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

NCT Number: NCT03535649

SAP Approve Date: 03 DEC 2018

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Statistical Analysis Plan

STUDY ID: VEDOLIZUMAB-5045

TITLE: CLINICAL EFFECTIVENESS AND SAFETY OF VEDOLIZUMAB INTRAVENOUS IN REAL WORLD CLINICAL PRACTICE IN ULCERATIVE COLITIS KOREAN PATIENTS: A MULTICENTER POST-MARKETING OBSERVATIONAL STUDY

SHORT TITLE: VEDOLIZUMAB IN ULCERATIVE COLITIS KOREAN PATIENTS

Prepared for: Takeda Pharmaceuticals Korea Co., Ltd.

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VERSION NUMBER AND DATE: V2.0; 03 DEC 2018

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan (V2.0, 03 DEC 2018) for Protocol Vedolizumab-5045 V4.2

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	25-SEP-2018	Ye Qing	Not Applicable – First draft
2.0	03-DEC-2018	Ivan John Clement	Updated based on Protocol Version 4.2 Updated to include analyses sets for data points recorded within ±7 days of protocol-defined visits

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1. ABBREVIATIONS

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

TB:	Tuberculosis
TNF-α:	Tumor Necrosis Factor alpha
UC:	Ulcerative Colitis

2. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of real world effectiveness and safety outcomes from daily clinical practice in Korean patients diagnosed with UC and having failed TNF-α antagonist therapy. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version V4.2, dated 24-OCT-2018 and case report forms (CRFs) V2.0, dated 17-OCT-2018 .

2.1 Ulcerative Colitis

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

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

progressive or persistent symptoms [Ananthakrishnan 2017]. UC patients are often unable to function normally in society by virtue of having uncontrolled disease.

Current UC treatments have been effective for many patients but have numerous limitations for those with moderate to severe disease. Pharmacologic treatments for UC include 5-aminosalicylic acids (5-ASAs), corticosteroids, and immunomodulators (thiopurines such as azathioprine and 6-mercaptopurine, along with methotrexate). Monoclonal antibodies (mAb) directed against tumor necrosis factor alpha (TNF-α) are recommended when adequate dosage and duration of treatment with corticosteroid or combination of corticosteroid and thiopurine do not improve symptoms, or if the treatment is not tolerable to the patient [Choi 2017]. In Korea, infliximab, adalimumab, and golimumab are used as anti-TNF therapies, all of which showed therapeutic effects in terms of remission induction and maintenance in patients with moderate to severe active UC [Choi 2017]. Although TNF-α antagonists represent an important addition to the pharmacologic armamentarium, they are effective in only a subset of patients, with approximately two-thirds of patients in controlled trials failing treatment at the end of the first year of therapy [Hanauer 2002, Rutgeerts 2005, Colombel 2007].

2.2 Vedolizumab

Vedolizumab is a humanized immunoglobulin G1 mAb directed against the human lymphocyte integrin $\alpha_4\beta_7$. The $\alpha_4\beta_7$ integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue through adhesive interactions with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa. Vedolizumab exclusively targets the $\alpha_4\beta_7$ integrin, antagonizing its adherence to MAdCAM-1 and thus impairing the migration of leukocytes into GI mucosa. By virtue of its gut-selective mechanism

of action, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with current treatments for UC.

