collected at Study Enrollment

The following data will be collected at the time of study enrollment:

- Demographic data
- Medical history:
    - General, including co-morbid conditions and other autoimmune disease(s)

- Prior serious and atypical infections and dates
- Malignancies
- Organ transplantation, including bone marrow or stem cell transplants
- Infusion-related reactions
- Hepatic injury

- UC/CD history
  - Dates and age of onset / diagnosis
  - Disease location(s)
  - Surgical history / disease management
- Health resources used within 1 year before study enrollment (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)
- UC and CD activity assessment:
  - Partial of full Mayo score for patients with UC
  - Harvey-Bradshaw Index score for patients with CD
  - Fecal calprotectin (if measured)
  - C-reactive protein (if measured)
  - Presence/site of extra-intestinal manifestations
- Any prior use of the following drugs, including specific drug used, indication, dose received, route of administration, and dates of use:
  - Tumor necrosis factor alpha (TNF-α) antagonists, azathioprine, 6-mercaptopurine (6-MP), methotrexate, or 5-aminosalicylic acid (5-ASA)
  - Drugs with known association with PML (e.g., alemtuzumab, belatacept, brentuximab vedotin, efalizumab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
  - Other immunomodulatory, anti-neoplastic, or immunosuppressive agents for UC or CD in 5 years before study enrollment
  - Other immunomodulatory, anti-neoplastic, or immunosuppressive agents for other indications in 5 years before study enrollment
  - Systemic corticosteroids in 6 months before study enrollment
  - Antibiotics to treat UC/CD in 5 years before study enrollment
- Patient reported Quality of Life assessment:
  - SIBDQ
  - SF-12

Prospective Data Collection

The following data will be collected at least every 6 months during the follow-up period. If additional, unscheduled visits are performed, the minimum data to be recorded are SAEs, Adverse Events of Special Interest, and adverse reactions.

- UC and CD activity assessment:
    - Partial or full Mayo score for patients with UC
    - Harvey-Bradshaw Index score for patients with CD
    - Fecal calprotectin (if measured)
    - C-reactive protein (if measured)
    - Presence of extra-intestinal manifestations
- Vedolizumab infusions, including dose and dates
- Any use of the following drugs, including specific drug used, indication, dose received, route of administration, and dates of use:
    - TNF-α antagonists, azathioprine, 6-MP, methotrexate, or 5-ASA
    - Other immunomodulatory, anti-neoplastic, or immunosuppressive agents
    - Drugs with known association with PML (e.g., alemtuzumab, belatacept, brentuximab vedotin, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
    - Systemic corticosteroids
    - Antibiotics to treat UC/CD
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)
- Patient reported Quality of Life assessment:
    - SIBDQ
    - SF-12
- Adverse Events of Special Interest:
    - Serious infections (infections that are SAEs, and opportunistic infection such as PML)
    - Gastrointestinal infections
    - Lower and upper respiratory infections
    - Other clinically significant infections, not SAEs, that are classified as moderate or severe and require anti-infective treatment
    - Malignancies
    - Infusion-related reactions and hypersensitivity
    - Hepatic injury
- All other SAEs
- Adverse reactions
- Pregnancies outcomes.

1.8 Study Size

The study aims to recruit 2,500 patients into the vedolizumab cohort and 2,500

patients into the other biologic agents cohort. It is anticipated that over the 7-year follow-up period, over 11,000 person-years of follow-up will accumulate in each cohort (with a mean duration of follow-up of 4.54 years), and within the vedolizumab cohort, the mean duration of vedolizumab exposure will be 1.5 years and at least 1,000 patients will have at least 24 months of vedolizumab exposure during the follow-up period.

For the primary safety analysis (serious infections rate), the sample size of 2,500 patients in each exposure cohort is sufficient to detect HR = 1.54 with 80% power, HR = 1.64 with 90% power and HR = 1.72 with 95% power, assuming a joint UC and CD background serious infection rate of 1.55 per 100 person-years, a mean duration of drug exposure of 1.5 years, risk window of up to 3 months after each exposure, and a type I error of 0.05 (2-sided).

1.9 Data Analysis

Statistical Methods

Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; as well as number and percent for categorical variables.

Analysis Population

Disposition data will be presented for all patients enrolled. All other analyses will be based upon the population enrolled who received at least 1 dose of vedolizumab or other biologic agents.

Additional subgroups may be examined, as deemed appropriate (e.g., prior immunosuppressant use, UC versus CD, baseline disease severity, etc.). A specific subgroup analysis will be carried out to assess safety in patients who have ever been exposed to natalizumab.

Disposition, Demographic, and Baseline Data

Disposition, demographic, and baseline data will be summarized by cohort with descriptive statistics and presented in listings.

Adverse Events of Special Interest

The primary safety analysis will focus on serious infections. Secondary analyses will look at individual serious infections, including PML, and the other Adverse Events of Special Interest. The safety analyses will present number of events, person-years of follow-up and crude incidence rates in each cohort. Time varying Cox proportional hazard models, with propensity score stratification will be used to generate adjusted hazard ratios. Analyses will be presented for all patients, and separately for UC and CD patients. Multivariate analysis with adjustment for confounders will assess risks with respect to duration of use, cumulative dose, and time since first use of vedolizumab.

Other SAEs, adverse reactions and pregnancy data will be summarized by cohort

with stratification by baseline characteristics.

Disease Severity

Change over time in UC and CD disease activity scores will be summarized using descriptive statistics by cohort with stratification by baseline characteristics, use of health resources will be summarized by treatment arm with descriptive statistics.

Patient reported Quality of Life

Changes over time in patient reported Quality of Life scores will be summarized using descriptive statistics by cohort.

1.10 Milestones

Study Milestone	Estimated Date
Start of data collection (first patient, first visit)	Q1 2015
Study progress reports	annually throughout the study
Safety summary reports	as required by competent authority
2.5-year follow-up analysis data base lock	01 July 2017 (after 50% of expected vedolizumab population has enrolled and completed at least 1 year of treatment)
2.5-year follow-up report	01 July 2018
End of data collection (7-year follow-up data lock)	30 June 2021
Final study report (7-year follow-up)	30 June 2022

2. AMENDMENTS AND UPDATES

Version 1: Original protocol

Version 2:

Major Amendments: None

Minor Amendments

- Study title expanded to include study design and exposures of interest
- Update milestones to include the date of 2.5-yr follow-up data lock in Section 3
- Text added to Section 6.1.1 that study is a hypothesis testing study, and text removed from Section 7.8 that the study is exploratory in nature.
- Further details of the study design and study population provided in Sections 7.1 and 7.2.1
- 3rd exclusion criteria excluded from Section 7.2.3
- Description of subject recruitment and the recruitment period in Section 7.2.5
- Description of the procedures for following investigator withdrawal from the study, and patients who switch to non-investigator physicians, and patient death ascertainment in Section 7.3
- Additional information added to definitions of Adverse Events of Special Interest in Section 7.4.1 Definition of respiratory infections expanded to include both upper and lower respiratory infections in Section 7.4.1.
- Explanation of the sample size projection included Section 7.6
- Revisions made to the power calculation in Section 7.6.1
- Predefined statistical power and hazard ratio added to Section 7.6.2
- Description of dealing with missing data included in Section 7.7
- Description of drug initiation included in Section 7.8
- Details on methods to control for indicated disease, exposure duration, and dealing with study drug switching or discontinuing included in Section 7.8
- Additional details on analyses of Adverse Events of Special Interest included in Sections 7.8.4 to 7.8.6
- Additional details of the 2.5-yr analysis included in Section 7.8.9
- Details of treatment allocation bias included in Section 7.10.3

- Description of adverse event management and reporting changed from a paper based collection to an electronic-based collection system in Section 9
- Mayo Score instrument expanded to include Endoscopic Findings for patients with recent endoscopy in Appendix F.

None of the above amendments substantially altered the study design or increased any potential risk to patients.

Version 3:

Major Amendments: None

Minor Amendments

- Sample size recalculated using log rank test for survival data in Sections 1.8 and 7.6,
- Specified that propensity score stratification would be used added to Sections 1.9 and 7.8.5
- Israel added as a study country in Section 7.2.1
- Information on recruitment window included in Section 7.2.2
- Text on censoring added to Section 7.3.5 and removed from Section 7.8.4
- Fecal calprotectin and C-reactive protein levels, if measured, included as disease activity markers in Section 7.4.3

None of the above amendments substantially altered the study design or increased any potential risk to patients.

Version 3.1 (without ProClinica Direct to Patient contact):

This version is identical to Version 3 except all activities pertaining to Direct to Patient Contact has been removed from the protocol (sections: 7.3.2, 7.3.3, 7.3.4, 7.10.6 and Appendix B). This protocol version may be used in Countries or investigator sites that do not permit or wish to have Direct to Patient Contact by the study management team.

3. MILESTONES

The planned study milestones are summarized below.

Study Milestone	Estimated Date
Start of data collection (first patient, first visit)	Q1 2015
Study progress reports	annually throughout the study
Safety summary reports	as required by competent authority
2.5-year follow-up data lock	01 July 2017 (after 50% of expected vedolizumab population has enrolled and completed at least 1 year of treatment)
2.5 -year follow-up report	01 July 2018
End of data collection (7-year follow-up data lock)	30 June 2021
Final study report (7-year follow-up)	30 June 2022

4. ABBREVIATIONS

5-ASA	5 aminosalicylate
6-MP	6-mercaptopurine
AE	adverse event
CD	Crohn's disease
DTPC	direct-to-patient contact
eCRF	electronic case report form
EDC	electronic data capture
GI	Gastrointestinal
IBD	inflammatory bowel disease
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
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
SD	standard deviation
SF-12	12-Item Short Form Health Survey
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	system organ class
TNF-α	tumor necrosis factor alpha
UC	ulcerative colitis

5. RATIONALE AND BACKGROUND

5.1 Background

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

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. The highest reported annual prevalence of UC and CD in North America is 249/100, 000 persons and 319/100,000 persons, respectively [1]. However, in Europe, the highest annual reported prevalence of UC and CD is 505/100,000 persons and 322/100,000 persons, respectively [1]. UC and CD are lifelong diseases that cause considerable morbidity in a relatively young patient population.

