Protocol

Study No:		MLN-0002_401
Product:		Vedolizumab
1.	**Study Title**	Entyvio (vedolizumab) long-term safety study Protocol version 1.2 16 April 2014
2.	**Marketing Authorization Holder**	Takeda Pharma A/S Dybendal Alle 10 2630 Taastrup Denmark
3.	**Responsible Parties**	Veronique Kugener MD, MSc, MBA Takeda International Inc One Takeda Parkway Deerfield, IL 60015

Ethics Statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Epidemiology Practices (GEP), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices (GVP), and all applicable regulatory requirements.

Table of Contents

4. Abstract

4.1 Title

A prospective, observational, cohort safety study of vedolizumab versus other biologic agents for inflammatory bowel disease

Original Protocol: 11 Jan 2013

4.2 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. .Both UC and CD are relapsing and remitting diseases and it is estimated that approximately 50% of patients will have inadequate response with, lost response to , or become intolerant to either conventional therapy or a TNFα antagonist at some point during their lifetime.

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 UC or CD 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 (MOA) 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 (IgG1) 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 (GALT) 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 MOA, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with current treatments for IBD.

This study is planned as an observational study after marketing authorization to assess the safety of vedolizumab versus other biologic agents.

The participating physicians will be representative of the gastroenterologists who will prescribe vedolizumab, where approved in the US and Europe, 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.

4.3 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 quality of life (QoL) results, during the course of the study.

4.4 Study 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.

This study is designed to permit all interested physician providers to participate as investigators, and all interested patients to participate as subjects.

Patients enrolled in this study will provide a defined set of data at baseline and undergo regular office visits and data collection, according to usual medical practice, as indicated in the Schedule of Recommended Assessments (Appendix A), until termination of the study.

Test Product, Dose, and Mode of Administration

Vedolizumab (humanized IgG1 monoclonal antibody to human α4β7 integrin), 300 mg by intravenous (IV) infusion, as prescribed by the physician according to local prescribing information in the participating countries.

Comparator Product(s), Dose, and Mode of Administration

Other biologic agents (adalimumab or certolizumab pegol by subcutaneous injection, or infliximab by IV infusion), as prescribed by the physician for UC or CD, according to local prescribing information in the participating countries.

Study Procedures

Adult patients who are initiating vedolizumab for approved indications, or similar patients who are initiating another biologic agent for UC or CD, will be recruited. Eligible patients will be enrolled in the study, provide baseline information, and be followed until termination of the study. Study assessments will be collected at least every 6 months by their treating physician. SAEs, AESI, and adverse reactions will be recorded at all visits.

Safety will be evaluated through:

- Adverse events of special interest (AESI), which comprise the following:
  - Serious infections (infections that are SAEs, including progressive multifocal leukoencephalopathy [PML])
  - Other clinically significant infections, not SAEs, that are classified as moderate or severe and require antibiotic treatment
  - Malignancies
  - Infusion-related reactions
- All other SAEs
- Adverse reactions

Data on UC/CD disease activity, health resources used, and QoL also will 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.

Duration of Study

7 years

4.5 Population

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

4.6 Variables

Safety

- AESI:
  - Serious infections
  - Other clinically significant infections
  - Malignancies
  - Infusion-related reactions
- Adverse reactions
- All other SAEs

Disease Activity and Quality of Life

- IBD activity assessment:
  - Partial Mayo score for patients with UC
  - Harvey-Bradshaw Index (HBI) score for patients with CD
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)
- QoL assessment (as permitted by competent authority):
  - Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
  - 12-Item Short Form Health Survey (SF-12)

4.7 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 comorbid conditions and other autoimmune disease(s)
  - Prior serious and atypical infections and dates
  - Malignancies
  - Organ transplantation, including bone marrow or stem cell transplants
- UC/CD history, including:
  - Dates and age of onset / diagnosis
  - Disease location(s)
  - Presence of extraintestinal manifestations
  - 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 IBD)

- IBD activity assessment:
  - Partial Mayo score for patients with UC
  - HBI score for patients with CD
- Any prior use of the following categories of 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)
  - Any agents that have a known association with PML (e.g., alemtuzumab, belatacept, brentuximab vedotin, efalizumab, etanercept, infliximab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
- Prior use of other immunomodulatory, anti-neoplastic, or immunosuppressive agents for IBD, including specific drug used, indication, 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
- QoL assessment:
  - SIBDQ
  - SF-12
- History of infusion-related reactions

Prospective Data Collection

The following data will be collected at least every 6 months during the follow-up period, according to standard practice in other long-term registries 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, AESI, and adverse reactions.