The efficacy of vedolizumab in UC patients was demonstrated in a phase III randomized, double-blind, placebo-controlled, multicenter study that assessed the effect of vedolizumab induction and maintenance treatment on UC clinical response in 374 and 521 (open-label) patients with active moderate to severe disease. Vedolizumab patients had a statistically significant improvement in clinical response (i.e., reduction in the Mayo score of ≥ 3 points and ≥ 30% from baseline, and decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1) and remission (i.e., Mayo score ≤ 2 and no sub-score > 1) at 6 weeks, mucosal healing (i.e., endoscopic sub-score of 0 or 1), durable clinical response (i.e., remission at both weeks 6 and 52) and remission at 52 weeks, and corticosteroid-free remission at week 52 in patients receiving glucocorticoids at baseline compared to placebo. Response rates at week 6 were 47.1% and 25.5% among patients in the vedolizumab and placebo groups, respectively (difference with adjustment for stratification factors, 21.7 percentage points; 95% confidence interval [CI]: 11.6 to 31.7; P<0.001). At week 52, 41.8% of patients who continued to receive vedolizumab every 8 weeks and 44.8% of patients who continued to receive vedolizumab every 4 weeks were in clinical remission, as compared with 15.9% of patients who switched to placebo (adjusted difference, 26.1 percentage points for vedolizumab every 8 weeks vs. placebo [95% CI: 14.9 to 37.2; P<0.001] and 29.1 percentage points for vedolizumab every 4 weeks vs. placebo [95% CI: 17.9 to 40.4; P<0.001]) [Feagan 2013].

Vedolizumab has also shown a favorable safety profile with low incidence rates of serious infections, infusion-related reactions and malignancies over an extended treatment period in another phase III, open-label, multicenter study which enrolled 2830 UC and Crohn's Disease (CD) patients

treated with vedolizumab. In this study, safety data from 6 trials were integrated and adverse events (AEs) were evaluated in patients who received ≥ 1 dose of vedolizumab or placebo. In total, these patients accumulated 4811 person-years (PYs) of vedolizumab exposure (median exposure range: 1-1977 days). No increased risk of any infection or serious infection was associated with this exposure. Serious clostridial infections, sepsis and tuberculosis (TB) were reported infrequently (≤ 0.6% of patients). No cases of progressive multifocal leukoencephalopathy (PML) were observed. Independent risk factors for serious infection in UC were prior failure of a TNF-α antagonist (Hazard Ratio (HR): 1.99; 95% CI: 1.16 to 3.42; p=0.0122) and narcotic analgesic use (HR: 2.68; 95% CI: 1.57 to 4.58; p=0.0003). Investigator-defined infusion-related reactions were reported for ≤ 5% of patients in each study. Eighteen vedolizumab-exposed patients (< 1%) were diagnosed with a malignancy [Colombel 2017].

Vedolizumab was approved in Korea on June 19th, 2015 for use in both UC and CD patients with inadequate response, lost response, or who were intolerant to TNF-α antagonist [Choi 2017].

2.3 Study Rationale

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

3. STUDY OBJECTIVES

3.1 Primary Objectives

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

3.2 Secondary Objectives

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

3.3 Exploratory Objectives.

CCI [redacted]

4. STUDY DESIGN AND PLAN

4.1 General Description

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

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

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

4.2 Schedule of Events

The schedule of events can be found in Section 6.1 of the protocol V4.2, dated 24-OCT-2018.

4.3 Study Population

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

4.3.1 Inclusion Criteria

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

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

4.3.2 Exclusion Criteria

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

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

4.4 Definitions of Study Variables

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

- **Index date:** the index date is defined as the date of the first treatment with vedolizumab, between August 1, 2017 and the date when at least 100 patients are collected.

- **Index period:** the index period is defined from August 1, 2017 up until 100 patients (at least) are collected; when eligible patient medical records (defined by index treatment date) should be identified.
- **Follow-up period:** the follow-up period is defined as the time between the index date and when all relevant data for outcomes will be collected until the occurrence of any of following: end of treatment, lost to follow up, or death.
- **Baseline**: the baseline is defined as the date of first vedolizumab IV dose. All patients would have active disease at baseline. If Mayo score at baseline is less than 3 (e.g., patients who were prescribed vedolizumab because of unacceptable adverse events (AEs) related to TNF-α antagonist therapy), these patients will be excluded from the effectiveness analyses due to TNF-α intolerance.