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-aminosalicylates (5-ASAs), corticosteroids, and immunomodulators (thiopurines such as azathioprine and 6-mercaptopurine (6-MP), along with methotrexate). The biologic agents infliximab (REMICADE®) and adalimumab (HUMIRA®), which are monoclonal antibodies (mAbs) directed against tumor necrosis factor alpha (TNF-α), have been approved for UC and CD in the EU and US. These agents have substantially improved the care of patients with UC or CD decreasing the need for hospitalizations and surgeries [2]. Although TNF-α antagonists represent an important addition to the pharmacologic armamentarium for UC and CD, 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 [3,4,5]. Another TNF-α antagonist, certolizumab pegol (CIMZIA®), is approved in the US for reducing the signs and symptoms of CD, and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy, but was not approved in the EU due to concerns over the benefit-to-risk profile. Natalizumab (Tysabri®), an α4β7 and α4β1 integrin antagonist, has also been approved in the US for CD patients experiencing inadequate response to other types of CD treatment, or who are unable to tolerate conventional therapies and TNF-α antagonists. This biologic agent has demonstrated maintenance benefit in CD [6]; however, it is not used often for this indication because of concerns over the safety profile.

The current treatments do not sufficiently address the unmet need in this population. Many patients still require frequent hospitalization, serial bowel resections, colectomies, and enteral nutrition, and regularly experience fistulae, GI abscesses, refractory diarrhea, and

rectal bleeding. These patients are often unable to function normally in society by virtue of having uncontrolled disease. Therefore, there is a pressing need for a therapy that functions via a mechanism of action distinct from existing agents.

5.1.2 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.

Detailed information regarding nonclinical and clinical pharmacology, toxicology, and clinical trials of vedolizumab is found in product prescribing information [7].

5.1.2.1 Ulcerative Colitis

The safety and efficacy of vedolizumab IV for the treatment of patients with moderately to severely active UC (Mayo score 6-12 with endoscopic subscore ≥2) was demonstrated in a randomized, double-blind, placebo-controlled study, comprising 2 phases and evaluating efficacy endpoints at Week 6 and Week 52 (C13006). Enrolled patients had failed corticosteroids, immunomodulators, and/or TNF-α antagonists.

Vedolizumab IV patients had a statistically significant improvement in clinical response, clinical remission, mucosal healing, durable clinical response, durable clinical remission, and corticosteroid-free remission compared to placebo. The beneficial effect of vedolizumab IV on clinical remission was observed both in patients with no prior TNF-α antagonist exposure, as well as in those who had failed prior TNF-α antagonist therapy.

5.1.2.2 Crohn's Disease

The safety and efficacy of vedolizumab IV for the treatment of patients with moderately to severely active CD (CDAI score of 220 to 450) was evaluated in 2 studies (C13007 and C13011). Study C13007 was a randomized, double-blind, placebo-controlled study comprising 2 phases that evaluated efficacy endpoints at Week 6 and Week 52. Study C13011 was a randomized, double-blind, placebo-controlled study that evaluated efficacy at Week 6 and Week 10 in the subgroup of patients defined as having failed TNF-α antagonist therapy, as well as in the overall population, which included patients naïve to TNF-α antagonist therapy.

In Study C13007, a significantly higher proportion of vedolizumab IV patients overall achieved clinical remission at Week 52, compared with placebo patients. In Study C13011, the subset of vedolizumab IV patients who had failed prior TNF- α antagonist therapy did not demonstrate significant benefit relative to placebo by Week 6. However, by Week 10, a higher proportion of vedolizumab IV patients who had failed prior TNF- α antagonist therapy achieved clinical remission.

5.1.2.3 Safety Profile for Ulcerative Colitis and Crohn's Disease

In the pivotal Phase 3 trial in UC (C13006), 12% of vedolizumab IV-treated patients experienced a serious adverse event (SAE), compared with 11% of placebo-treated patients. The most frequent SAE was UC, which occurred in 8% and 7% of vedolizumab- and placebo-treated patients, respectively. Two percent of vedolizumab IV-treated patients had at least one SAE in the Infections and Infestations system organ class (SOC), as compared to 3% of the placebo-treated patients. The most common of the adverse drug reactions occurring in ≥ 3% of vedolizumab IV patients, and in excess of 1% over placebo patients, included nasopharyngitis, headache, and cough.

In the pivotal Phase 3 trial of induction and maintenance in CD (C13007), 24% of vedolizumab IV-treated patients experienced at least 1 SAE, compared with 16% of placebo-treated patients. Gastrointestinal disorders were very common (16% vedolizumab- and 12% of placebo-treated patients), with CD the most common SAE (12% and 9%, respectively). SAEs within the Infections and Infestations SOC were also common (6% and 3%, respectively), with anal abscess the most common SAE reported within this SOC (2% and <1%, respectively). The most common of the adverse drug reactions occurring in more than 3% of vedolizumab IV patients and in excess of ≥1% over placebo patients in Study C13007 were pyrexia, nasopharyngitis, nausea, and arthralgia.

In a pivotal Phase 3, placebo-controlled trial of vedolizumab IV induction treatment in CD (C13011), patients received vedolizumab 300 mg IV or placebo at Weeks 0, 2, and 6. The majority of patients had failed at least 1 TNF-α antagonist prior to enrolment. Safety data observed in the TNF-α antagonist failure safety subpopulation were generally similar to those observed in the overall safety population.

An open-label study of vedolizumab 300 mg IV, every 4 weeks, is ongoing to evaluate long-term safety in patients with CD or UC who had previously been enrolled in a vedolizumab IV study (rollover patients); de novo patients (not previously enrolled in vedolizumab studies) were also enrolled. Results from an interim analysis of the safety data from rollover patients appear to be consistent with the data from placebo-controlled clinical studies of vedolizumab IV.

In pivotal Phase 3 studies, other reported SAEs, including extra-intestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis), were uncommon (< 1%). Malignancy was diagnosed in 15 patients receiving vedolizumab IV across all clinical studies (9 patients with UC and 6 patients with CD). Patients with IBD have an increased risk for colon cancer [1] and colon cancer was reported in 4 vedolizumab IV-treated patients; carcinoid tumor of the appendix was diagnosed in 1 vedolizumab IV-treated patient. One case of B-cell lymphoma was reported in a patient who had received 21 infusions of vedolizumab IV.

5.2 Study Rationale

This study is planned as an observational study to compare the safety of long-term treatment with vedolizumab, after marketing authorization, with the safety of long-term treatment with other biologic agents for UC or CD. Other biologic agents are likely alternative treatments physicians will consider for patients initiating vedolizumab and therefore the appropriate comparator group for benefit-risk assessments. The participating physicians, with regard to countries and sites, will be representative of the gastroenterologists who will prescribe vedolizumab or other biologic agents to patients with UC or CD according to the local prescribing information in the participating countries. The patients enrolled in this study will similarly correspond to the target population of patients who are initiating vedolizumab, or similar patients who are initiating other biologic agents for UC or CD in the participating countries. This protocol has been designed to accommodate the use of products according to approved product labels of all participating countries.

Although there were no cases of PML associated with vedolizumab treatment during clinical trials in more than 2900 subjects, and the mechanism of action studies with vedolizumab suggest that PML is unlikely to occur, PML cannot be ruled out in long-term treatment with immunomodulatory mAbs and other immunosuppressant agents, with which vedolizumab patients may have been previously treated [8]. Therefore, the safety outcome measures for subjects treated with vedolizumab or other biologic agents in this study will include, but not limited to, serious infections, including PML and other opportunistic infections; gastrointestinal infections, lower and upper respiratory infections; other clinically significant infections (not SAEs, that are classified as moderate or severe and require anti-infective treatment); malignancies; infusion-related reactions; and hepatic injury.

6. RESEARCH QUESTION AND OBJECTIVES

6.1 Objectives

6.1.1 Primary Objective

The objective of this hypothesis testing study is to assess the long-term safety of vedolizumab versus other biologic agents in patients with UC or CD.

- The primary safety outcome is serious infections.
- Secondary safety outcomes include, but are not limited to, PML, gastrointestinal infections, lower and upper respiratory tract infections, other clinically significant infections (not SAEs but are classified as moderate or severe and require antibiotic treatment), malignancies, infusion-related reactions and hypersensitivity, and hepatic injury, other SAEs, adverse reactions and pregnancy outcomes.

6.1.2 Secondary Objectives

To describe changes in UC/CD disease activity, health resources used, and changes in patient reported Quality of Life, during the course of the study.

7. RESEARCH METHODS

7.1 Study Design

This is a prospective, observational, international, multi-center study, designed primarily to assess long-term safety in patients who are initiating vedolizumab, or similar patients who are initiating other biologic agents for UC or CD. This study is designed to permit all interested physician providers to participate as Investigators, and all interested eligible patients at investigator sites to participate as subjects. Physicians will prescribe vedolizumab or other biologic agents according to the local prescribing information in the participating countries, and there are no restrictions on the use of commercially available medications. As an observational study, this study will not change the patient/physician relationship, nor influence the physician's drug prescribing or the therapeutic management of the patient. The study design allows investigators to modify or change patients' UC/CD treatment as needed during the study period without having to withdrawal the patient from the study.

Duration of follow-up is 7 years. Study visits, procedures, and evaluations are summarized in the Schedule of Recommended Assessments, Appendix A, and described in detail below.

Vedolizumab cohort

Patients with UC or CD who initiate vedolizumab therapy will be recruited into the vedolizumab cohort. Patients may have prior exposure to biologic agents or be naïve to biologics. Patients may not have prior exposure to vedolizumab at cohort entry (see footnote to Section 7.2.2 for guidance on recruitment window).

