Clinical Study Protocol

EU PAS Number: EUPAS32684

Title: Long Term Outcomes of Drug Program for Biological Treatment in Adult Patients With Ulcerative Colitis in Poland

Study Number: Vedolizumab-5055

Document Version and Date: Version 2.0, 22 November 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

NON-INTERVENTIONAL STUDY

PROTOCOL

Study Title:

Long term outcomes of Drug Program for biological treatment in adult patients with ulcerative colitis in Poland.

MAZUREK Study

Study Protocol Number: Vedolizumab-5055

Sponsor: Takeda Polska Sp. z o.o. ul. Prosta 68, 00-838 Warsaw, Poland (Takeda Poland)

Study phase: Medical Affairs, Non-registration Company Sponsored (Non-interventional Study)

Version Number: 2.0 (22/11/2023)

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2.0 LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
5-ASA	5 aminosalicylate
6-MP	6-mercaptopurine
AE	adverse event
AESI	adverse event(s) of special interest
APS	abdominal pain score
CD	Crohn's disease
CRP	C Reactive Protein
DP	Drug Program
eCRF	electronic case report form
GCP	Good Clinical Practices
GEP	Good Epidemiology Practices
GI	gastrointestinal
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
hsCRP	high sensitivity C Reactive Protein
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFX	infliximab
PML	progressive multifocal leukoencephalopathy
SAE	serious adverse event
SAP	statistical analysis plan
TNF-α	tumor necrosis factor alpha
UC	ulcerative colitis
VDZ	vedolizumab

3.0 ADMINISTRATIVE INFORMATION

3.1 Contacts

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

Data Management, CRO (advice on e-CRF)	[redacted] [redacted] The CRO, Biostat Sp. z o.o., ul. Kowalczyka 17, 44-206 Rybnik [redacted] [redacted]
Study coordination [redacted]	[redacted] Takeda Polska sp. z o.o. Warszawa Ul Prosta 68 Tel: [redacted] [redacted]
Responsible Medical contact (carries overall responsibility for the conduct of the study)	[redacted] Takeda Polska sp. z o.o. Warszawa Ul Prosta 68 Tel: [redacted] [redacted]

3.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- Guidelines for Good Pharmacoepidemiology Practices (GPP)
- All relevant local laws and regulations, including, without limitation, data privacy laws, disclosure laws, and regulations.

SIGNATURES

…….	…….	……	……..
[redacted]	Date	Takeda Polska sp z o.o	Date
The CRO, Biostat Sp. z o.o.			
……	……	……	……..
Takeda Polska sp z o.o.	Date	Takeda Polska sp z o.o.	Date

4.0 SUMMARY

The aim of this non-interventional study (NIS) is to assess outcomes of the treatment introduced in the scope of Drug Program addressed to adult patients with ulcerative colitis in Poland after biological treatment cessation describing relapse rate in this cohort in consecutive periods of time.

AMENDMENTS AND UPDATES

Summary of Changes from Previous Version(s)

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 28 Jan 2021**	**Section of Study Protocol**
The limitation enabling recruiting to the study only patients beginning the treatment not earlier thank 1st July 2018 and not later than 31st Jan 2019 was lifted to enable to reach recruitment goal		Section 4.7, 9.1
Updated study milestones – dates of start of data collection, interim analysis, end of data collection and final report of the study, were changed		Section 5.0
Amendment Number 2	**Amendment Date 22 Nov 2023**	**Section of Study Protocol**
Change in sponsor contacts		Section 3.1
A footnote has been added regarding the update of the drug program; *Since 1st Jan 2022, DP allows to continue vedolizumab treatment until at least one of the criteria set out in items 1–2 is met.* *1) The absence of treatment response defined as a reduction in disease activity by at least 3 points on the Mayo scale or at least 20 points in PUCAI score;* *2) Adverse effects of the treatment.* *The Mazurek study includes the patients who finished vedolizumab treatment in regard to the DP (valid until 31st Dec 2021) requirements.*		Section 4.2
Updated study milestones – date of interim analysis was changed		Section 5.0
Management and reporting of adverse event section was updated according to updated Takeda SOP - PROC-0002555 (Version 7)		Section 10.0

4.1 Title

Long term outcomes of Drug Program (DP) for biological treatment in adult patients with ulcerative colitis in Poland.