- IBD activity assessment:
  - Partial Mayo score for patients with UC
  - HBI score for patients with CD
- 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, or 5-ASA
  - Any agents that have a known association with PML (e.g., alemtuzumab, belatacept, brentuximab vedotin, etanercept, infliximab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
- Use of concomitant systemic corticosteroids, including specific drug used (if known), indication, dose range, route of administration, and dates of use
- Use of concomitant antibiotics to treat UC/CD, including specific drug used, dose received, route of administration, and dates of use
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)

- QoL assessment:
  - SIBDQ
  - SF-12
- AESI:
  - Serious infections
  - Other clinically significant infections
  - Malignancies
  - Infusion-related reactions
- All other SAEs
- Adverse reactions
- Female patients are required to report any pregnancy occurring during the study, along with a select set of information regarding the outcome of pregnancy and neonatal condition.

4.8 Study Size

The sample size for this study was chosen to provide a reliable estimation of incidence rates for uncommon SAEs and AESI. The proposed sample size was determined through consideration of: 1) the expected rates of SAEs/AESI, 2) the feasibility of enrollment based on the projected market uptake of vedolizumab, and 3) the observed attrition rates from the clinical trials after initiation of vedolizumab therapy.

Approximately 2500 patients per treatment cohort (vedolizumab versus other biologic agents) will be enrolled and followed for the course of the study. Based upon an expected discontinuation rate of 55% during the first 2 years and 10% thereafter, it is anticipated that at least 1000 patients per cohort will be able to be followed for 24 months.

The incidence of SAEs/AESI not reported during the study can be estimated for each cohort at no greater than 1.2 per 1000 patients overall, and no greater than 3 per 1000 patients for those treated for at least 24 months, using the "rule of 3". Based upon these estimates, this sample size would allow detection of uncommon risks, including cancers, associated with vedolizumab, and detection of PML occurring at the rate observed among the overall postmarketing population of natalizumab patients.

Use of the comparator cohort will also allow calculation of relative rates for vedolizumab against other biologics. Using the event rates for serious infections from the Therapy, Resource, Evaluation, and Assessment Tool™ (TREAT™) registry study (2.06 per 100 person-years in patients treated with infliximab, and 1.42 per 100 person-years in the patients treated with other agents), the proposed sample size will have approximately 80% power to detect a relative risk for serious infections of approximately 1.6 for vedolizumab compared with other biologics, assuming similar rates to TREAT.

4.9 Data Analysis

Statistical Methods

A formal statistical analysis plan (SAP), providing analytical and data presentation details, will be finalized prior to data base lock.

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 also may be examined, as deemed appropriate (e.g., prior immunosuppressant use, UC versus CD, baseline disease severity, etc.).

Disposition, Demographic, and Baseline Data

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

Safety Data

Safety results will be summarized by treatment cohort with descriptive statistics and presented in listings.

The primary analysis will estimate the risks of AESI, comprising serious or other clinically significant infections, malignancies, and infusion-related reactions for each cohort. For each type of event, the risk of the event will be calculated as the quotient of the total number of events and the number of patients at risk. Each risk estimate will have 95% confidence intervals (CIs) calculated. Relative risk estimates between treatment cohorts will be calculated, adjusted for important confounders such as disease severity.

The safety outcomes also will be assessed in order to determine whether reported events are time/exposure dependent.

Pregnancies and key pregnancy outcome variables will be summarized by treatment cohort and presented in listings.

Disease and Quality of Life Data

IBD disease activity scores, vedolizumab or other biologic agent administrations, concomitant IBD medications, health resources used, and QoL results will be summarized by treatment cohort with descriptive statistics. Changes over time in IBD disease activity scores and QoL results also will be summarized by treatment cohort with descriptive statistics.

4.10 Milestones

Study Milestone	Estimated Date
Start of data collection (first patient, first visit)	01 July 2014
End of data collection (data base lock)	30 June, 2021
Study progress reports	(annually throughout the study)
Safety summary reports	as required by competent authority
Interim analysis	01 July 2018 (after 50% of expected vedolizumab population has enrolled and completed at least 1 year of treatment)
Final study report	30 June 2022 (≤1 year after last patient, last visit)

5. Amendments and Updates

Version 1: original protocol.

6. Milestones

The planned study milestones, per Good Pharmacovigilance Practices (GVP),[1] are summarized below.

Study Milestone	Estimated Date
Start of data collection (first patient, first visit)	01 July 2014
End of data collection (data base lock)	30 June 2021
Study progress reports	(annually throughout the study)
Safety summary reports	as required by competent authority
Interim analysis	01 July 2018 (after 50% of expected vedolizumab population has enrolled and completed at least 1 year of treatment)
Final study report	30 June 2022 (≤1 year after last patient, last visit)

7. Rationale and Background

7.1 Background

7.1.1 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.2 However, in Europe, the highest annual reported prevalence of UC and CD is 505/100,000 persons and 322/100,000 persons, respectively.2 UC and CD are lifelong diseases that cause considerable morbidity in a relatively young patient population. Both UC and CD are relapsing and remitting diseases and it is estimated that approximately 50% of patients will have inadequate response with, lost response to , or become intolerant to either conventional therapy or a TNFα antagonist at some point during their lifetime.