Other biologic agents cohort

Patients with UC or CD who initiate therapy with another biologic agent indicated for UC or CD will be recruited into the other biologic agents cohort. Patients may have prior exposure to biologic agents or be naïve to biologic agents. Patients may not have prior exposure to vedolizumab at cohort entry.

Patients recruited to the other biologic agents cohort should be similar to those in the vedolizumab cohort, and are changing treatment at cohort entry (switching from a branded TNF-α to a bio-similar of the same TNF-α is not considered a treatment change in this study) In both groups the treating physician has made a decision to modify treatment, and it is this decision that triggers eligibility for inclusion in the study. Like the vedolizumab cohort, the other biologic agents cohort may contain patients with prior exposure to biologic agents or patients that are naive to biologic agents. It is anticipated standard of care that all patients who initiate vedolizumab or another biologic agent will have previously failed conventional therapy.

Patients in both cohorts will be followed until the end of the study, during which time they will be assessed by the investigator at least every 6 months. Adverse Events of Special Interest (Section 7.4.1), other SAEs and adverse reactions (Section 7.4.2) will be recorded at all study visits. Information should be collected on all pregnancies and pregnancy outcomes in female participants during the study (Section 7.5.2). The Sponsor will report Adverse Events of Special Interest, SAEs, and adverse reactions to regulatory authorities in accordance with local requirements and Sponsor's post marketing commitments.

7.2 Setting

7.2.1 Study population

The study population is patients aged 18 years or older with UC or CD who are initiating or switching biologic agents. The population includes patients who are naïve to biologic agents and patients with previous biologic agent use.

The study is planned for at least the following countries: Austria, Belgium, Canada, Croatia, Czech Republic, Denmark, France, Germany, Ireland, Israel, Italy, Netherlands, Norway, Romania, Sweden, Switzerland, UK, and USA. Additional countries may be added.

7.2.2 Inclusion Criteria

A patient must meet **all** of the following criteria to be eligible for recruitment in the study.

1. Signed informed consent, by the patient or a legally acceptable representative, obtained before any study-related activities are undertaken.
2. Male and female patients, aged at least 18 years.
3. Initiating vedolizumab or initiating a biologic agent for UC or CD (see footnote below).
4. Signed release form, by the patient or a legally acceptable representative, permitting abstraction of the patient's medical records at Baseline and during participation in the study.

   Footnote: Where possible patient should be recruited on or before day of first dose of vedolizumab or other biologic agent. To help fit recruitment around busy clinics, patients may be recruited up to 2 weeks after first dose of vedolizumab or other biologic.

7.2.3 Exclusion Criteria

A patient who meets **any** of the following criteria is not eligible for recruitment in the study.

1. The patient is enrolled in a clinical trial in which treatment for UC or CD is managed through a protocol.
2. Prior treatment with vedolizumab (see recruitment guidance in footnote to Section 7.2.2).

7.2.4 Selection of Study Sites

Study sites in participating countries will be selected from different sources, including investigators with experience in late phase clinical studies in UC and CD that had demonstrated the ability to successfully recruit patients into these studies.

Physicians in participating countries who are interested in participating as investigators will be considered for inclusion, subject to fulfilling minimum criteria, until site and patient recruitment targets are met. Physician education materials released at product launch included information on the cohort study and how to apply to participate as an investigator.

7.2.5 Recruitment of Patients

Study sites will recruit participants from patients attending their clinics.

At the site level, equal number of patients will be recruited into each cohort, and the proportion of UC patients will be similar in each cohort.

In settings where vedolizumab use is limited to second line biologic (i.e. only used in biologic failures), the comparator group should also only be recruited from patients initiating another second line biologic treatment.

7.3 Patient Management

7.3.1 Patient Withdrawal from Study

A patient may be withdrawn from the study prior to completion for any of the following reasons:

- Withdrawal of patient consent;
- Any other reason, such that continuation of the patient's participation is thought by the Investigator to be inappropriate.

If a patient withdraws or is withdrawn, the reason should be documented in the electronic case report form (eCRF).

The study design allows investigators to modify or change patients' UC/CD treatment as needed during the study period without having to withdrawal the patients from the study.

7.3.2 Investigator Withdrawal from the study

If an investigator retires or leaves their current practice during the study period, the study sponsor, in collaboration with the current investigator, would invite the replacement physician taking over care of the participants at that site to join the study as a new investigator.

7.3.3 Patient Switch to Non-investigator Physician

If a patient's new physician is not interested in participating in the study, the patient's participation in the study will cease at time of switch to a non-investigator physician..

7.3.4 Patient Death

Patient death will be captured by the following route:

- Reported by investigator

7.3.5 Patient Follow-up

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

- End of Study period (30 June 2021)
- Patient lost to follow-up
- Patient withdrawal from study
- Patient death
- Patient enters an interventional clinical trial of UC or CD.

7.4 Outcome Variables

7.4.1 Adverse Events of Special Interest

Serious infections

The primary safety outcome is serious infections. This is defined as any event coded to a MedDRA Preferred Terms (PT) within the MedDRA system organ class (SOC) of Infections and Infestations that meet the Seriousness definition (Section 9.1.5), and opportunistic infections such as PML.

The diagnosis of PML is based upon histopathological, radiological, laboratory, and clinical criteria using the American Academy of Neurology guidelines for PML diagnosis [9], details of the criteria are provided in Appendix C.

All reports of suspected PML (reports coded to the following MedDRA PTs: human polyomavirus infection, JC virus infection, JC virus test positive, leukoencephalopathy, polyomavirus test positive, progressive multifocal leukoencephalopathy) will be reviewed by an independent PML adjudication committee and assessed against the PML diagnostic criteria of the American Academy of Neurology. Where incomplete information is provided, the investigator shall seek to obtain all relevant information.

Gastrointestinal infections. This is defined as events within the Infections and Infestation SOC that are coded to the MedDRA High Level Group Term (HLGT) gastrointestinal infections. The investigator should record and report all gastrointestinal infections, including those occurring as a result of UC or CD.

Lower and upper respiratory infections. This is defined as events within the Respiratory, thoracic and mediastinal disorders SOC that are coded to the MedDRA HLGT respiratory tract infection. They will be grouped by the respective upper and lower respiratory tract infection HLT. As respiratory infections are common and often mild in nature, the investigator should ask study participants at each clinic visit if they have had any respiratory infections since last visit, and collect all relevant information (Section 9.2).

Other clinically significant infections. This is defined as events within the Infections and Infestation SOC that are not included in any of the above (Serious infections, gastrointestinal infections, upper respiratory infections and lower respiratory infections) and are classified as moderate or severe (Section 9.1.2) and require anti-infective treatment.

For each of the above infections, information should be sought by the investigator on site of infection, symptoms, duration of symptoms, prior history, laboratory results if undertaken, treatment provided, outcome, and any other relevant information.

Malignancies. All malignant and benign neoplasms should be recorded on the eCRF. The analyses will focus on malignancies and include all events within the MedDRA Malignant tumours sub-SMQ. This SMQ includes all malignancies and carcinomas in situ.

The investigator should seek all available clinical and histopathology information on the malignancy, including site, cell type, size, stage and grade (including nodal status and metastases), clinical history, prior history of malignancy or pre-malignant disorders, family history, history of screening and diagnostic tests, and history of risk factors and medication history.

Infusion-related reactions and hypersensitivity All suspected cases of infusion reactions, hypersensitivity and anaphylaxis should be reported on the eCRF, regardless of time since last drug exposure.

Events that are coded to PTs in the following MedDRA SMQ will be considered as suspected reports of hypersensitivity:

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

All suspected reports will be adjudicated by a clinician using the hypersensitivity criteria of the National Institute of Allergy & Infectious Diseases [10] which are provided in Appendix D.

The investigator shall seek all information on clinical history, presenting signs and symptoms, time interval between biologic exposure and onset of symptoms, and treatments received.

Hepatic injury Events coded to PTs 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 non-infectious SMQ,
- Liver related investigations signs and symptoms (Narrow SMQ),
- Liver infections SMQ.

The investigator shall seek all relevant information on the hepatic injury, including signs and symptoms, initial and follow-up laboratory results (including serology results), time course of the hepatic injury, diagnosis, concurrent medications and doses, pre-existing liver disease, infections, suspected etiology (and investigator to rule out alternative etiologies), and outcome.

Reports of suspected DILI together with supporting source documents will be reviewed and adjudicated by an independent Liver Safety Evaluation Committee. The Liver Safety Evaluation Committee consists of 5 hepatologists who will evaluate the hepatic adverse events to assess the likelihood of a DILI due to Entyvio or another biologic agent used for UC /CD. The structured adjudication criteria developed by the Drug Induced Liver Injury Network [11] will be used and are presented in Appendix E.

7.4.2 Other Adverse Events

Other safety endpoints of interest include:

- All other SAEs. This is defined as all SAEs not included in any of the above Adverse Events of Special Interest
- Adverse reactions. This is defined as all (serious and non-serious) events considered to be related to vedolizumab.
- Pregnancy and pregnancy outcome.

7.4.3 Disease Activity

Disease activity will be assessed using:

- Partial Mayo score for patients with UC [12] (Appendix F).
- Full Mayo score for patients with UC with endoscopy within 3 months prior to cohort entry [12] (Appendix F)
- Harvey-Bradshaw Index score [13] for patients with CD (Appendix G)
- Fecal calprotectin (if measured). If fecal calprotectin it is measured as part of patient clinical management, the test result should be recorded, The measurement of fecal calprotectin is not mandatory in the study
- C-reactive protein (if measured), If CRP is measured as part of patient clinical management, the test result should be recorded, The measurement of CRP is not mandatory in the study
- Presence/site of extra-intestinal manifestations

7.4.4 Health resource utilization

Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD) during the study period will be recorded at each clinic visit.