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

4.4.1 Demographics and Risk Factors Data

- Year of birth.
- Age at baseline
- Age groups
- Sex.
- Body mass index, or height and weight, at baseline (i.e., start of vedolizumab treatment).
- Previous and current (at baseline) smoking status.
- UC/Inflammatory Bowel Disease family history.
- Selected comorbidities:
    - Multiple sclerosis.
    - Rheumatoid arthritis.

- Psoriatic arthropathy.
- Vasculitis.
- Systemic lupus erythematosus.
- Dermatopolymyositis.
- Systemic sclerosis.
- Ankylosing spondylitis.
- Primary sclerosing colangitis.
- Autoimmune hepatitis.
- Diabetes Mellitus.
- Hypertension.
- Dyslipidemia.

4.4.2 Clinical Data

- Date of first UC signs/symptoms.
- Date of UC diagnosis.
- UC intestinal location/s (using Montreal classification i.e. E1 ulcerative proctitis, E2 distal UC, E3 pancolitis) and extraintestinal manifestations at baseline.
- Partial or complete Mayo score at baseline and follow-up, respectively. This score comprises 4 sections assessing the severity and activity of UC in terms of: 'stool pattern', 'most severe rectal bleeding of the day', 'endoscopic findings', and 'global assessment by physician'. All 4 items are ranked based on severity with 0 being normal and 3 being most severe. Each item acquires 0-3 points, resulting in a maximum final score of 12. Partial score does not include endoscopic findings.

4.4.3 Laboratory and Endoscopic Data

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

4.4.4 Treatment Data

- UC medication history prior to start of vedolizumab IV (especially, TNF-α antagonist therapy).
- UC-related hospitalizations, emergency department and outpatient medical visits. Note: planned hospital admissions for vedolizumab IV therapy are not to be considered AEs and not to be collected as hospitalizations.
- UC-related surgeries.
- Start and all dates of vedolizumab infusions, dose and dose escalation (if any).
- Concurrent use of other UC medications at time of starting vedolizumab IV, including dates start / stop:
    - Other biologic agents (infliximab, adalimumab, golimumab).
    - Immunomodulators.
    - 5-ASAs.
    - Corticosteroids.
    - Antibiotics.
    - Opioid pain medications.
    - Others.
- Date and reasons for vedolizumab IV discontinuation, and type of medication switch.

4.4.5 Adverse Events Data

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

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

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

Serious Infections

Serious infection is defined as any event coded to MedDRA terms within the MedDRA SOC of Infections and Infestations that meets the seriousness definition (see Section 11.1.4).

Opportunistic Infections

Opportunistic infections include:

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

- Kaposi's sarcoma. This is defined as events coded to the MedDRA HLT Kaposi's sarcoma.
- Mycobacterium avium complex. This is defined as events coded to the MedDRA term Mycobacterium avium complex infection.
- TB: This is defined as all events coded to the MedDRA HLT TB infections, including new infections and reactivation of latent infections, of pulmonary and extrapulmonary sites.
- Pneumocystis carinii pneumonia. This is defined as events coded to the MedDRA terms Pneumocystis carinii pneumonia and acute Pneumocystis carinii pneumonia.
- Pneumonia, recurrent. This is defined as events coded to the MedDRA term pneumonia recurrent.
- PML: This includes events coded to the MedDRA terms PML, human polyomavirus infection, John Cunningham virus (JCV) infection, JCV test positive, leukoencephalopathy, and polyomavirus test positive. Cases of PML shall meet the histopathological, radiological, laboratory, and clinical criteria of the American Academy of Neurology guidelines for PML diagnosis [Berger JR 2013].
- *Salmonella septicemia*, recurrent. This is defined as events coded to the MedDRA terms Salmonella sepsis or Salmonella septicemia.
- *Toxoplasmosis* of brain. This is defined as events coded to MedDRA term cerebral toxoplasmosis.

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

Hepatic Viral Infections

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

Gastrointestinal Infections

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

Respiratory Infections

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

Malignancies

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

Infusion-Related Reactions and Hypersensitivity

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

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

Hepatic Injuries

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

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

Serious Adverse Events

All AEs that meet the seriousness criteria (see Section 11.1.4).