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 inflammatory bowel disease (IBD) indicate that there is a significant unmet medical need for safer and more effective therapies. Pharmacologic treatments for IBD 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 IBD by inducing and maintaining remission and decreasing the need for hospitalizations and surgeries.[3] Although TNF-α antagonists represent an important addition to the pharmacologic armamentarium for IBD, they are effective in only a subset of patients, with roughly two-thirds of patients in controlled trials failing treatment at the end of the first year of therapy. [4,5,6] 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

excellent maintenance benefit in CD[7]; 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 (MOA) distinct from existing agents.

7.1.2 Vedolizumab

Vedolizumab is a humanized immunoglobulin G1 (IgG1) 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 (GALT) 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 MOA, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with current treatments for IBD.

Detailed information regarding nonclinical and clinical pharmacology, toxicology, and clinical trials of vedolizumab is found in the Investigator's Brochure (IB)[8].

7.1.2.1 Ulcerative Colitis

The safety and efficacy of vedolizumab 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 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 on clinical remission was observed both in patients with no prior TNF-α antagonist exposure, as well as in those who had failed prior α antagonist therapy.

7.1.2.2 Crohn's Disease

The safety and efficacy of vedolizumab 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 patients overall achieved clinical remission at Week 6, compared with placebo patients. In Study C13011, the subset of vedolizumab 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 patients who had failed prior TNF-α antagonist therapy achieved clinical remission.

7.1.2.3 Safety Profile for Ulcerative Colitis and Crohn's Disease

In the pivotal Phase 3 trial in UC (C13006), 12% of vedolizumab-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-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 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-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 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 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 enrollment. 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 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.

In pivotal Phase 3 studies, other reported SAEs, including extraintestinal infections (bronchitis, pneumonia, urinary tract infection, sepsis), were uncommon (< 1%). Malignancy was diagnosed in 15 patients receiving vedolizumab across all clinical studies (9 patients with UC and 6 patients with CD). Patients with IBD have an increased risk for colon cancer,[2] and colon cancer was reported in 4 vedolizumab-treated patients; carcinoid tumor of the appendix was diagnosed in 1 vedolizumab-treated patient. One case of B-cell lymphoma was reported in a patient who had received 21 infusions of vedolizumab.

7.2 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. 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, where approved in the US and Europe, 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 progressive multifocal leukoencephalopathy (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.9 Therefore, the primary outcome measures for subjects treated with vedolizumab or other biologic agents in this study will be incidence of adverse events of special interest (AESI): serious infections, including PML; other clinically significant infections; malignancies; and infusion-related reactions. All adverse reactions and SAEs will be collected and reported.

8. Research Question and Objectives

8.1 Objectives

8.1.1 Primary Objective

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

8.1.2 Secondary Objectives

To describe changes in UC/CD disease activity using disease activity scores, health resources used, and quality of life (QoL) results, during the course of the study.

9. Research Methods

9.1 Study Design

9.1.1 Overall Design of the Study

This is a prospective, observational, international, multi-center, cohort study, to be conducted in North America and Europe, 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 patients to participate as subjects. Physicians will prescribe vedolizumab or other biologic agents according to the local prescribing information in the participating countries, and there will be 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. Duration of the study is 7 years.

Study visits, procedures, and evaluations are summarized in the Schedule of Recommended Assessments, Appendix A, and described in detail below.

Patients with UC or CD who are initiating vedolizumab, or similar patients who are initiating another biologic agent, will be recruited continuously and screened to determine eligibility. After eligible patients are enrolled, baseline data will be collected.

Patients will be followed until termination of the study, during which time they will be assessed by their treating physician at least every 6 months. SAEs (Section 11.2), AESI (Section 9.3.1), and adverse reactions (Section 11.1.4) will be recorded at all visits. SAEs (Section 11.2) and adverse reactions (Section 11.1.4) will be reported according to Sponsor and competent authority requirements, as described in Section 11.3 and the Study Reference Manual. Females will be required to report the occurrence of pregnancy, and a select set of information regarding the outcome of pregnancy and neonatal condition, during the study (Section 9.4.2).

9.1.2 Patient Discontinuation and Study Site or Study Termination

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). As described in Section 9.9.5, patients may be contacted directly by study personnel if they leave the Investigator's care.

9.2 Setting

9.2.1 Inclusion Criteria

A patient must meet **all** of the following criteria to be eligible for participation 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 for approved indications, or initiating a biologic agent for UC or CD.
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.