4.2 Rationale and Background

This study is designed to evaluate relapse rate in patients with ulcerative colitis treated with infliximab or vedolizumab administered in the scope of the DP[1] (valid until 31st Dec 2021) after compulsory treatment cessation due to DP[1] formal requirement, since there is a data gap with regards to durability of efficacy of treatment in this setting.
Results of the study may support efforts to reform current practice in Poland and improve patients' access to prolonged treatment, if needed.

4.3 Study sites

Approximately 7 GI centers in Poland where DP is applicable will participate in the study. The final number of sites may be different based on investigators' (gastroenterologists) willingness to participate in the study. One or more investigators (gastroenterologists) per site are expected to participate in the study.

4.4 Objectives

Primary objective:

1. To assess relapse rate in patients who completed DP[1] with response/remission for ulcerative colitis at week 26 after biological treatment cessation with infliximab or vedolizumab

Secondary objectives

1. To assess relapse rate in patients who completed DP[1] with response/remission for ulcerative colitis with response within week 52, 78 and 104 after treatment cessation with infliximab or vedolizumab.
2. To evaluate need for steroid therapy within week 26, 52, 78 and 104 as a result of relapse.
3. To evaluate need for biological treatment within week 26, 52, 78 and 104 as a result of relapse.
4. To assess in real life effectiveness of biological treatment with infliximab or vedolizumab in patients with UC in DP[1] (effectiveness in induction, effectiveness in maintenance therapy, use of steroids or IMM).

[1]DP valid until 31st Dec 2021 enabled maintenance treatment with vedolizumab until no response to treatment is observed, but no longer than 54 weeks from the moment of administration of the first dose in induction therapy.
Since 1st Jan 2022, DP allows to continue vedolizumab treatment until at least one of the criteria set out in items 1–2 is met.

1) The absence of treatment response defined as a reduction in disease activity by at least 3 points on the Mayo scale or at least 20 points in PUCAI score;
2) Adverse effects of the treatment.
The Mazurek study includes the patients who finished vedolizumab treatment in regard to the DP (valid until 31st Dec 2021) requirements.

5. To assess in real life safety of biological treatment with infliximab or vedolizumab in patients with UC in DP[1].

Exploratory objectives:

[redacted]

4.5 Sponsor and CRO

4.5.1 Sponsor Personnel

Sponsor will keep a record of all relevant sponsor personnel. Takeda Poland located in Warsaw will be in charge of relevant document submission to Independent Ethics Committee (IEC).

4.5.2 Contract Research Organization (CRO)

The CRO, Biostat Sp. z o.o., ul. Kowalczyka 17, 44-206 Rybnik, Poland will be in charge of data management, Statistical Analysis Plan, analysis and generation of a study report. Data management tasks will be conducted according to the CRO's SOPs.

Details of the tasks and responsibilities are regulated in the contract between the sponsor and the CRO. The CRO will keep a record of all involved CRO personnel.

4.6 Essential Documents

The following essential documents must be received by Sponsor/CRO before the study is initiated at a site:

- Written agreement, including a section of protocol agreement between the Sponsor and the Investigator.
- Patient Information Sheet and Informed Consent Form in local language notified to Independent Ethics Committee (IEC) as locally required
- EC notification according to local regulations

4.7 Study Size

The study population includes consecutive patients aged 18 years or older with UC who received treatment with biologics (infliximab or vedolizumab) in the DP[1]. **It is planned that sample size should reach approximately 70 patients who completed DP[1] with response/remission.** Total number of patients enrolled to the study will be higher due to fact that data will also be collected from patients who lost response before treatment completion in the Drug Program

4.8 Data Analyses

In general, summary statistics (mean, median, standard deviation, minimum, and maximum) will be provided for continuous variables, and the number and percentage of each category will be provided for categorical data.

Selected endpoints pertaining to secondary and exploratory objectives will be tested. Scope and methodology of statistical tests as well as any changes to the original statistical methodology will be described in the statistical analysis plan (SAP), a separate document provided by the CRO.