4.5 Data Collection

IQVIA will coordinate data collection with each site. All eligible UC patient medical records will be identified, wherever feasible, through the following steps:

1. Participating sites will be asked to list exhaustively all UC patients with at least 1 prescription of vedolizumab IV up until 100 patients are enrolled.
2. Full eligibility criteria will be confirmed by the principal investigator or any designee.
3. Retrospecitve Patient's data defined per IRB policy will be abstracted only after reception of the waiver of requirement to obtain informed consent.
4. Prospective Patient's data defined per IRB policy will be abstracted only for patients who consented to participate in the study.

The data sources of this non-interventional study are the CRFs. Collection of data includes but not limited to subject demographics, risk factors, clinical history, laboratory and endoscopic data, UC medication and surgeries history, UC current medications and spontaneous adverse events. Delegated site staff will be asked to complete a clinical CRF based on the patient's medical records

at baseline, 6 weeks, 14 weeks, 22 weeks, end of follow up, and unscheduled visits. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the requested language standard. The Site Study Responsible must sign-off the complete data set for each patient, confirming the collected data. AEs data reported according to Section 11 and data on SAEs collected according to Section 4 should be signed-off separately by a physician who is involved in the study.

All patient and clinician data will be handled preserving confidentiality.

4.6 Conventions

Given the real world nature of the data, multiple imputation methods for missing data will introduce bias as missing data cannot be considered completely at random (MCAR) or at random (MAR). Due to the observational nature of this study, non-imputing process will be applied, except with date data where the exact day is missing; day "15" will be assumed. Efficacy measures are not assessed after a participant discontinues vedolizumab. The exception to this will be the analysis of proportion of patients at 6 weeks, 14 weeks, 22 weeks, end of follow up, and unscheduled visits who remain on vedolizumab. Therefore, the analysis will be based on available data. The number of patients with missing data for each variable will be summarized and reported.

5. DATA QUALITY CONTROL AND ASSURANCE

5.1 Quality Control

Sponsor's standard operating procedures for the analysis of observational studies shall be followed. Any deviation from the Statistical Analysis Plan (SAP) or additional unplanned analyses shall be identified as such in the study report. Prior to the initiation of the study, physician and site personnel will be trained on the study. Training will include a detailed discussion of the protocol, performance of study procedures, and completion of the CRFs.

All clinical data will be documented via the CRF. After entry of the data, computer logic checks will be run to check for inconsistent data. Any necessary corrections will be made to the database and documented via addenda, queries, and source data clarification forms.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers; review of protocol procedures with the investigator and associated personnel before the study and edit checks as data is entered into the study database via the CRF.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. The sponsor will review CRFs for accuracy and completeness after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.

5.2 Audit from Quality Assurance Unit

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

5.3 Inspection by Institutional Review Board / Institutional Ethics Committee or Competent Authority

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

5.4 Data Management

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

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

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

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

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

5.5 Reports

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

5.6 Plans for Disseminating and Communicating Study Results

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

5.7 Archiving of Study Documentation

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

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

- Written IEC / IRB approval / vote according to local regulations.
- Authority approval according to local regulations, if required.
- The completed clinical report forms.

After final database lock the Site Study Responsible must at a minimum store the list of participating patients, the waiver of requirement to obtain informed consent and the signed informed consent forms for collection of pregnancy-related data and for prospective data collection (according to IRB policy) from treatment baseline and follow up visits on site for 5 years. The Site Study Responsible should store additional study documentation for a longer period of time as required by any local regulations and / or hospital requirement.

Additionally, data collected via the clinical report forms and abstracted via Electronic Data Capture (EDC) must be archived by the Site Study Responsible for 5 years after study completion. Data on the EDC will thereafter be destroyed, unless required to be store for a longer period of time by any local regulations and / or hospital requirement.