9.2.2 Exclusion Criteria

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

1. The patient is enrolled in a clinical trial in which treatment for CD or UC is managed through a protocol.
2. Prior treatment with vedolizumab.
3. Any other reason that, in the Investigator's opinion, makes the patient unsuitable to participate in this study.

9.3 Variables

9.3.1 Safety

The primary outcome measures in this safety study are AESI, as defined below. The following safety data will be recorded:

- AESI:
  - Serious infections (infections that are SAEs, including PML)
  - Other clinically significant infections, not SAEs, that are classified as moderate or severe (Section 11.1.2) and require antibiotic treatment
  - Malignancies
  - Infusion-related reactions

- All other SAEs
- Adverse reactions

9.3.2 Disease Activity

- IBD activity assessment:
  - Partial Mayo score[9] for patients with UC (Appendix D)
  - Harvey-Bradshaw Index (HBI) score[11] for patients with CD (Appendix E)
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)

9.3.3 Quality of Life

QoL assessments (as permitted by competent authority):

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

9.4 Data Sources

9.4.1 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 enrollment into the study.

- Demographic data
- Medical history:
  - General, including comorbid conditions and other autoimmune disease(s)
  - Prior serious and atypical infections and dates
  - Malignancies
  - Organ transplantation, including bone marrow or stem cell transplants
- UC/CD history, including:
  - Dates and age of onset / diagnosis
  - Disease location(s)
  - Presence of extraintestinal manifestations
  - 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 IBD)

- IBD activity assessment:
  - Partial Mayo score for patients with UC
  - HBI score for patients with CD
- 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 IBD medication
  - Any agents that have a known association with PML(alemtuzumab, belatacept, brentuximab vedotin, efalizumab, etanercept, infliximab, leflunomide, mycophenolate mofetil, mycophenolic acid, natalizumab, ofatumumab, and rituximab)
- Prior use of other immunomodulatory, anti-neoplastic, or immunosuppressive agents for IBD, 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
- QoL assessments:
  - SIBDQ
  - SF-12
- History of infusion-related reactions

9.4.2 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 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, AESI, and adverse reactions.

- 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 IBD medication
  - Any agents that have a known association with PML (alemtuzumab, belatacept, brentuximab vedotin, etanercept, infliximab, 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 Mayo score for patients with UC
  - HBI score for patients with CD
- Health resources used (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)
- QoL assessments:
  - SIBDQ
  - SF-12
- AESI:
  - Serious infections (infections that are SAEs, including PML)
  - Other clinically significant infections, not SAEs, that are classified as moderate or severe (Section 11.1.2) and require antibiotic treatment
  - Malignancies
  - Infusion-related reactions
- All other SAEs
- Adverse reactions
- Female patients are required to report any pregnancy occurring during the study, along with a select set of information regarding the outcome of pregnancy and neonatal condition:
  - Pregnancy history (date confirmed)
  - Pregnancy outcome (full-term, pre-term, fetal loss/stillbirth, miscarriage, induced abortion)
  - Neonatal characteristics:
    - Apgar scores (if known)
    - Respiratory distress or other complications
    - Admission to Neonatal Intensive Care Unit / length of stay
    - Congenital anomalies

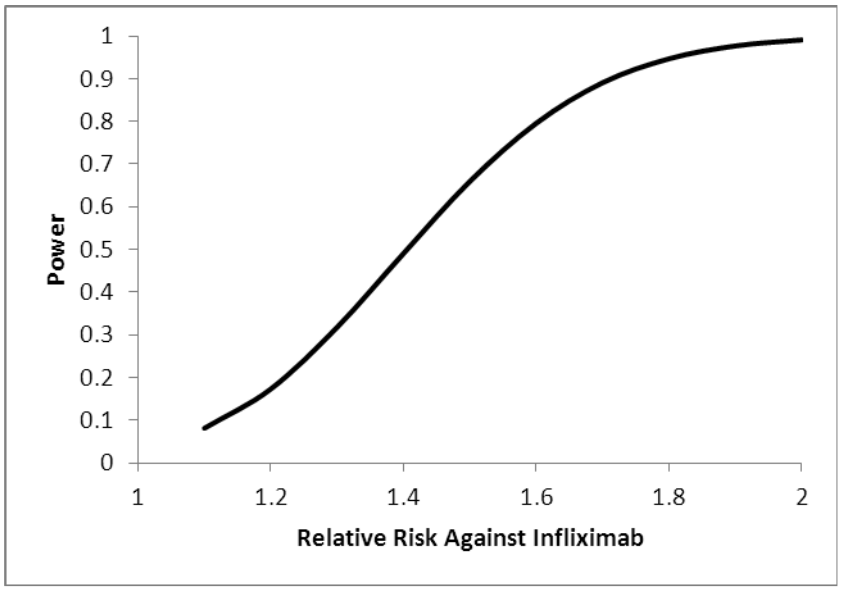
9.5 Study Size

The sample size for this study was chosen to provide a reliable estimation of incidence rates for uncommon SAEs and AESI. The proposed sample size was determined through consideration of: 1) the expected rates of SAEs/AESI, 2) the feasibility of enrollment based on the projected market uptake of vedolizumab and 3) the observed attrition rates during the clinical trials after initiation of vedolizumab therapy.