5.0 MILESTONES AND TIMELINES

Milestone	Planned Date	Comments
Start of data collection	Jul 2020	Depends on all internal and external approval processes completion
Interim Analysis (52 week FU)	Dec 2023	
End of data collection	Jan 2024	
Final report of the study	May 2024	

6.0 ETHICS

This non-interventional study carries no additional burden for the patient according to the requirements of the Pharmaceutical Law except obtained informed consent to participate in the study

6.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and all relevant local regulations. Special attention will be paid to data protection as described in Directive 95/46/EC.

Sponsor will ensure that the protocol, any amendments and the Patient Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (ECs) according to local requirements.

Takeda Poland as the sponsor is responsible for meeting the ICH requirements for yearly updates to the ECs, if applicable.

6.2 Independent Ethics Committee

According to all relevant local regulations, the Sponsor will:

- notify the relevant IEC of the protocol, any amendments and the Patient Information Sheet / Informed Consent Form

The Sponsor will submit required documents to the IEC, such as but not limited to:

2) notification of substantial changes of the study documents

3) notification of the end-of-study

4) a summary of the study results

Sponsor/CRO will keep an updated list of all submission dates of all documents submitted to the EC and will provide the site responsible with a copy of this list and further documents as applicable upon request.

6.3 Authorities

The sponsor will submit required documents to the competent authority (CA) and/or other national or regional authorities, if applicable. Sponsor will keep an updated list of submission dates and a copy of all documents submitted.

6.4 Patient Information and Written Informed Consent

The Investigator must provide the patient with oral and written information about the study in a form that the patient can understand. ICF must sign by the patient before any study-related procedure is initiated. Before consenting, the patient must be left with ample time to consider and to pose questions.

Since the study is non-interventional the consent only concerns the data collection per se and is no consent to any experimental procedure or treatment.

The patient must agree that his / her data will be processed and stored in an anonymized form for evaluation of this study and any later overviews.

The patient has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form, it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept unless its deletion is actively requested by the patient. The original, signed Informed Consent Forms must be kept on the Site.

7.0 RATIONALE AND BACKGROUND

7.1 UC treatment

Both ulcerative colitis (UC) and Crohn's Disease (CD) as inflammatory bowel diseases (IBD) have unknown aetiology, often relapsing and remitting and usually start early in life what causing long lasting burden for patients and a challenge for health care systems [1-3]. The treatment strategy for ulcerative colitis [UC] is mainly based on its severity and distribution [proctitis, left-sided, extensive] [4].

Patients with steroid-dependent disease should be treated with a thiopurine, anti-TNF, vedolizumab, or methotrexate. In case of treatment failure, second-line medical therapy with an alternative anti-TNF, vedolizumab, or colectomy should be considered [5].

Anti-TNF or vedolizumab may be used as first-line biological therapy. Vedolizumab is effective in patients failing anti-TNF [5]. In patients responding to vedolizumab, maintenance therapy with vedolizumab is appropriate [5]. No withdrawal rate of anti-TNF nor vedolizumab therapy has been reported in UC studies. In a systematic review it was reported that 28% of UC patients relapse within 12 months after anti-TNF withdrawal.[6]

7.2 Study Rationale

Biological treatment in patients with ulcerative colitis in Poland is provided within frames of Drug Program (DP). It is one of many reimbursement programs authorized by MoH to grant patients access to highly specialized therapies i.e. biologics in IBD.

Inclusion/exclusion criteria for DP with infliximab or vedolizumab are in line with its approved label, but according to the DP[1] conditions, the treatment of individual patient had to be ceased after 54 weeks of therapy with vedolizumab and after 52 weeks of therapy with infliximab, regardless of actual status of the disease (response/remission) at this time point. There is a data gap with regards to evaluation of real-life response/remission durability.
This study is designed to evaluate relapse rate in patients with ulcerative colitis treated with biological drugs administered in the DP [1] after compulsory treatment cessation.

Results of the study may support efforts to reform current practice in Poland and improve patients' access to prolonged treatment maintenance if needed.