The Sponsor and their affiliates, on top of the above onsite archiving requirements and according to local guidelines and the standard operating procedures (SOPs) of the Sponsor, will archive all General Personal Information, Sensitive Information, study-related documentation, and data (including data abstracted via an EDC) for 10 years after study completion – and it will be administered by a Personal Information Administrator according to the SOPs of the sponsor. The storage and disposal status will be recorded. Archived General Personal Information, Sensitive Information, study-related documentation, and data will be stored in a locked cabinet or in a computer with a confidential environment, and it will be discarded with specific disposal procedures

depending on the media type. Paper records will be incinerated, shredded, or punched. Digital records will be formatted and written over to avoid reconstruction of data.

6. PLANNED ANALYSES

6.1 Interim Analysis

One interim analysis will take place for this study once at least 50 subjects have enrolled into the study. Primary and secondary outcomes will be considered for such analysis, with effectiveness analyses performed on patients with valid Mayo score data for primary and secondary analyses.

Definitions of study variables for the interim analysis will be based on those required for the final analysis contained in this analysis plan, unless otherwise stated within the interim analysis report. The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will also be provided for the interim analysis.

6.2 Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Real-World Evidence Solutions (RWES) Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets.

7. ANALYSIS SETS

7.1 All Subjects Enrolled Set [ENR]

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

7.2 Full Analysis Set [FAS]

The full analysis set (FAS) will contain all enrolled subjects who received at least one dose of study medication and had active disease at baseline. If Mayo score at baseline is less than 3 (e.g., patients who were prescribed vedolizumab because of unacceptable adverse events (AEs) related to TNF-α antagonist therapy), these patients will be excluded from the effectiveness analyses due to TNF-α intolerance.

The FAS will further be sub-divided into two subsets:

1. FAS with protocol-defined visits: Only relevant data points recorded at the protocol-defined visits (W6, W14, W22) will be considered for analyses
2. FAS with allowed visit-deviation window: The following data points will be considered for analyses
    a. Date recorded within 7 days before or 7 days after the protocol-defined visits at W6 and W14
    b. Date recorded within 4 weeks before or 4 week after the protocol-defined visit at W22

7.3 Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all enrolled subjects who receive at least one documented dose of study medication.

If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis.

The SAF will further be sub-divided into two subsets:

1. SAF with protocol-defined visits: Only relevant data points recorded at the protocol-defined visits (W6, W14, W22) will be considered for analyses
2. SAF with allowed visit-deviation window: The following data points will be considered for analyses

a. Date recorded within 7 days before or 7 days after the protocol-defined visits at W6 and W14
b. Date recorded within 4 weeks before or 4 week after the protocol-defined visit at W22

8. STATISTICAL ANALYSIS

8.1 General Considerations

The statistical analysis will be performed using R Version 3.5.1 or SAS® 9.4 software or a later version (SAS Institute, North Carolina, USA) via SAS Enterprise Guide version 6.1. The statistical results will be displayed using tables, listings and/or graphs.

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

Patient disposition will be presented, inclusive of discontinuation and reason for discontinuation. Patient demographics, risk factors, clinical characteristics and laboratory data (at baseline and follow-up, if applicable) will be summarized as descriptive statistics.
The following rules will be followed to define the number of decimal positions to report in study results:

- For categorical variables:
  - 1 for the percentage.
- For most of the continuous variables:

- 1 for the mean, SD, median, Q1 and Q3, minimum and maximum
- For continuous variables with low values, 2 decimals for all measures will be reported.

A set of draft table shells will be created in advance to describe the statistical analysis that will be done to fulfill the objectives of this study. Based on the analysis results the tables will be modified accordingly.