7.4.5 Quality of Life

Patient reported Quality of Life assessments (as permitted by competent authority):

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ; Appendix H)
- 12-Item Short Form Health Survey (SF-12; Appendix I)

7.5 Data Sources

7.5.1 Baseline Data Collected at Study Enrollment

An initial Baseline Visit will be scheduled for patients who are considered for study participation. After written informed consent is obtained, each screened patient will be assigned a unique study identification number. Study eligibility will be determined by review of the inclusion/exclusion criteria. Patients who are enrolled in the study will then have the following information recorded and undergo the baseline assessments.

The following data will be recorded at the time of enrolment into the study.

- Demographic data
- Medical history:
    - General, including co-morbid conditions and other autoimmune disease(s)
    - Prior serious and atypical infections and dates
    - Malignancies
    - hepatic injury
    - Infusion-related reactions
    - Organ transplantation, including bone marrow or stem cell transplants
- UC/CD history, including:
    - Dates and age of onset / diagnosis
    - Disease location(s)
    - Surgical history / disease management
    - Health resources used within 1 year before study enrollment (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)
- UC and CD activity assessment:
    - Partial Mayo score for patients with UC
    - Full Mayo score for patients with UC with endoscopy in 1 month prior to follow-up visit.
    - Harvey-Bradshaw Index score for patients with CD
    - Fecal calprotectin, most recent value and date (if measured)
    - C-reactive protein, most recent value and date (if measured)
    - Presence of extra-intestinal manifestations
- Any prior use of the following categories of drugs, including specific drug used, indication, dose received, route of administration, and dates of use:

- TNF-α antagonists, azathioprine, 6-mercaptopurine (6-MP), methotrexate, 5-aminosalicylic acid (5-ASA), or any approved UC or CD medication
- Any agents that have a known association with PML(alemtuzumab, belatacept, brentuximab vedotin, efalizumab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
- Prior use of other immunomodulatory, anti-neoplastic, or immunosuppressive agents for UC or CD, including specific drug used, dose received, route of administration, and dates of use, within 5 years before study enrollment
- Prior use of other immunomodulatory, anti-neoplastic, or immunosuppressive agents for other indications, including specific drug used, indication, dose received, route of administration, and dates of use, within 5 years before study enrollment
- Prior use of systemic corticosteroids, including specific drug used (if known), indication, dose range, route of administration, and dates of use, within 6 months before study enrollment
- Prior use of antibiotics to treat UC/CD, including specific drug used, dose received, route of administration, and dates of use, within 5 years before study enrollment

- Patient Reported Quality of Life assessments:
  - SIBDQ
  - SF-12

7.5.2 Prospective Data Collection

The sites will record the following data at least every 6 months during the study, and at additional visits if needed for induction or management of disease exacerbation, according to standard practice in other long-term observational studies of patients using biological drugs for treatment of UC and CD. If additional, unscheduled visits are performed, the minimum data to be recorded are SAEs, Adverse Events of Special Interest, adverse reactions and adverse events.

- Treatment and/or study discontinuation: date, reason (e.g., AEs, surgery, death, loss of efficacy)
- Vedolizumab infusions, including dose and dates
- Any use of the following categories of drugs, including specific drug used, indication, dose received, route of administration, and dates of use:
  - TNF-α antagonists, azathioprine, 6-MP, methotrexate, 5-ASA, or any approved UC or CD medication

- Any agents that have a known association with PML (alemtuzumab, belatacept, brentuximab vedotin, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
- Use of systemic corticosteroids, including specific drug used (if known), indication, dose range, route of administration, and dates of use
- Use of antibiotics to treat UC/CD, including specific drug used, dose received, route of administration, and dates of use

- IBD activity assessment:
  - Partial or full Mayo score for patients with UC
  - Harvey-Bradshaw Index score for patients with CD
  - Fecal calprotectin, all test results and dates (if measured)
  - C-reactive protein, all test results and dates (if measured)
  - Presence of extra-intestinal manifestations
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC or CD)
- Patient Reported Quality of Life assessments:
  - SIBDQ
  - SF-12
- Adverse Events of Special Interest
  - Serious infections and opportunistic infections such as PML
  - Gastrointestinal infections
  - Lower and upper respiratory infections
  - Other clinically significant infections
  - Malignancies
  - Infusion-related reactions and hypersensitivity
  - Hepatic injury
- Other safety information
  - All other SAEs
  - Adverse reactions
  - Any other adverse events the investigator becomes aware of
  - Pregnancies in female study participants. Information will be collected at notification on:
    - Date last menstrual period

- Date pregnancy confirmed
- Pregnancy history

- Pregnancy outcome information will be collected, including:
  - Pregnancy outcome (full-term, pre-term, fetal loss/stillbirth, miscarriage, induced abortion)
  - Neonatal characteristics (Apgar scores , Respiratory distress or other complications, Admission to Neonatal Intensive Care Unit / length of stay,
  - Congenital anomalies

7.6 Study Size

The study aims to recruit 2,500 patients to the vedolizumab cohort and 2,500 patients to the other biologic agents cohort, who will then be followed-up for up to 7 years. This sample size was based on the following factors: likely recruitment rate of sites and patients, duration of vedolizumab exposure, and anticipated loss to follow-up rate in the study. Details on the underlying assumptions for each of these factors are provided in Appendix J.

It is anticipated that each cohort will accumulate over 11,000 person-years of follow-up and have more than 2,000 patients with at least 4 years of follow-up. A vedolizumab exposure discontinuation rate of 55% during the first 2 years, and 10% thereafter is expected, based on phase 3 clinical trial data. It is anticipated this will result in at least 1,000 patients with at least 24 months of exposure in each cohort, and 2812 person-years of vedolizumab exposure during follow-up. If this target is not reached additional patients and/or time may be added to the study until this target is reached.

The incidence of SAEs and Adverse Event of Special Interest with no reported events during the study can be estimated for each cohort at no greater than 1.2 per 1000 patients per cohort overall, and no greater than 3 per 1000 patients for patients treated for at least 24 months, using the "rule of 3". Based upon these estimates, the sample size would allow detection of uncommon risks associated with vedolizumab, including common cancers and the detection of PML, occurring at the rate observed among the overall post marketing population of natalizumab patients [14].

7.6.1 Power Calculation

The serious infection rate among CD patients treated with infliximab was 2.06 per 100 person-years in the TREAT registry, based on 5-years of follow-up [15]. A comparison of serious infection rate in UC and CD patients using the HealthCore Integrated Research Database, found that UC patients had a serious infection rate approximately half that of CD

patients [16]. Based on these two studies, we have assumed an expected serious infection rate of 2.06 per 100 person-years for CD patients, and 1.03 per 100 person-years for UC patients, the later represents 50% of the observed rate in CD patients reported in the TREAT study. We have also assumed for the present study that 50% of the patients recruited will have UC and 50% will have CD, giving an expected joint (UC + CD) serious infection rate of 1.55 per 100 patient-years.

Table 1 presents the sample size estimates for a range of risk windows and hazard ratios. The estimates utilized a background serious infection rate of 0.0155 per person year (1.55 per 100 person-years), and assume mean duration of drug exposure of 1.5 years, a mean duration of follow-up of 4.54 years in each cohort (Appendix J), a 2-sided type I error, 90% power,and equal sized cohorts. The risk windows are (i) up to 3 months after each exposure, which based on 1.5 years mean exposure, would provide a 1.75 year follow-up period (ii) 15 months after each exposure, which would yield a 3 year follow-up period, and (iii) unrestricted risk window to end of follow-up, the mean of which is estimated 4.54 years. The estimates include allowance for cumulative loss to follow-up of 2.4%, 4.2% and 6.6% in the respective risk windows. Sample size estimates were calculated using a log-rank test for survival curves for the 2 cohorts and were performed in SAS 9.4.

Table 1. Estimated serious infection events and sample size in both exposure cohorts combined by hazard ratio, for 90% power and 5% type I error.

	Risk window up to 3 months after each exposure (1.75-year follow-up period)		**Risk window up to 18 months after each exposure (3-year follow-up period)**		**Risk window to end of follow-up (4.54-year follow-up period)**	
HR	**Events**	**Sample size**	**Events**	**Sample size**	**Events**	**Sample size**
1.1	4618	164910	4623	97172	4665	65568
1.2	1267	43216	1268	25476	1280	17198
1.3	616	20090	616	11848	621	8002
1.4	377	11798	377	6960	380	4704
1.5	262	7870	262	4644	264	3140
1.75	141	3852	141	2274	142	1540
2.0	94	2366	94	1398	95	946

2.5	57	1228	57	728	57	494
3.0	42	790	41	468	41	318

Table 2 presents additional sample size estimates using the same assumptions as above, but with the most restrictive risk window for serious infections: from cohort entry to 3 months after each exposure (Section 7.8.4), with mean follow-up during the restricted risk window of 1.75 years.

Table 2. Estimated serious infection events and sample size in both cohorts combined by hazard ratio, type I error (α-level), and power, for a risk window of up to 3 months after each exposure.

	Power					
	80%		**90%**		**95%**	
	α level					
HR	**0.05 Event (sample size)**	**0.025 Event (sample size)**	**0.05 Event (sample size)**	**0.025 Event (sample size)**	**0.05 Event (sample size)**	**0.025 Event (sample size)**
1.1	3450 (123184)	4177 (149178)	4618 (164910)	5454 (194788)	5711 (203946)	6637 (237034)
1.2	947 (32282)	1146 (39092)	1267 (43216)	1497 (51046)	1567 (53444)	1821 (62116)
1.3	460 (15008)	557 (18174)	616 (20090)	727 (23730)	761 (24846)	885 (28878)
1.4	282 (8814)	341 (10672)	377 (11798)	445 (13936)	466 (14590)	542 (16958)
1.5	196 (5878)	237 (7118)	262 (7870)	309 (9294)	324 (9732)	376 (11310)
1.75	105 (2878)	127 (3484)	141 (3852)	166 (4548)	174 (4762)	202 (5536)
2.0	71 (1768)	85 (2140)	94 (2366)	111 (2794)	117 (2926)	135 (3400)
2.5	43 (918)	52	57	67	70	82

		(1112)	(1228)	(1452)	(1520)	(1766)
3.0	31 (592)	38 (716)	42 (790)	49 (934)	52 (978)	60 (1136)

The sample size of 2.500 patients in each exposure cohort (5,000 in total) for the shortest risk window will be sufficiently large enough to detect HR = 1.54 with 80% power, HR = 1.64 with 90% power and HR = 1.72 with 90% power, based on α=.05.