Approximately 2500 patients per treatment cohort (vedolizumab versus other biologic agents) will be enrolled and followed for the course of the study. Based upon an expected discontinuation rate of 55% during the first 2 years and 10% thereafter, it is anticipated that at least 1000 patients will be able to be followed for 24 months.

The incidence of SAEs/AESI not reported 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, this 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 postmarketing population of natalizumab patients.[12]

Use of the comparator cohort will also allow calculation of relative rates for vedolizumab against other biologics. Power calculations were performed using the event rate for serious infections from the Therapy, Resource, Evaluation, and Assessment Tool™ (TREAT™) registry study (2.06 per 100 person-years in patients treated with infliximab, and 1.42 per 100 person-years in the patients treated with other agents).[13] Cohort size for these calculations was 2500 patients, with 2812 patient-years of exposure, and an alpha of 0.05. The power results for relative risk against infliximab rates from TREAT are plotted below; the proposed sample size will have approximately 80% power to detect a relative risk for serious infections of approximately 1.6 for vedolizumab compared with other biologics, assuming similar rates to TREAT.



9.6 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 enroll 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.

9.7 Data Analysis

A formal statistical analysis plan (SAP), providing analytical and data presentation details, will be finalized prior to data base lock.

9.7.1 Study Populations and Analysis Methods

- 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 also may be examined, as deemed appropriate by indication (UC versus CD) or confounding factors (e.g., previous treatment and duration; Section 9.9.3) or effect modification (e.g., baseline disease severity, prior surgeries or other hospitalizations, prior infusion reactions; Section 9.9.4).
- All summarizations and analyses will be performed using SAS® Version 9.2 or later.
- 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.

9.7.2 Disposition, Demographic, and Baseline Clinical Analyses

Disposition, demographic, and baseline clinical data will be summarized descriptively by treatment cohort and presented in listings.

9.7.3 Safety Analyses

SAEs and AESI will be coded, using MedDRA Version 13.1 or later. Safety results will be summarized by treatment cohort with descriptive statistics and presented in listings.

The primary analysis will estimate the risks of AESI, comprising serious infections, other clinically significant infections, malignancies, and infusion-related reactions for each cohort. For each type of event, the risk of the event will be calculated as the quotient of the total number of events and the number of patients at risk. Each risk estimate will have 95% confidence intervals (CIs) calculated. Relative risk estimates for vedolizumab compared with other treatements will be calculated with adjustment for important confounders such as disease severity.

The safety outcomes also will be assessed by duration of exposure to determine whether reported events are time dependent.

Pregnancies and key pregnancy outcome variables will be summarized by treatment cohort and presented in listings.

9.7.4 Disease Activity and Quality of Life Analyses

IBD disease activity scores, vedolizumab administrations, concomitant IBD medications, health resources used, and QoL results will be summarized by treatment cohort with descriptive statistics. Changes over time in IBD disease activity scores and QoL results also will be summarized by treatment cohort with descriptive statistics.

9.7.5 Interim Analysis

An interim analysis of key safety results will be performed after 50% of the expected vedolizumab population has been enrolled and completed at least 1 year of treatment. Assuming that the vedolizumab arm will be slower to recruit initially than the comparator arm this will provide a more informative interim view of vedolizumab safety. Details will be described in the SAP.

9.8 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.

9.9 Limitations of the Research Methods

9.9.1 Selection Bias

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

Benchmark populations for comparison of outcomes (Section 9.7.3) 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 (Section 9.2.1).

9.9.2 Information Bias

Because treatment for some of the AESI of clinically significant infections may be performed by the patient's primary health care practitioner rather than the study site, 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.

9.9.3 Confounders

Prior and/or concomitant exposure to immunosuppressive agents and/or TNF-α antagonists could increase the likelihood of PML, 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 analyses and calculation of relative risks between vedolizumab and the comparator cohort to explore these possible associations.

9.9.4 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 IBD drug failures, and duration of disease at the time of enrollment, are likely to be associated with risk for safety events during the study period. In addition, risk of outcomes such as PML appears to increase with treatment duration for some IBD therapies.[5,12] Subgroup analyses may be used, if deemed appropriate, to clarify these effects.