8.2 Analysis Plan for Demographic and Clinic Characteristics

- Descriptive statistics will be presented for patient demographics. The following measures will be assessed as of the patient's baseline:
  - Patient age at enrollment (mean, SD, median, Q1 and Q3, minimum and maximum; categories: 18-34, 35-44, 45-54, 55-64, 65-74, 75+, missing)
  - Sex (male, female, missing)
  - Height (mean, SD, median, Q1 and Q3, minimum and maximum, missing)
  - Weight (mean, SD, median, Q1 and Q3, minimum and maximum, missing)
  - Body mass index (mean, SD, median, Q1 and Q3, minimum and maximum, missing)
  - Smoking classification (Never smoked, current smoker, former smoker, unknown)
  - Family history of ulcerative colitis or intestinal bowel disease (yes, no, unknown)
  - Number of patients with each of the comorbidities before or at baseline (See 4.4.1), and number of patient with any of these comorbidities

8.3 Analysis Plan for Clinical Data

- Descriptive statistics will be presented for patient clinical characteristics. The following measures will be assessed as of the patient's baseline and follow up:
  - Number of patients with each UC intestinal location at baseline (See 4.4.2)
  - Number of patients with Ulcerative colitis extraintestinal manifestations up to 12 months before or at baseline (yes, no, unknown)
  - Partial and complete Mayo score (mean, SD, median, Q1 and Q3, minimum and maximum, unknown)

– Mayo score breakdown: 'stool pattern', 'most severe rectal bleeding of the day', 'endoscopic findings', and 'global assessment by physician' (0, 1, 2, 3, unknown)

8.4 Analysis Plan for Laboratory and Endoscopic Data

• Descriptive statistics will be presented for laboratory and endoscopic data for all patients.

The following measures will be assessed as of the patient's baseline and follow up:

– Clinical laboratory values: fecal calprotectin and C-reactive protein (mean, SD, median, Q1 and Q3, minimum and maximum, missing)
– Blood laboratory values: erythrocyte sedimentation rate, hemoglobin, albumin, platelet count and Clostridium difficile (mean, SD, median, Q1 and Q3, minimum and maximum, missing)
– Biopsy / histologic findings (low, moderate, high, none)

8.5 Analysis Plan for Treatment Data

• Descriptive statistics will be presented for treatment data for all patients. The following measures will be assessed as of the patient's baseline and follow up:

– Number and duration of medication for ulcerative colitis prior to start of vedolizumab IV
– UC-related hospitalizations, emergency department and outpatient medical visits. Note: planned hospital admissions for vedolizumab IV therapy are not to be considered AEs and not to be collected as hospitalizations. (mean, SD, median, Q1 and Q3, minimum and maximum, missing)
– UC-related surgeries (colectomy, proctectomy, bowel resection, strictureplasty, perianal surgery, ileostomy, total proctocolectomy, etc)
– Number of vedolizumab infusions start from index date till week 6, week 14, week 22 and end of follow-up (mean, SD, median, Q1 and Q3, minimum and maximum, missing)
– Number of patients under each type of dose at baseline, week 6, week 14 and week 22.
– Number of patients given dose escalation during each period between index date to week 22.
– Number of patients with concurrent use, and duration of concurrent use, of other UC medications at time of starting vedolizumab IV (See 4.4.4)
– Top reasons for vedolizumab IV discontinuation, type of medication switch, and the number of patients under each group.

8.6 Statistical Tests and Confidence Intervals

Unless otherwise specified in the description of the analyses, a two-sided 95% confidence interval will be considered as a default (alpha= 5%). If no confirmatory testing is planned, p-values are provided as descriptive representations of the data.

8.7 Missing data

Missing baseline data will not be imputed.

8.8 Examination of Subgroups

No subgroup analyses will be performed for this study.

9. MEDICATIONS

Medications will be presented for the SAF and coded using Anatomical Therapeutic Chemical (ATC) class coding, under which ATC class medications will be summarized by ATC Level 3. See Appendix 2 for handling of partial dates for medications. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which:
    - Started prior to, on or after the first dose of study medication and started no later than 14 days following end of study medication,
    - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.
- 'Post' medications are medications which started more than 14 days following the last dose of study medication.