7.6.2 Confirmation of Power and sample size at 2.5-year follow-up

The observed rate of serious infection and duration of vedolizumab therapy in the study will be assessed at the 2.5-year follow-up analysis to confirm the above sample size and power calculations. If needed, the sample size and/or duration of follow-up will be increased (but not decreased) to meet the following target:

- Statistical power of 90%
- Hazard ratio of 1.64

7.7 Data Management

All data collected in the context of this study will be stored and evaluated in accordance with regulatory requirements and applicable guidance for electronic records.

Electronic data collection will be performed using eCRFs. Sites will enter data into the electronic data capture (EDC) system according to the schedule presented in Appendix A and according to instructions from the Sponsor and/or designee. Patients will be identified by use of the identification number assigned to them when they enrol in the study.

Before the first patient's data are recorded, the Sponsor and/or designee will meet with the Investigator and the study center's personnel to train them on recording the data on the eCRFs using the EDC system.

Only authorized personnel will have access to the EDC system. Data will be entered into eCRFs in accordance with instructions from the Sponsor and/or designee.

Each Investigator is responsible for ensuring that accurate data are entered into the EDC system in a timely manner.

On-line logic checks will be built into the system, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to

the clinical study center and answered electronically by that study center's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable), as well as the Investigator's approval of all changes performed on the data, will be collected.

The Investigator will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor and/or designee via the system, providing missing or corrected data, approving all changes performed on the patient data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

All submitted eCRFs will be checked for missing information and queries will be generated during the course of the study to prevent the occurrence of most missing data, with special focus on completeness of drug exposure data, SAEs, and Adverse Events of Special Interest. All adverse events will be coded, using MedDRA Version 13.1 or later. Drug Exposures will be coded to WHO Drug Dictionary.

7.8 Data Analysis

This section provides information on the statistical analysis. A more detailed description is provided in the Statistical Analysis Plan (SAP). The SAP will be finalised prior to data lock for the 2.5-year follow-up analysis. All analyses will be performed using SAS® Version 9.3 or later.

7.8.1 Disposition, Demographic, and Baseline Clinical Analyses

Disposition data will be presented for all patients enrolled. All other analyses will be based upon the population enrolled who received at least 1 dose of vedolizumab or other biologic agents. Demographic, and baseline clinical data will be summarized descriptively by exposure cohort by disease (UC and CD), and exposure status at cohort entry (conventional therapy failure vs. biologic failure). Covariates will have a 'missing' category for patients with missing data, and will be included in the analyses. Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables; and frequency (n and percent) for categorical variables.

7.8.2 Drug Exposure

Drug exposure will be treated as a time updating variable. At cohort entry, all patients will be naïve to vedolizumab, although prior use of other biologics is permitted.

Vedolizumab and other biologic agent exposures will be treated as time updating variables using the methods of Stricker and Stijnen [17]. Risk estimates for safety endpoints will be presented according to duration, cumulative dose, and time since first dose to vedolizumab.

Discontinuation of vedolizumab, switching from vedolizumab to comparator, and switching from comparator to vedolizumab will be permitted during the follow-up period. In the primary analyses, patients who discontinue vedolizumab without switching to comparator would have exposure end at time of vedolizumab discontinuation, but follow-up would continue through to the end of the study. Patients who discontinue vedolizumab and switch to a comparator would have their time at risk prior to switching allocated to the vedolizumab group; then after switching, time at risk through to end of the study would be allocated to the comparator group. A similar approach will be taken for patients in the comparator group who switch or discontinue treatment. A sensitivity analyses will be undertaken using a more conservative alternative analytical approach, with patient follow-up censored at switching.

Latency periods between start of drug exposure and onset of safety endpoints for specific outcomes would be incorporated into the analytical models where appropriate. For infections and hypersensitivity reactions, no latency period is applied, while for malignancies a 6 month latency period will be applied.

7.8.3 Safety Analyses

Section not used. See 7.8.4 – 7.8.7 for safety analyses.

7.8.4 Adverse Events of Special Interest

For each Adverse Event of Special Interest, a descriptive analysis of event characteristics will be presented together with a summary of distribution by demographic and other baseline characteristics. Data will also be presented as number of events, person-years at risk, and a crude incidence rate with 95% CIs for all patients, and separately for UC and CD patients, and by exposure cohort.

Analyses will be based on first occurrence of an event. Patients with a history of an event prior to cohort entry will be excluded from the analyses for that adverse event of interest, to enable the analyses to focus on incident events only. The analyses will include all events in both exposure cohorts, including events coded as not related to study drugs.

Analyses will include assessment of duration, cumulative dose, and time since first dose of vedolizumab. Further details of exposure assessment are provided in Section 7.8.2. Sub-group analyses will focus on patients who were switching biologics at cohort entry, patients who were naive to biologics at cohort entry, and patients with/without prior natalizumab exposure.

Serious infections The primary safety analysis will focus on serious infections and test the hypothesis that there is no difference in the incidence rate for serious infections between the vedolizumab and the comparator cohort. The primary analysis will be based on the first event of any serious or opportunistic infection including PML. Secondary analyses will look at first event of each specific serious and opportunistic infection, including PML. Analyses

will assess several risk windows, ranging from up to 3 months after each infusion, to any time during follow-up.

Cases classified as definite or probably PML will be included in the analyses. Cases classified as possible PML and not PML will be included in the study report but not in the main analyses.

Malignancies Analyses will focus on malignant neoplasms and carcinomas in situ. Benign neoplasms will be included in the study report but not in the main analyses. Analyses will examine all malignancies pooled, then separately for each of the most common malignancies. Persons with a history of the malignancy or a pre-malignant disorder prior to cohort entry will be excluded from the analysis for that malignancy. Additionally, follow-up time for malignancies will commence 6 months after cohort entry to minimize the likelihood of including pre-existing malignancies.

Infusion-related reaction and hypersensitivity: Currently vedolizumab is available for infusion only, whereas some other biologics are available as subcutaneous injections. The infusion-related reaction analyses will thus only focus on risk within persons who receive a biologic by infusion, while the hypersensitivity analysis will be based on all study participants. Validated cases of infusion-related reaction will be included in the analyses. Suspected cases not validated will be included in the study report but not in the main analyses.

Hepatic Injury: Cases of DILI adjudicated as "Definite", "Highly likely" and "Probably" will be included in the analyses, as these are the events most likely to be due to drug-related hepatotoxicity. Cases adjudicated as "Possibly", Unlikely, "Excluded" and "Unassessable" will be included in the study report but not in the main analyses.

7.8.5 Cox Proportional Hazard Models

For each Adverse Event of Special Interest, time varying Cox proportional hazard models will be used to generate adjusted hazard ratios (HRs) with 95% CIs. Analyses will be done using all patients, and separately for UC and CD patients. Baseline and time-updating variables will be assessed to determine if they are confounding factors. A confounding factor is defined as a variable that causes at least a 5% shift in the HR.

To minimize risk of treatment allocation bias (channelling bias) due to imbalances in baseline characteristics between the two exposure cohorts, propensity scores (propensity to be prescribed vedolizumab versus a comparator biologic agent at cohort entry) will be created based on regression modelling of baseline covariates. The Cox proportional hazard models will utilize propensity score stratification [18]. The generation of propensity scores will be based on logistic regression modeling of baseline variables with a stepwise selection criterion. Two approaches of propensity score stratification for HR estimates will be

performed. First, the propensity score will be included as a categorical variable in the multivariate proportional hazard model. Second, propensity score stratum-specific HRs will be generated in which the hazards function within each stratum will be generated using multivariate proportional hazard models. Further details on the methodology for creation and use of the propensity scores are provided in the Statistical Analysis Plan.

7.8.6 Additional analyses of Adverse Events of Special Interest

A specific sub-group analysis will be carried out to assess safety in patients who have ever been exposed to natalizumab.

A sensitivity analysis will be undertaken where appropriate to assess the impact of inclusion vs. exclusion of patients with missing covariate data from the analyses.

Additional subgroups also may be examined, as deemed appropriate by indication (UC versus CD) or confounding factors (e.g., previous treatment and duration; Section 7.10.4) or effect modification (e.g., baseline disease severity, prior surgeries or other hospitalizations, prior infusion reactions; Section 7.10.5).

7.8.7 Other Adverse Events

Other SAEs, adverse reactions, pregnancies and pregnancy outcomes will be summarized using descriptive statistics by cohort with stratification by baseline characteristics.

7.8.8 Disease Activity, Use of Healthcare resources, and Quality of Life Analyses

Changes over time in UC and CD disease activity scores, medications, use of health resources, and Quality of Life scores will be summarized by cohort, with stratification by baseline variables, using descriptive statistics.

7.8.9 Analysis timelines

Two follow-up analyses of the study's safety data are planned:

- 2.5-year follow-up of the cohorts
- 7-year follow-up of the cohorts.

The 2.5-year follow-up analysis will be performed after 50% of the expected vedolizumab population has been enrolled and completed at least 1 year of treatment. The 7-year follow-up will be based on a data lock of 30 June 2021.