9.9.5 Patients Lost to Follow-Up

Because the follow-up duration will be until termination of the study, the proportion of discontinued patients might be significant. The frequency of loss to follow-up may be reduced by use of retention strategies to develop a sense of community among participating patients, and to minimize patient attrition (Appendix H).

It is expected that some patients will transfer their medical care to a new physician over the course of their participation in the study. The informed consent document for the study (Section 10.1) will include a provision for patients to be contacted directly by study personnel if they leave the Investigator's care.

10. Protection of Human Subjects

10.1 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 9.9.5). ICFs and assent forms will conform to the requirements of 21 CFR 50.20-27 and International Conference on Harmonisation (ICH) E6 4.8, Principles of Good Clinical Practices (GCP). 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.

10.2 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 enrollment 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).

10.3 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.

10.4 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.

10.5 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.

10.6 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.

11. Management and Reporting of Adverse Events [Note: This section will be updated to reflect the outcome of the GVP VI update once the wording is finalised]

11.1 Adverse Events and Adverse Events of Special Interest

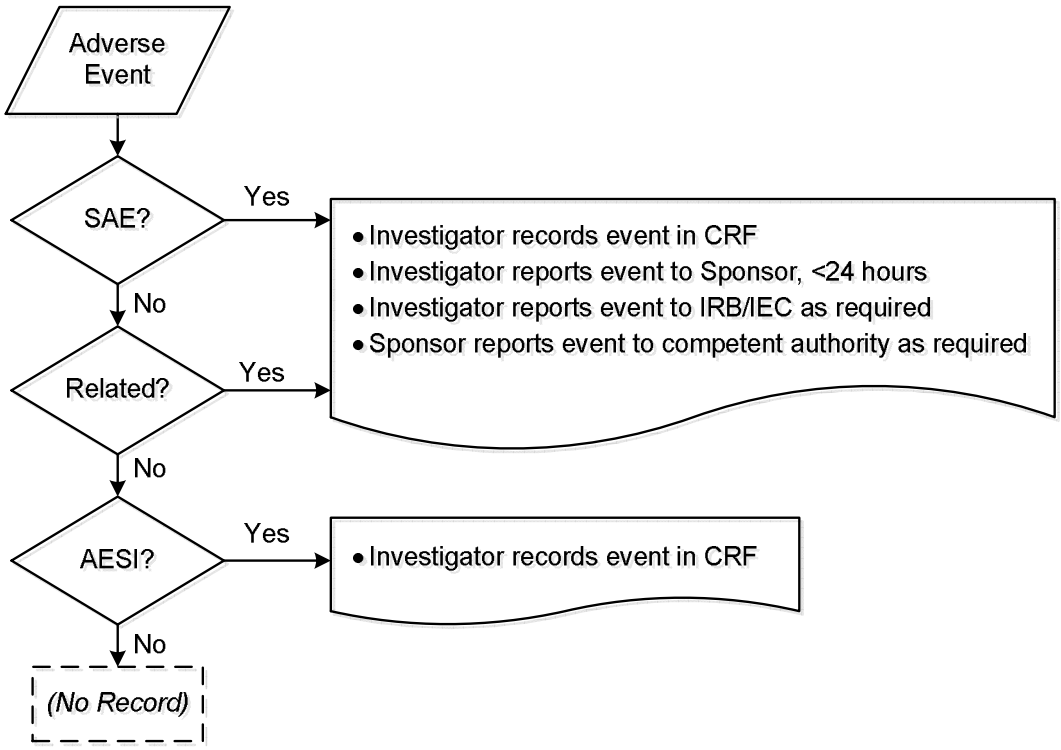
11.1.1 Adverse Event Definitions and Flow Chart

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Only those AEs that meet the definition of SAEs, adverse reactions, or AESI will be recorded and reported in this study.

- SAEs are defined in Section 11.2.
- Adverse reactions are defined in Section 11.1.4.
- AESI are serious infections, other clinically significant infections, malignancies, and infusion-related reactions (Section 9.3.1).

A flow chart of the decision process for AE recording and reporting is provided below:



11.1.2 Assessment of 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 11.2).

11.1.3 Assessment of 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):[14]

- 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.

11.1.4 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 11.1.3.

11.1.5 Documentation of Adverse Events

Documentation of AEs will commence after a patient has provided informed consent, and the condition of each study patient will be monitored throughout the study. Subjects will be questioned whether they have experienced any AE.

All AEs that are spontaneously reported by the patient; and/or in response to a question from study personnel; or revealed by observation, physical examination, or other diagnostic procedures; will be assessed for relationship to vedolizumab or other biologic treatment as described in Section 11.1.3. AESI, adverse reactions, and SAEs will be recorded on the appropriate page of the CRF. 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).

AESI, adverse reaction, and SAE records will include start and end dates, severity, relationship to vedolizumab or other biologic treatment, whether the event is serious, action taken, and outcome.