8.0 RESEARCH QUESTION AND OBJECTIVES

Primary objective:

1. To assess relapse rate in patients who completed DP[1] with response/remission for ulcerative colitis within week 26 after biological treatment cessation with infliximab or vedolizumab

Secondary objectives

1. To assess relapse rate in patients who completed DP[1] with response/remission for ulcerative colitis with response within week 52, 78 and 104 after treatment cessation with infliximab or vedolizumab.
2. To evaluate need for steroid therapy within week 26, 52, 78 and 104 as a result of relapse.
3. To evaluate need for biological treatment within week 26, 52, 78 and 104 as a result of relapse.
4. To assess in real life effectiveness of biological treatment with infliximab or vedolizumab in patients with UC in DP[1] (effectiveness in induction, effectiveness in maintenance therapy, use of steroids or IMM).
5. To assess in real life safety of biological treatment with infliximab or vedolizumab in patients with UC in DP[1].

Exploratory objectives:

[redacted]

9.0 RESEARCH METHODS

9.1 Study Design

Multicentre, non - interventional study including retrospective data collection with prospective follow-up with approximately **70 UC patients who completed DP[1] with response/remission** age 18 years or older who received treatment with biologics (infliximab or vedolizumab) in the scope of DP.

The study is based on data collection from all patients enrolled to treatment in DP[1]. Investigators need identify all patients who started treatment in DP[1] per indicated timeframes and list them in subject screening log. Investigator or designee will contact all these patients and confirm whether they willing to participate in the study. If patient agrees, Investigator will invite the patient for a V1. If the patient refuses to participate in the study, following information need to be recorded in the screening log and entered to eCRF. Patients who did not completed full course of treatment in the frames of DP[1] and agreed to participate in the study (retrospective data collection) will be invited for a V1 in order to sign ICF, as a mandatory point to collect their data from medical charts.

Prospective follow-up will be conducted only for patients that completed treatment in DP[1] with response or remission (54 weeks for vedolizumab and 52 weeks for follow-up). Retrospective data will be collected only from patients being on treatment in the Drug Program. Whether patient was excluded from DP in accordance to exclusion criteria defined in DP[1], only data generated during the treatment will be applicable for collection (VDZ or IFX). Following data will be used to describe 3rd and 4th secondary objectives [redacted]. First prospective assessment of UC symptoms (relapse rate) for patients who completed full course of treatment in DP[1] with response or remission (54 weeks for VDZ and 52 weeks for IFX) will be performed at week 26 after last infusion. Patients still in remission or presenting response will be prospectively followed up to week 104 after last infusion. Follow-up will end when relapse occurs or at V4 (104 weeks after treatment cessation). Following data will be used to describe primary objective and secondary objectives (1st, 2nd and 4th).

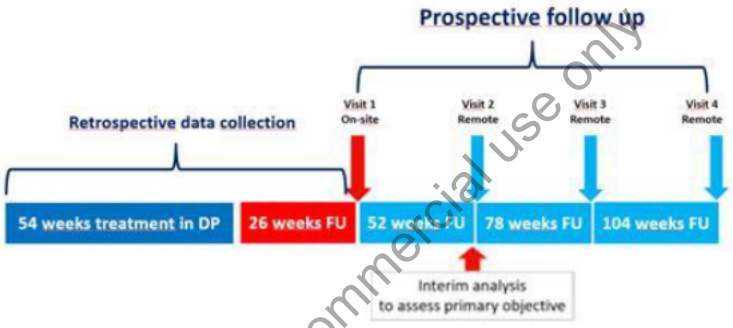

Fig 1. Study design

Each center will provide data with regards to all patients enrolled to DP (valid until 31st Dec 2021) in this site in the given time frame.

First patients will enter this study once all study start-up activities are completed and patients' treatment in DP (valid until 31st Dec 2021) with infliximab or vedolizumab is completed.

Table 2. Study Schedule

Study visits	**Study procedure**	**Procedures in cases losing response**
Week 26 after last dose in DP[1]	**VISIT 1 on site** ICF eCRF (retrospective and prospective data collection)	N/A
Week 52 after last dose in DP[1]	**VISIT 2 – remote** Patient interview eCRF	If relapse - Exclusion from the study

Week 78 after last dose in DP[1]	**VISIT 3 - remote** Patient interview eCRF	If relapse - Exclusion from the study
Week 104 after last dose in DP[1]	**VISIT 4 – remote** Patient interview eCRF	If relapse - Exclusion from the study

9.2 Legal

In Poland the Non-interventional Study is defined in art. 37al. of Pharmaceutical Low issued Sep 6th; 2001. It represents the translation of Art 2c of Directive 2001/20/EC into National law.