As part of the 2.5-yr follow-up, analyses will include a re-assessment of statistical power and sample size, based on the observed serious infection rate occurring in the study. The 2.5-year analyses will also include exploratory analyses of each Adverse Event of Special Interest to calculate the optimum risk windows. There is no intention to stop this observational study based on the outcomes of the 2.5-year follow-up analyses. As is typical

of other long term prospective cohort studies, there is no splitting of α between the 2.5-year follow-up and 7-year follow-up analyses.

7.9 Quality Control

Designated study personnel will participate in a training program that will encourage consistency of process and procedures at the investigative sites and ensure collection of high-quality data for this study. All sites will be trained on the protocol, study logistics, and the EDC system. Retraining will be conducted as needed. Investigators will be reminded of the processes and importance of reporting adverse reactions, SAEs, and other information.

Initial monitoring will be performed to ensure that informed consent forms (ICFs) have been completed for all enrolled patients. Subsequently, escalated monitoring may be performed at selected sites as needed, according to the Monitoring Plan. At monitoring visits, the progress of the study and any procedural or data issues will be discussed with the Investigator and/or designee. The Investigator will make patient source documents available for review and will permit the Sponsor, representatives of the Sponsor, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or regulatory authorities to inspect facilities and original records relevant to this study. The Investigator will allocate adequate time to discuss findings and relevant issues and, after the visit, to complete appropriate corrective actions as necessary.

7.10 Limitations of the Research Methods

7.10.1 Selection Bias

The Investigators will attempt to consecutively enrol all patients who consent and meet the selection criteria, regardless of health status or other considerations.

Benchmark populations for comparison of outcomes will be extracted from available data sources for baseline levels of disease severity and duration that are comparable to the inclusion criteria for this study.

7.10.2 Information Bias

Because treatment for some of the Adverse Events of Special interest may be provided by the patient's primary health care practitioner or another physician, rather than the study investigator, reporting of these events could be biased by patient recall and by differential availability of medical records, e.g., for patients treated through health maintenance organizations versus private clinics. Study site training will therefore include emphasis on consistent solicitation of event and treatment information from patients.

7.10.3 Treatment allocation bias

Observational studies are particularly prone to treatment allocation bias (channelling). It is possible patients in one exposure cohort may have more advanced disease or more patients who failed conventional therapy or have switched biologic therapies, or there are imbalances in other baseline covariates between exposure cohorts which could produce biased risk estimates.

To minimize this bias, propensity score methodology will be used in the analyses to control for baseline differences between exposure cohorts.

7.10.4 Confounders

Prior and/or concomitant exposure to immunosuppressive agents and/or TNF-α antagonists could increase the likelihood of PML, other opportunistic infections, and malignancies. Therefore, subgroup analyses may be used, if deemed appropriate, to distinguish between background risk associated with these agents, and use of vedolizumab. Similarly, history of malignancy could be related to incidence of new malignancies; prior infection and vaccination status to opportunistic infections; and previous treatment with other monoclonal antibodies to incidence of infusion-related reactions. The data on medical and disease history collected at Baseline may be used in subgroup and stratified analyses and calculation of hazard ratios.

7.10.5 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 enrolment, are likely to be associated with risk for safety events during the study period. In addition, risk of outcomes such as opportunistic infections appears to increase with treatment duration for some IBD therapies [8, 15]. Subgroup analyses may be used, if deemed appropriate, to clarify these effects.

7.10.6 Patients Lost to Follow-Up

Because the follow-up duration will be until termination of the study, the proportion of patients lost to follow-up might be significant

8. PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent

Before any protocol-specified assessments are carried out, the Investigator or designee will explain details of the protocol and study procedures to patients and/or their legally acceptable representative. Patients will be informed that they are free to withdraw from the study at any time.

Each patient, or a legally acceptable representative, must sign an ICF, approved by the IRB/IEC, indicating their consent to participate. The ICF will include a provision allowing study personnel to contact the patient individually in the event that the patient leaves the Investigator's care (Section 7.3.3). ICFs and assent forms will conform to the requirements of 21 CFR 50.20-27 and International Conference on Harmonisation E6 4.8, Principles of Good Clinical Practices. The original signed ICFs must remain in the patient's file in the clinic. Each patient will receive a copy of the signed ICF.

Each patient enrolled in the study, or a legally acceptable representative, also must sign a medical records release form permitting abstraction of medical data for entry in the study EDC system. Individual patient data included in the study database will be treated in compliance with all applicable laws and regulations regarding privacy protection.

8.2 Institutional Review Board / Independent Ethics Committee Approval

Investigators will be required to obtain approval from the appropriate IRB/ IEC, and will be responsible for maintaining all related documents, before enrolment of any patient into the study. The Investigator is responsible for informing the IRB/IEC of the completion of the study and should provide any required study status and/or safety report(s).

8.3 Adherence to the Protocol

The study must be conducted as described in the approved protocol, except for an emergency situation in which proper care for the safety of the patient requires intervention. Any significant deviation from the protocol must be reported immediately to the Sponsor and IRB/IEC.

8.4 Protocol Amendment

Any amendment to the protocol will be created by the Sponsor, and subsequently submitted by the site to the IRB/IEC and appropriate regulatory authority 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 must be obtained.

8.5 Retention of Patient Records

When the study is completed, the Investigator must retain the essential documents for as long as needed to comply with regulatory guidelines and Sponsor requirements. The Investigator will notify the Sponsor prior to moving or destroying any of the study documents.

8.6 Confidentiality

The information in this and related documents from the Study Sponsor includes 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.

Individual patient medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted below, is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare.

Data generated as a result of this study are to be available for inspection on request of the Sponsor's representative, the IRB/IEC, or local regulatory agency.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Events

An AE is any unfavourable 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.

All AEs (serious and non-serious; related and unrelated) reported by patients will be captured in the eCRF AE report form within 24 hours after the investigator becomes aware of the event. All AEs must be recorded on the eCRF, whether or not considered causally related to vedolizumab.

9.1.2 Severity

The Investigator will use the following definitions of severity in the evaluation of AEs:

- **Mild:** An AE that is easily tolerated and does not interfere with daily activities.
- **Moderate:** An AE that is sufficiently discomforting so as to interfere with daily activities.
- **Severe:** An AE that prevents normal everyday activity. Note that "severe" is not synonymous with "serious": an AE may be assessed as severe without meeting the criteria for an SAE (Section 9.1.5).

9.1.3 Relationship to Study Drug

The following definitions of relationship should be used to characterize the suspected causality of each AE as either related or not related to vedolizumab or other biologic treatment. This assessment should be based on the Investigator's consideration of all available information about the event, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (e.g., underlying illness, concurrent conditions, concomitant treatments) [19]:

- **Related**: There is a reasonable possibility that the drug caused the event.
- **Not related**: There is not a reasonable possibility that the drug caused the event.

9.1.4 Adverse Reactions

For the purposes of this study, an adverse reaction is an AE that is considered related to vedolizumab or other biologic treatment according to the definition in Section 9.1.3.

9.1.5 Serious Adverse Events

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

- Is fatal or life threatening, i.e., in the view of the Investigator, 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 inpatient 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 disease progression 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.

9.2 Collection and Recording of Adverse Event Information

Collection of AEs will commence after a patient has provided informed consent, all AEs are reported on the eCRF Adverse Event form.

At each study visit, patients will be asked by the investigator if any infections, malignancies, infusion reaction, hepatic injury, hospitalisations, or any other SAEs or any other adverse reaction have occurred since last clinic visit. Any other AEs mentioned by the patient should also be recorded on the eCRF, even if not considered related to vedolizumab or other biologics.

Additionally, any adverse events reported by the patient to other study personnel; or to clinic staff during infusions, revealed by observation, physical examination, or other diagnostic procedures should be recorded on the eCRF.

When possible, signs and symptoms indicating a common underlying pathology should be noted as a single, comprehensive event (i.e., an overall diagnosis, whether suspected or confirmed, should be provided wherever possible).

Sufficient information should be reported to enable the adverse event to be fully described. All reports should at a minimum include: a comprehensive description of the event, event start and end dates, severity, relationship to vedolizumab or other biologic treatment, whether the event is serious, action taken, and outcome. Guidance on additional information to be collected for specific safety events (infections, PML, malignancies, infusion reactions, and liver injuries) is provided in Section 7.4.1.

Where needed, the investigator should consult with the relevant treating physician to obtain any missing or incomplete information on an adverse event. After submission of the initial adverse event report into the eCRF, the Investigator may be contacted by the Sponsor to request additional information on the event or for data clarification. All new information obtained on the event must be entered into the eCRFs Adverse Event form within 24 hours of Investigator awareness of the new information.

9.3 Reporting of Adverse Events

All adverse events collected during the study will be included in the study report.

The following adverse events within the vedolizumab arm of the study will be reported to regulatory authorities in accordance with local reporting requirements or the Sponsor's post marketing commitments:

- Serious infections
- Gastrointestinal infections
- Lower and upper respiratory infections
- Other clinically significant infections
- Malignancies
- Infusion-related reactions and hypersensitivity
- Hepatic injury
- Other SAEs
- Other adverse reactions

The Sponsor assumes responsibility for reporting of the above adverse events occurring in patients exposed to vedolizumab to regulatory authorities. The Investigator is responsible for ensuring that all commitments are fulfilled to the IRB/IEC that approved the study protocol.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Sponsor and/or designee will prepare progress reports as required by competent authority. In addition, these data may be summarized periodically for presentation at professional conferences and sessions, as appropriate.

2.5-year and 7-year follow-up analyses are planned and will be submitted by the Sponsor to regulatory authorities no later than 1 year after data lock. 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 [20] will be followed, and this study will be entered into the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register of studies (encepp.eu/encepp/studiesDatabase.jsp) and Clinicaltrials.gov.

None of the parties involved in the management/conduct/analysis of this study may publish any study-related data without the written permission of Takeda Pharmaceutical Company Limited.