11.2 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.
- Is a 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.

11.3 Reporting of Specified Adverse Events

A flow chart of the decision process for AE recording and reporting is provided in Section 11.1.1.

11.3.1 Reporting of Serious Adverse Events and AESI

SAE and AESI reporting will commence after a patient has provided informed consent. All SAEs and AESI (which include all deaths) must be reported, whether or not considered causally related to vedolizumab.

In the event of an SAE or AESI, the Investigator will notify the Sponsor or designee, as instructed in the Study Reference Manual, within 24 hours after the Investigator becomes aware of the event. A written report using the provided form, including the Investigator's assessment of causality, must be sent by fax within 24 hours to the designated contact for SAE reporting. The event must also be documented in source documentation and on the eCRF. See the Study Reference Manual for complete instructions.

After receipt of the initial report, the information will be reviewed, and the Investigator will be contacted to request additional information or for data clarification. If required, a follow-up report, including all new information obtained on the event, must be prepared and sent to the designated contact for SAE/AESI reporting. Follow-up reports will be filed as necessary until the event has resolved or attained a stable outcome.

The Sponsor assumes responsibility for appropriate reporting of SAEs/AESIs 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.

11.3.2 Reporting of Non-Serious Adverse Reactions

Each non-serious AE that the Investigator categorizes as related to vedolizumab or other biologic treatment (Section 11.1.3) should be reported by the Investigator to the regulatory authorities, as instructed in the Study Reference Manual.

The Investigator is responsible for ensuring that all commitments are fulfilled to the IRB/IEC that approved the study protocol.

12. 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.

An interim analysis will be performed after enrollment of 50% of the planned vedolizumab population, and an interim study report will be submitted to competent authority.

The Sponsor and/or designee will submit a final study report to competent authority, no later than 1 year after study completion or termination by the Sponsor.

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines[15] 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).

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.

13. References

1. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP): Module VIII – Post-authorisation safety studies. EMA/813938/2011. 22 June 2012.
2. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42; quiz e30. Epub 2011 Oct 14.
3. Sandborn WJ. Current directions in IBD therapy: what goals are feasible with biological modifiers? Gastroenterology. 2008 Nov;135(5):1442-7.
4. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002 May 4;359(9317):1541-9.
5. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76. Erratum in: N Engl J Med. 2006 May 18;354(20):2200.
6. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology. 2007 Jan;132(1):52-65.
7. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P; International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2) Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005 Nov 3;353(18):1912-25.
8. Vedolizumab (MLN0002) Investigator's Brochure. <Edition **, dd Mon yyyy>. Millennium Pharmaceuticals, Inc. *[this reference to be replaced with summary of product characteristics / label, after approval]*
9. Berger JR, Houff SA, Major EO. Monoclonal antibodies and progressive multifocal leukoencephalopathy. MAbs. 2009 Nov-Dec;1(6):583-9.
10. Lewis JD, Chuai S, Nessel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008 Dec;14(12):1660-6.
11. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet. 1980 Mar 8;1(8167):514.

12. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012 May 17;366(20):1870-80.
13. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, Langholff W, Londhe A, Sandborn WJ. Serious infection and mortality in patients with Crohn's disease: More than 5 years of follow-up in the TREAT™ registry. Am J Gastroenterol. 2012 Sep;107(9):1409-22.
14. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. EMA/873138/2011. 22 June 2012.
15. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, for the STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies. PLoS Med. 2007; 4(10): e296. doi:10.1371/journal.pmed.0040296

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), extraintestinal manifestations, surgical history / disease management, and health resources used due to IBD 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 IBD 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 IBD (e.g., surgical procedures, GI endoscopy, and/or medical admissions for treatment of IBD)		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 IBD medication		X
Any use of agents that have a known association with PML		X
IBD activity assessment: Partial Mayo score for patients with UC HBI score for patients with CD	X	X[c]
QoL assessment (SIBDQ, SF-12)	X	X[c]
SAEs		X[a]
AESI		X[a]
Adverse reactions		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; AESI = adverse event(s) of special interest; CD = Crohn's disease; GI = gastrointestinal; HBI = Harvey-Bradshaw Index; QoL = quality of life; 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, AESI, 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

[3] To be reported within 30 days after delivery

Appendix B Abbreviations and Acronyms

5-ASA	5 aminosalicylate
6-MP	6-mercaptopurine
AE	adverse event
AESI	adverse event(s) of special interest
CD	Crohn's disease
COF	patient contact order form
DTPC	direct-to-patient contact
eCRF	electronic case report form
EDC	electronic data capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practices
GEP	Good Epidemiology Practices
GI	gastrointestinal
GVP	Good Pharmacovigilance Practices
HBI	Harvey-Bradshaw Index
HIRD™	HealthCore Integrated Research Database
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IV	intravenous
mAb	monoclonal antibody
MAdCAM-1	mucosal addressin cell adhesion molecule-1
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
PML	progressive multifocal leukoencephalopathy
PPD	purified protein derivative
QoL	quality of life
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
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF-α	tumor necrosis factor alpha
TREAT™	Therapy, Resource, Evaluation, and Assessment Tool™
UC	ulcerative colitis

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

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)	☒	☐	☐	16
1.1.2 The objectives of the study?	☒	☐	☐	17
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)	☒	☐	☐	18
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is an observational safety study intended to evaluate the long-term safety of vedolizumab and other biologic agents.