Additionally, concomitant medications for patients experiencing respiratory and gastrointestinal infections will be described and listed out.

10. STUDY OUTCOMES

10.1 Primary outcomes

The primary outcome analysis will be performed for the FAS.

10.1.1 Primary Outcome Variables

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

10.1.2 Primary Analysis of Primary Outcome Variables

- Descriptive analyses will be performed to measure the clinical effectiveness of vedolizumab IV in UC Korean patients by the clinical response at 6 weeks.

  The following measures will be assessed as of the 6th week's follow up:

  – Reduction in each Mayo score sub-category, as defined by the following components: 'stool frequency', 'rectal bleeding', 'endoscopic findings', and 'global assessment by physician' in comparison to baseline. If all components are available, the reduction in full Mayo score will then be reported; otherwise, if all components except 'endoscopic findings' are available, the reduction in partial Mayo score will be reported. Values will be reported with mean, SD, and 95% confidence interval

  - Response rate i.e. the number of patients having clinical response at 6 weeks, relative to the number of patient who has continuous dosing of vedolizumab and valid partial Mayo score at 6 weeks

- Safety of vedolizumab IV will be assessed by the incidence rates of AESIs (as described in Section 4.4.5), SAEs, and pregnancy outcomes occurred during the study period. The proportion of patients experiencing AESIs, SAEs, and pregnancy outcomes, and their relation to study drug, will be summarized by presenting the rate and 95% CIs according to Pearson-Clopper. Additionally, safety analysis will be presented: (1) based on events occurring between first and last dose of vedolizumab (also AEs at 14 weeks of post-discontinuation in occurred cases), and (2) based on events occurring between first dose of vedolizumab and end of study follow-up.

10.2 Secondary Effectiveness

The secondary outcome analysis will be performed for the FAS:

10.2.1 Secondary Effectiveness Variables

- Clinical response to vedolizumab IV at 14 weeks, and clinical remission at 6 and 14 weeks (i.e., score ≤ 2 and no sub-score > 1) will be assessed using the complete Mayo score*.
- Clinical effectiveness of vedolizumab IV on mucosal healing at 6 and 14 weeks (i.e., level of mucosal damage in comparison to baseline) will be assessed by the Mayo endoscopic sub-score of 0 or 1.
- Clinical effectiveness of vedolizumab IV on complete mucosal healing at 14 weeks (i.e., level of mucosal damage in comparison to baseline) will be assessed by the Mayo endoscopic sub-score of 0.
- Clinical effectiveness of vedolizumab IV on endoscopic response rate at 14 weeks will be assessed by a decrease of at least 50% from baseline Mayo endoscopic sub-score.

* If available; if not, the partial Mayo score will be used.

10.2.2 Analysis of Secondary Effectiveness Variables

- Descriptive analyses will be performed to measure the clinical response of vedolizumab IV in UC Korean patients using the complete Mayo score.

  The following measures will be assessed as of the 14th week's follow up:

  – Reduction in each Mayo score sub-category, as defined by the following components: 'stool frequency', 'rectal bleeding', 'endoscopic findings', and 'global assessment by physician' in comparison to baseline. If all components are available, the reduction in full Mayo score will then be reported; otherwise, if all components except 'endoscopic findings' are available, the reduction in partial Mayo score will be reported. Values will be reported with mean, SD, and 95% confidence interval

  – Response rate i.e. the number of patients having clinical response at 14 weeks, relative to the number of patients who have continuous dosing of vedolizumab and valid partial Mayo score at 14 weeks

- Descriptive analyses will be performed to measure the clinical effectiveness of vedolizumab IV on mucosal healing at 6 and 14 weeks.

  The following measures will be assessed as of the 6th and 14th week's follow up:

  – Proportion of patients having Mayo endoscopic sub-score of 0 or 1

  – Response rate i.e the number of patients have clinical response in mucosal healing at 6 weeks (or 14 weeks), relative to the number of patients who has continuous dosing of vedolizumab and valid partial Mayo score at 6 weeks (or 14 weeks).