Art 2c DIR/2001/20/EC

´non-interventional trial´: a study where the medical product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization.

The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decisions to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

Non-intervention in the context of Non-interventional trials implies that the assignment of a patient to a particular therapeutic strategy remains in the sole responsibility of the treating physician and must not be dictated by the study-specific observation- and evaluation plan. For this reason, the decision to include a patient in the study has to be taken after the decision on the treatment and the prescription of the medicinal product and has to be independent of treatment decisions.

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

9.3 Patient Selection Criteria

1. Patients willing to participate in the study and signed ICF.
2. UC consecutive patients age 18 years or older who received treatment with biologics (infliximab or vedolizumab) in the scope of DP[1].

9.4 Variables

Disease Activity

- MAYO Score (Full MAYO score or partial MAYO score depending on data availability)
  - Disease extent - Montreal Scale
  - EIMs
  - Concomitant treatment

- Steroids and its discontinuation
- Immunomodulators
- Sulfasalazine, mesalazine

- Past biological therapies – its number and outcomes (e.g. effectiveness, reasons for discontinuation if occurred)

Treatment effectiveness of infliximab and vedolizumab in the scope of DP[1]

Safety

Following safety data will be recorded:

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

Relapse in prospective Follow-up:

- Surgeries due to UC
- Hospitalizations due to UC
- Steroids use (new course or dose increase)
- New treatment (new immunomodulator or biologics)

Additional variables

- Number of stools with blood per day
- Total number of stools

9.5 Data Sources

Patients' medical records will be the source of all data that will be recorded in the CRFs. Therefore, only data available and already existing in patient's files will be recorded. This is a non-interventional study and no additional patient's data, assessments, laboratory tests or visits except those collected/ performed as a routine clinical practice will be required for purpose of this study.

9.6 Data Collected

Baseline Data Collected at Study Enrollment:

After written informed consent is obtained, unique study identification number will be assigned in eCRF to each enrolled patient

In the retrospective period data will be collected only for patients that were on treatment in the Drug Program. Whether patient was excluded form biologic treatment in accordance to exclusion criteria defined in DP[1], only data generated during the treatment will be applicable for collection (VDZ or IFX). Patient that completed treatment in DP[1] with response /remission will be followed-up until relapse occurs (prospective period).

Based on the Drug Program definition, relapse in due course of DP[1]will be defined as 3 points increase in Mayo Score/Partial Mayo Score (retrospective period).

In order to confirm relapse remotely in the prospective part of the study at least one of following event must occur:

1. Hospitalization due to UC symptoms exacerbation
2. Colectomy due to UC
3. New course of biological treatment due to UC symptoms exacerbation
4. New course of steroids due to UC symptoms exacerbation.
5. Necessity to increase a dose of steroids due to UC symptoms exacerbation.
6. New course of an immunomodulator (such as azathioprine, 6-mercaptopurine, methotrexate, ciclosporin or tofacitinib) due to exacerbation of UC

Retrospective data collection:

1. Demographic data (gender, age, height, body weight, BMI, smoking status, place of residence – postal code or city name only)
2. Clinical characteristics of UC (time of diagnosis/disease duration, location and presence of EIMs)
3. Treatment history (including both conventional and biologic therapy)
   - Previous use of biologic therapy (including specific drugs used, dose received, efficacy, reason for discontinuation)
   - Use of the following categories of drugs, including specific drug, dose received:

     [redacted]

     (b) Corticosteroids

[redacted]

6. IBD activity assessment: Mayo Score / partial Mayo Score
7. CRP/hsCRP

Prospective Data Collection:

1. Use of systemic corticosteroids (new treatment course or dose increase)
2. Surgery due to UC
3. Hospitalizations due to UC
4. Use of immunomodulators
5. Use of biologics

Additional variables

1. Number of stools with blood per day
2. Total number of stools

9.7 Study Size

Assuming that relapse rate after 26 weeks of treatment cessation will be equal to 20% it was calculated that minimum 25 patients should be qualified. However, to increase precision of estimation (that is narrow a width of confidence interval for relapse rate estimation) it was decided that approx. 70 patients who completed DP[1] with response/remission from up to 7 sites will be included. Total number of patients enrolled to the study will be higher due to fact that data will also be collected from patients who lost response before treatment completion in the Drug Program[1].