Section 2: Source and Study Populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	18
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	18
2.2.2 Age and sex?	☒	☐	☐	19
2.2.3 Country of origin?	☒	☐	☐	18
2.2.4 Disease/indication?	☒	☐	☐	18
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)	☒	☐	☐	19

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?	☒	☐	☐	17
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18
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)	☒	☐	☐	25
3.4 Is sample size considered?	☒	☐	☐	23
3.5 Is statistical power calculated?	☐	☐	☒	

Comments:

No inferential analyses are planned.

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.)	☒	☐	☐	21
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	21
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	21
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g., International Classification of Diseases (ICD)-10)	☐	☐	☒	
4.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	25
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)	☒	☐	☐	20

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)	☒	☐	☐	21
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)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	25

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?	☒	☐	☐	19
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)	☐	☐	☒	

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?	☒	☐	☐	27

Section 7: Biases and Effect Modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	27
7.2 Does the protocol address known confounders? (e.g., collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	27
7.3 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	27
7.4 Does the protocol address other limitations?	☒	☐	☐	28

Comments:

Section 8: Analysis Plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	☒	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	25,25
8.3 Are descriptive analyses included?	☒	☐	☐	2525
8.4 Are stratified analyses included?	☒	☐	☐	27
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	27
8.5.2 Effect modifiers?	☒	☐	☐	27
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☒	☐	☐	27
8.6.2 Effect modification?	☒	☐	☐	27

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)	☒	☐	☐	24
9.2 Are methods of quality assurance described?	☒	☐	☐	26
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)	☒	☐	☐	23
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?	☒	☐	☐	11
9.7 Are communication methods to disseminate results described?	☒	☐	☐	35
9.8 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

This is a prospective / observational study.

Section 10: Ethical Issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	29
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	30

Comments:

This is an observational study.

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.

Appendix D Components of the Partial 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)**

Appendix E 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

Appendix F Short Inflammatory Bowel Disease Questionnaire

How to complete the questionnaire:

1. For each question, circle the number that corresponds to your answer.
2. Be sure to answer every question.
3. Complete the SIBDQ once every 2 months or before each visit to your healthcare provider.
4. Share the completed questionnaire and the symptom tracker with your healthcare provider during each visit.

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

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

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
    5. A little of the time

2. Most of the time
3. A good bit of the time
4. Some 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

Write in the number for each of your answers:

Now add all the numbers up, then divide that total by 10 for your score: _____
TOTAL ÷ 10 = SCORE

Appendix G 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 H Possible Retention Strategies

Because patient follow-up will continue until termination of the study, the proportion of discontinued patients might be significant. The frequency of loss to follow-up could be reduced by use of retention strategies to develop a sense of community among participating patients, and to minimize patient attrition:

- Providing patients with a Welcome Packet. The patient Welcome Packet might include a brochure with study information, enrollment form (completing contact information and permission to access to additional non-family contact), a calendar with the study follow-up schedule, web portal information to provide a customized internet experience, and links to information matching patient interests.
- Obtaining secondary contact information for the patient.
- Frequent patient communication through multiple channels, including phone, email, and website.
- Periodic patient newsletters with study progress and other project information materials.
- Monitoring patient visit status and providing site reports of missed visits; and tracking reasons for missed visits and patient discontinuation.
- Establishing a patient investigator transfer and transition plan for patients who change health care providers.
- Establishing a patient rewards or remuneration [NA only] program.

To the maximum extent possible, patient retention strategies should be performed via direct-to-patient contact (DTPC), with patient information firewalled from study data. This method allows for standard and consistent global patient contact processes, meets regulatory requirements in the US and EU, maximizes access to patient data and information without burdening sites, and increases patient availability for long-term tracking on non-interventional studies that do not have study visit schedules. In order to employ DTPC, a patient contact order form (COF) is obtained at time of consent. The COF collects patient and secondary contact information and a contact schedule according to patient preferences, including preferred days and hours to be contacted, and referred communication channels: phone, email, texting, etc. The DTPC approach defines triggers for contacting back-ups, i.e., contact with the health care provider and/or relatives.