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Appendix A Schedule of Recommended Assessments

	Baseline	At Least Every 6 Months[a]
Informed consent	X	
Demography	X	
Medical history, including comorbid conditions and other autoimmune disease(s), prior serious and atypical infections, malignancies, and organ transplantation, including bone marrow or stem cell transplants	X	
UC/CD history, including dates and age of onset / diagnosis, disease location(s), surgical history / disease management, and health resources used due to UC/CD within 1 year before study enrollment	X[b]	
Prior use of TNF-α antagonists, azathioprine, 6-MP, methotrexate, 5-ASA, systemic corticosteroids, antibiotics for UC/CD, or any approved UC/CD medication	X	
Prior use of agents that have a known association with PML	X	
History of infusion-related reactions	X	
Health resources used due to UC/CD (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of UC/CD)		X
Vedolizumab or other biologic treatment administration	X	X
Any use of TNF-α antagonists, azathioprine, 6-MP, methotrexate, 5-ASA, systemic corticosteroids, antibiotics for UC/CD, or any approved UC/CD medication		X
Any use of agents that have a known association with PML		X
IBD activity assessment: Partial Mayo score for patients with UC Harvey-Bradshaw Index score for patients with CD Fecal calprotectin (if measured) C-reactive protein (if measured) Extra-intestinal manifestations	X	X[c]
Patient reported Quality of Life assessment (SIBDQ, SF-12)	X	X[c]
SAEs		X[a]
Adverse Events of Special Interest		X[a]
Adverse reactions, adverse events		X[a]
Pregnancy and neonatal characteristics (females only):		X

Pregnancy history: Date confirmed, vedolizumab exposure at estimated time of conception, vedolizumab exposure during pregnancy		X[d]
Pregnancy outcome: Full-term, pre-term, fetal loss/stillbirth, miscarriage, induced abortion		X[e]
Neonatal characteristics: Apgar scores (if known), Respiratory distress or other complications, admission to neonatal intensive care unit / length of stay, congenital anomalies		X[d]

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; CD = Crohn's disease; GI = gastrointestinal; SAE = serious adverse event; SF-12 = 12-Item Short Form Health Survey; SIBDQ = Short Inflammatory Bowel Disease Questionnaire; TNF-α = tumor necrosis factor alpha; UC = ulcerative colitis

[a]If additional, unscheduled visits are performed, the following data should be recorded, at a minimum: SAEs, Adverse Events of Special Interest, and adverse reactions.

[b]Within 1 year before study enrollment

[c]To be collected at the routine GI visit nearest to the 6-month time point

[d]To be reported as information becomes available

[e]To be reported within 30 days after delivery

Appendix B Patient Retention Strategies

This appendix not in use.

Appendix C PML Case Definition

Table 1 Criteria for PML diagnosis, based on clinical, radiographic, and laboratory data

Certainty of PML diagnosis	Compatible clinical features	Compatible imaging findings	CSF PCR for JC virus
Definite	+	+	+
Probable	+ -	- +	+ +
Possible	+ -	+ -	-/ ND +
Not PML	- + -	- - +	- - -

Abbreviations: ND = not done or equivocal result.

Table 2 Criteria for PML diagnosis, based on histopathology

Certainty of PML diagnosis	Classic Histopathologic triad [1]	Immuno-histochemistry or electron microscopy	Tissue PCR for JC virus
Definite	+ + +	+ -/ND +	+ + -/ND
Probable [2]	+	-	-/ND
Possible	-	+	-/ND
Not PML	-	-	-/ND

Abbreviations: ND = not done. [1] Classic histopathologic triad: demyelination, bizarre astrocytes, enlarged oligodendroglial nuclei. [2] The presence of clinical and radiographic focal features that support the diagnosis not resulting from the possible presence of other confounding diseases increases this category to definite PML.

Source: [9]

Appendix D Clinical criteria for diagnosis of hypersensitivity

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

And at least one of the following:

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

OR

2. Two or more of the following that occur rapidly after exposure (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia [collapse] syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

OR

3. Reduced BP after exposure (minutes to several hours): systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

Abbreviations: PEF, Peak expiratory flow; BP, blood pressure.

Source: [10].

Appendix E Drug-induced liver injury algorithm

	Numerical Scale	Summary	Timing	Competing causes	Drug and Signature
Definite	>95% likely	The relationship between the drug and liver injury is essentially certain. The evidence that the drug caused the injury is "beyond a reasonable doubt."	The timing of onset and recovery are highly compatible with drug induced liver injury	No other potentially competing drug is being (or has been) received and all other possible diagnoses are unequivocally excluded	Liver injury is highly typical for the particular drug in question, which is well known to cause hepatotoxicity (a "signature" is thus typically present). In the event that the drug is new and there is no previous record of toxicity, all other elements of the association must be certain.
Highly likely	75 to 95% likely	The link between the drug and liver injury is very strong, but may not be absolutely certain. The evidence for the drug causing the injury is "clear and convincing" but may not be definite.	The timing of onset and recovery are highly compatible with drug induced liver injury, although subtle variations in timing may be present.	Other potential diagnoses have been ruled out and other known hepatotoxins are unlikely to cause the liver injury	The drug in question has been known to cause liver injury but the signature may be somewhat atypical for this agent; or it has been less certainly linked to liver injury in the past. In the event that the drug is new

					and there is no previous record of toxicity, other elements of the association must be certain.
Probable	50 to 75% likely	Liver injury is compatible with the drug but the clinical picture may not be entirely typical. The "preponderance of the evidence" supports the link between the drug and the liver injury.	The timing of onset and recovery are compatible with drug induced liver injury, but variations may be present	Other potential diagnoses have been largely ruled out and other known hepatotoxins are unlikely to cause the liver injury.	The agent has been linked to liver injury in the past, although this association may be weak. A signature, if present, may be atypical for this agent.
Possible	25 to 50% likely	Liver injury is possibly due to the drug, but the clinical picture may not be typical or convincing. Because there is less than "preponderance of evidence," attribution of the liver injury is weak but cannot be excluded.	The temporal association between liver injury and receipt of the drug is often weak.	Other potential diagnoses have not necessarily been eliminated from the differential diagnosis. Other known hepatotoxins may have possibly caused the liver injury.	The agent may have been only equivocally linked to liver injury and the pattern may not be typical.
Unlikely	5 to 25% likely	Liver injury is not compatible with the	Although there may be a temporal	Other potential diagnoses have not	The agent has been only weakly linked

		drug. The bulk of the evidence is against an association between the drug and liver injury	association between the liver injury and receipt of the drug, the relationship is atypical	been excluded, and in fact are more likely to be responsible for the liver injury than the drug in question. Other known hepatotoxins may have possibly caused the liver injury.	to liver injury and/or the pattern is highly atypical.
Excluded	<5 % likely	The evidence for an etiological factor other than the drug causing the injury is beyond a reasonable doubt			
Unassessable		Insufficient information for assessment			

Source: [11].

Appendix F 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	
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: [12].

Appendix G Harvey-Bradshaw Index for Crohn's Disease

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].

Appendix H 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 which 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 one 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

Appendix I 12-Item Short Form Health Survey (SF-12)

Patient Name _____

Patient Signature _____ Date _____

In general, would you say your health is:

Excellent (1)
Very Good (2)
Good (3)
Fair (4)
Poor (5)

Does your health limit you in these activities? If so, how much?

Moderate activities, such as: moving a table, pushing a vacuum cleaner, bowling, or playing golf:

Yes, limited a lot (3)
Yes, limited a little (2)
No, not limited at all (1)

Climbing several flights of stairs:

Yes, limited a lot (3)
Yes, limited a little (2)
No, not limited at all (1)

During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health?

Accomplished less than you would like:

Yes (2)
No (1)

Were limited in the kind of work or other activities:

Yes (2)
No (1)

During the past 4 weeks, were you limited in the kind of work you do or other regular activities as a result of any emotional problems? (such as feeling depressed or anxious)

Accomplished less than you would like:

Yes (2)
No (1)

Didn't do work or other activities as carefully as usual:

Yes (2)
No (1)

During the past 4 weeks, how much did pain interfere with your normal work? (including both work outside the home and housework)

Not at all (1)
A little bit (2)
Moderately (3)
Quite a bit (4)
Extremely (5)

How much of the time during the past 4 weeks…

Have you felt calm and peaceful?

All of the time (1)
Most of the time (2)
Some of the time (3)
A little of the time (4)
None of the time (5)

Did you have a lot of energy?

All of the time (1)
Most of the time (2)
Some of the time (3)
A little of the time (4)
None of the time (5)

Have you felt downhearted and blue?

All of the time (1)
Most of the time (2)
Some of the time (3)
A little of the time (4)
None of the time (5)

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities? (like visiting with friends, relatives, etc.)

All of the time (1)
Most of the time (2)
Some of the time (3)
A little of the time (4)
None of the time (5)

Appendix J Exposure, Follow-up and Sample Size Assumptions

Anticipated recruitment rate

Appendix J Table 1 displays the projected recruitment. Recruitment initiation and timelines will vary by country depending on commercial factors and timelines for reimbursement. A site recruitment plan has been established with assumptions built in that include Europe initiating recruitment of sites in Q1 2015 and United States initiating recruitment of sites in Q2 2015. The recruitment plan targets recruitment of more than 300 study sites and assumes that between 0.2 and 1 patient per site per month will be recruited into each arm of the study.

It is planned that the recruitment rate for the vedolizumab and comparator groups will run in parallel and at the same rate.

Appendix J Table 1 Projected Recruitment in Study MLN-0002_401

Year	Number of patients recruited in vedolizumab group	Cumulative number of patients recruited in vedolizumab group	Cumulative number of patients recruited in vedolizumab & comparator groups
2015	754	754	1508
2016	1088	1842	3684
2017	659	2500	5000

Anticipated duration of vedolizumab exposure

Predictions of duration of vedolizumab exposure are based on attrition rates from the vedolizumab clinical study data from Studies C13006, C13007, and C13008.