9.8 Data Management

The CRO is responsible for Data Management carried out according to a Data Management Plan. This data management plan, which will include the description of plausibility checks, remote monitoring and, adverse event workflows will be prepared before the start of data entry.

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.

The patients will be identified in the database only by Study ID, Site ID, unique patient number, date of birth, and gender.

9.8.1 Data Collection Tools and Flow

The physician will refer to hospital records, including scales (partial Mayo Score), for documentation if applicable.

The Study Site will receive a training manual and access to the e-CRF data collection tools (Case Report Forms (e-CRFs) from Biostat Sp. z o.o. Whenever possible, complete data sets should be entered. The Investigator must sign off the complete data set for each patient, confirming the collected data. e-CRFs are automatically signed off when an authenticated user approves the entered data. Retrospective data should be entered to eCRF within 3 weeks after patient provided signed ICF. Prospective data (on-site and remote interview) should be entered to eCRF within 7 working days.

At each scheduled monitoring visit, the Investigator or designee will cooperate with the Sponsor's representative(s) for the frequent review of study documents to ensure the accuracy and completeness of the data capture system

9.8.2 Query management

Queries will be created by data management team when CRFs are filled incorrectly or contain contradictory information as per specification described in data management plan. Due to use of eCRF it is not expected that there will be invalid numeric entries, nevertheless the data management team will validate database integrity independently of the pre-programmed e-CRF quality checks and create queries if necessary. Due to retrospective nature of the study, eCRF will allow physician to indicate that certain data are missing.

In case of incomplete or inconsistent entries regarding AEs or SAEs, the Sponsor will contact the respective physician for clarification. Prior to database lock, a reconciliation of related safety information with the sponsor's safety database will be performed.

9.9 Data Analysis

All data collected will be analyzed descriptively. Standard descriptive statistic methods will be applied including number of patients, arithmetic mean, standard deviation, minimum, median and maximum. For categorical variables tables of frequencies (absolute and relative frequencies) will be presented. Relapse rates and response rates will be presented with 95% confidence intervals.

[redacted]

The safety endpoints will be presented as incidence rate calculated using person-time analyses. The safety analysis set will include all subjects treated with infliximab or vedolizumab. Reported adverse events will be coded using MedDRA dictionary and all adverse event summaries will present preferred terms and System Organ Class.

9.9.1 Statistical Analysis Plan

As this study is non-interventional, epidemiological methods will be employed for data analyses.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the SAP, a separate document provided by the CRO. The SAP will be finalized before study database lock. The analysis will be performed in accordance with the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [R5].

Statistical analyses will be performed using R (version 3.5 or higher)..

Descriptive analysis will be performed on all collected data except data collected only for the purpose of data cleaning.

9.10 Quality Control

QA audit documentation will be conducted locally with supervision of QA Takeda Poland responsible person.

10.0 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

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 unfavourable 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 a serious adverse event (SAE)
• A laboratory test result that requires the subject/patient to receive specific corrective therapy
• A laboratory abnormality that leads to the discontinuation of therapy
• A laboratory abnormality that the healthcare provider considers to be clinically significant.

10.1.2 Serious Adverse Event

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

• Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded
• In the view of the healthcare provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability/incapacity
• Results in a congenital anomaly/birth defect
• An SAE may also be any other medically important event that, in the opinion of the healthcare 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.)

10.1.3 Adverse Drug Reactions

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

10.1.4 Product Quality Complaints

A product quality complaint (PQC) is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness or performance of a product or device and combination product after it is released for distribution.

10.1.5 Special Situation Reports

• Pregnancy: Any case in which a pregnant 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: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product
• Lack of efficacy of Takeda Product
• Accidental/Occupational exposure
• Use outside the terms of the marketing authorization, also known as “off-label”
• Use of falsified medicinal product
• Use of counterfeit medicinal product
• Drug–drug interactions and drug–food interactions
• Inadvertent or accidental exposure with or without an AE
• Unintended benefit
An SSR should be reported even if there is no associated AE.