10.3 Exploratory Effectiveness

10.3.1 Exploratory Effectiveness Variables

CCI [redacted]

CCI [redacted]

10.3.2 Analysis of Exploratory Effectiveness Variables

CCI [redacted]

11. SAFETY OUTCOMES

All outputs for safety outcomes will be based on safety analysis set (SAF).

11.1 Definitions

11.1.1 Adverse Event

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

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

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

11.1.2 Adverse Drug Reaction

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

11.1.3 Special Situation Reports and Product Quality Issues

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

- Pregnancy: any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: infant exposure from breast milk.
- Overdose: all information of any accidental or intentional overdose.
- Drug abuse, misuse or medication error: all information on medicinal product abuse, misuse or medication error (potential or actual).
- Suspected transmission of an infectious agent: all information on a suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product.
- Occupational exposure.
- Use outside the terms of the marketing authorization, also known as "off-label".
- Use of falsified medicinal product.

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

11.1.4 Serious Adverse Event

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

- Results in death. Note that death is an outcome of an event, so the event(s) causing the death should be recorded.

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

A SAE may also be any other medically important event that, in the opinion of the health care provider, may jeopardize the subject / patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization and includes any event or synonym described in the Takeda Medically Significant AE List (see ***Table 1***).

Table 1. **Takeda medically significant AE list.**

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

GI hemorrhage	Pulmonary hypertension
GI perforation	**Skin and subcutaneous tissue**
GI obstruction	Toxic epidermal necrolysis
Necrotizing colitis	Stevens-Johnson syndrome
Peritonitis	**Urinary System**
	Acute renal failure

GI: gastrointestinal

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

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

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

11.3 Reporting of Adverse Drug Reactions and Special Situation Reports to Regulatory Agencies

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

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

12. REFERENCES

Dobson, A. J. (2002). An introduction to generalized linear models, 2nd ed. Chapman & Hall/CRC.

EMA. (n.d.). Guideline on Missing Data in Confirmatory Clinical Trials. Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. Biometrics , vol 52, 1324-1333.

Robins, J. M. & Finkelstein, D. M (2000). Correcting for Noncompliance and Dependent Censoring in an AIDS Clinical Trial with Inverse Probability of Censoring Weighted (IPCW) Log-Rank Tests. Biometrics, vol 56, 779-788.

12.1 APPENDIX 1. Programming Conventions for Outputs

DATES & TIMES

Depending on data available, dates and times will take the form <yyyy-mm-dd-hh:mm:ss.>

SPELLING FORMAT

English US.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Treatment group (if applicable)
- center-subject ID,
- date (where applicable),

12.2 APPENDIX 2. Partial Date Conventions

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study medication (med) start date, then not TEAE If start date >= study medication start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are

START DATE	STOP DATE	ACTION
		unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

Algorithm for Prior / Concomitant Medications:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

12.3 APPENDIX 3. Missing data guidance

General considerations

The number of missing cases will be reported for each variable of interest in the analysis. The flow of study participants through the entire study period will be characterized in terms of the number of subjects who completed the study.

Variable Level Missing Data

Complete Case Analysis

Study patients with one or more missing variables will be dropped from the analyses that use these variables.

Sensitivity analyses employing single imputation will be used to check the robustness of the complete case analysis. If differences between the complete case and sensitivity analyses are observed, investigation of the causes of these differences will be undertaken.

Single Imputation

Last Observation Carried Forward (LOCF)

This method specifies that variables which are measured repeatedly during the study but which are missing at a given time point will be imputed to be equal to the last observed value for that variable.

Time-to-Event Data

For time-to-event endpoints, censored observations can be checked for being informative on the outcome (by modelling the censored observations) and estimates can be adjusted for informative censoring (see e.g. Robins & Finkelstein 2000).