- For the first 12 months on study, we expect 35% of patients to stop vedolizumab (the vast majority will remain under follow-up in the study, but no longer using vedolizumab) This is based on the attrition rate observed in patients during the first year of vedolizumab treatment in Study C13007, the phase 3 Crohn's disease study. The attrition rate observed in patients during the first year of vedolizumab treatment in Study C13006, the phase 3 ulcerative colitis study, was 23%. The higher rate observed in Study C13007 was utilized in order to take a more conservative approach in projecting attrition rates for the post approval safety study.

- For the second 12 months on vedolizumab, a further 25% of patients are predicted to stop vedolizumab, based on observed discontinuation rates in the first 6 months in Study C13008 for patients who entered this study from studies C13006, C13007, or C13011.

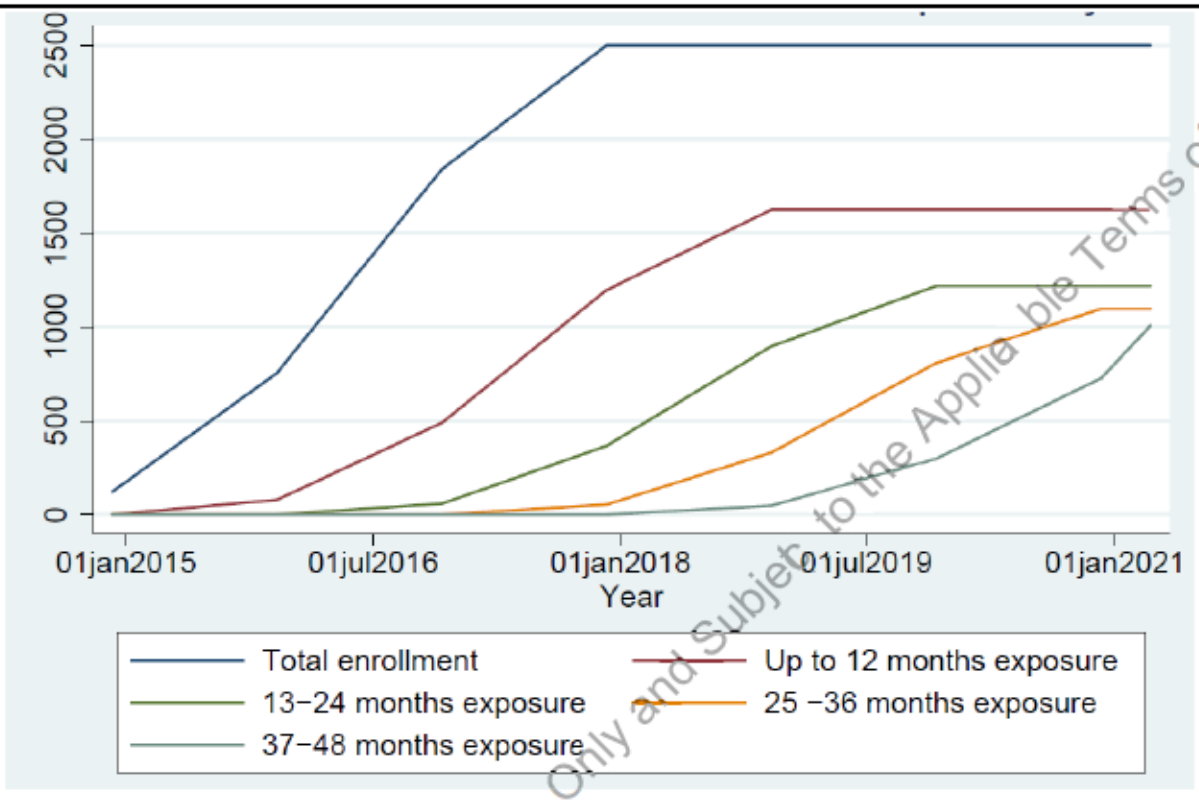
- For each subsequent 12 month periods, an additional 10% of patients are expected to stop vedolizumab, based on the most recent attrition rates from the Study C13008 study in patients who entered this study from studies C13006, C13007, or C13011.

This is illustrated in Appendix J Table 2 and in Appendix J Figure 1.

Appendix J Table 2 **Estimates of Duration of Vedolizumab Exposures in Study MLN-0002_401**

	01-Dec-15	01-Dec-16	01-Dec-17	01-Dec-18	01-Dec-19	01-Dec-20	21-Mar-21	Cumulative Number Exposed
Enrolled	**754**	**1088**	**658**					**2500**
At least 12 months exposure		490	1197	1625				1625
At least 24 months exposure			368	898	1219			1219
At least 36 months exposure				331	808	1097		1097
At least 48 months exposure					298	727	1042	1042
At least 60 months exposure						268	691	691
At least 72 months exposure							255	255
At least 87 months exposure								

Appendix J Figure 1 Vedolizumab Total Enrollment and Cumulative Exposure by Time (Study MLN-0002_401)



Duration of follow-up

Appendix J Table 3 presents the anticipated patient follow-up time. Non-interventional studies differ from clinical studies in that patients continue under observation even if they discontinue use of vedolizumab or switch to other treatments. Thus, duration of patient follow-up will be longer than duration of exposure. This is particularly important with endpoints such as malignancies that have a latency period.

In observational studies, duration of follow up is governed by the rate of loss to follow up rather than stopping of treatment. Predicted loss to follow-up is based on similar long term non-interventional studies in UC and CD patient populations which have implemented Direct to Patient Contact strategies, and close interaction with investigators, similar to planned for this study. We anticipate a 10% loss to follow-up over the entire 7 year period (approx 1.4% loss per year).

Appendix J Table 3 Estimates of Duration of Follow Up in Study MLN-0002_401 – Per Study Arm

	01-Dec-15	01-Dec-16	01-Dec-17	01-Dec-18	01-Dec-19	01-Dec-20	21-Mar-21	Cumulative Duration of Follow Up
1.4% Loss to Follow Up per year (with direct to patient contact)								
Enrolled	**754**	**1088**	**658**					**2500**
At least 12 months follow up		743	1072	648				2463
At least 24 months follow up			732	1056	638			2426
At least 36 months follow up				721	1040	629		2389
At least 48 months follow up					710	1024	624	2358
At least 60 months follow up						699	1016	1716
Person-years of follow-up in interval		743	1804	2425	2388	2352	1640	
Cumulative person-years of follow-up		743	2547	4972	7360	9712	11352	11352

Mean duration of follow-up = 4.54 years (11352/2500)

Appendix K European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

London, 25 July 2011
Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 19/08/2011

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each of the questions of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer "N/A" (Not Applicable) can be checked, and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

Section 1: Research Question	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain:				
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	19
1.1.2 The objectives of the study?	☒	☐	☐	20
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	20, 33
1.2.3 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 2: Source and Study Populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☒	☐	☐	21, 20
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	21, 20
2.2.2 Age and sex?	☒	☐	☐	19, 22
2.2.3 Country of origin?	☒	☐	☐	21, 20
2.2.4 Disease/indication?	☒	☐	☐	21, 20
2.2.5 Co-morbidity?	☐	☐	☒	
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	21

Comments:

Section 3: Study Design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	19, 22-25
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	21
3.3 Does the protocol describe the measure(s) of effect? (e.g. 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)	☒	☐	☐	33,34
3.4 Is sample size considered?	☒	☐	☐	31
3.5 Is statistical power calculated?	☒	☐	☐	31

Comments:

Section 4: Data Sources	Yes	No	N/A	Page Number(s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	27
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	27
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	29
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g., International Classification of Diseases (ICD)-10)	☐	☐	☒	31
4.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	
4.3.3 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	
4.4 Is the linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☐	☒	

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? (e.g., operational details for defining and categorising exposure)	☒	☐	☐	35
5.2 Does the protocol discuss the validity of exposure measurement? (e.g., precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	29
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☒	☐	☐	33
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	35
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	36

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?	☒	☐	☐	24, 33
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	24, 33

Comments:

Section 7: Biases and Effect Modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	39
7.1.2 Information biases? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	39

Section 7: Biases and Effect Modifiers	Yes	No	N/A	Page Number(s)
7.2 Does the protocol address known confounders? (e.g., collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	40
7.3 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	40
7.4 Does the protocol address other limitations?	☒	☐	☐	40

Comments:

Section 8: Analysis Plan	Yes	No	N/A	Page Number(s)
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	33
8.2 Is the choice of statistical techniques described?	☒	☐	☐	33
8.3 Are descriptive analyses included?	☒	☐	☐	33
8.4 Are stratified analyses included?	☒	☐	☐	33
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	33
8.5.2 Effect modifiers?	☒	☐	☐	33
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	33
8.6.2 Effect modification?	☒	☐	☐	33

Comments:

Safety study; subgroup analyses as needed.

Section 9: Quality Assurance, Feasibility, and Reporting	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	34
9.2 Are methods of quality assurance described?	☒	☐	☐	39

Section 9: Quality Assurance, Feasibility, and Reporting	Yes	No	N/A	Page Number(s)
9.3 Does the protocol describe quality issues related to the data source(s)?	☐	☐	☒	
9.4 Does the protocol discuss study feasibility? (e.g., sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	31
9.5 Does the protocol specify timelines for:				
9.5.1 Study start?	☒	☐	☐	12
9.5.2 Study progress? (e.g., end of data collection, other milestones)	☒	☐	☐	12
9.5.3 Study completion?	☒	☐	☐	12
9.5.4 Reporting? (i.e., interim reports, final study report)	☒	☐	☐	12
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12
9.7 Are communication methods to disseminate results described?	☒	☐	☐	47
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 10: Ethical Issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	41
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	42

Comments:

Name of the Coordinating Study Entity[1]: _____

Name of the (Primary) Lead Investigator[2]: _____

Date: / /

Signature: _____

[1] A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

[2] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.