10.1.6 Collection and notifying of Adverse Events, Special Situation Reports and Product Quality

Complains to Takeda Pharmacovigilance

• SAEs, AEs, ADRs, SSRs and PQCs in the healthcare record or other applicable source data that are part of the study objectives or endpoints Events/complaints which are part of the study objectives or endpoints will be systematically identified and collected from healthcare records or other applicable source records and summarized as part of any interim analysis and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

• SAEs, AEs, SSRs and PQCs in the healthcare records or other applicable source data that are not part of the study objectives and endpoints Events/complaints which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

• SAEs, AEs, ADRs, SSRs and PQCs spontaneously reported to the investigator(s) or research team

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 PQC where the event/complaints pertains to a Takeda product (or unbranded generic),

such information should be forwarded to the relevant 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**. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

Adverse event reports and SSRs shall be sent to: Email: AE.POL@takeda.comProduct and Quality Complaints shall be sent to: Email: reklamacjePL@takeda.com

0.2 Collection and recording of adverse events, special situation reports and product quality complaints

Collection and recording of SAEs, AEs, SSRs and PQCs will commence once the study participant has provided informed consent.

The investigator should notify Takeda within **1 working day of becoming aware of a fatal or life-threatening SAE, within 4 calendar days for other SAEs, and within 7 calendar days for all other events/complaints**. This is typically achieved by the investigator completing the adverse event report pages of an eCRF or by submitting an AE Report Form to Takeda.

The investigator may be contacted by Takeda to obtain additional information on the event or for data clarification. The investigator shall make best efforts to obtain the requested additional information and will notify Takeda within **1 working day of obtaining the additional information for a fatal or life-threatening SAE, within 4 calendar days for other SAEs, and within 7 calendar days for all other events/complaints.**

Adverse event reports and SSRs shall be sent to: Email: AE.POL@takeda.com

Product and Quality Complaints shall be sent to: Email: reklamacjePL@takeda.com**10.3 Reporting of Adverse Drug Reactions to Regulatory Agencies and IRB/EC**

Takeda is responsible for reporting serious and non-serious ADRs suspected of being related to Takeda products to regulatory authorities. The investigator is responsible for reporting ADRs to the IRB/EC, if required by national law or regulation, within the timelines required by such law or regulation. The investigator shall maintain records of all such submissions.

11.0 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1 Reports

A Final Study Report based on the results obtained will be prepared and submitted to Global Medical Affairs for distribution. The Final Study Report should be available within one year from database lock and submitted to the Competent Authority according to local regulation.

11.2 Publications

Takeda aims to have the results of this study published. Takeda has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners. All information relating to the study is considered confidential and the property of the sponsor until its publication. It may not be revealed to others without the prior written consent of the sponsor and may not be used for any reason other than for the execution of this study. Only the sponsor or its representatives may extend the information obtained in this study to physicians and regulatory bodies, unless this is demanded by means of an order. The results of this study will be published in scientific journals and/or presented at conferences.

11.3 Archiving of study documentation

During the study the Investigator must as a minimum file the list of participating patients and the written informed consents. After final database lock the Investigator must as a minimum store the list of participating patients and the signed Informed Consent Forms on site for 15 years. The Investigator should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

12.0 REFERENCES

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6. Gisbert JP, Marin AC, Chaparro M. The Risk of Relapse after Anti-TNF Discontinuation in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. Am J Gastroenterol 2016;111:632-47.
7. SmPC Vedolizumab as of August 2015

13.0 Appendices

13.1 Appendix A

Data collection overview

Activity	Visit 1 on-site (26 weeks after DP cessation) +/-2 weeks	Visit 2 remote (52 weeks after DP cessation) +/-2 weeks	Visit 3 remote (78 weeks after DP cessation) +/-2 weeks	Visit 4 remote (104 weeks after DP cessation) +/-2 weeks
Informed consent	X			
Retrospective data collection (data described in Key variables section)	X			
Demographics	X			
Medication history/Patient interview	X	X	X	X
Concomitant medications	X	X	X	X
Remote interview		X	X	X

Footnotes:

1. Subject demographics
    a. gender
    b. age
    c. height, body weight, BMI
    d. smoking status current and passed,
    e. woivodship (area) of residence

2. Clinical characteristics of UC
    a. Time of diagnosis/disease duration,
    b. Disease extent according to Montreal Classification
    c. Presence of EIMs such as:
        i. arthritis,
        ii. arthralgia,
        iii. ankylosing spondylitis,
        iv. erythema nodosum ,
        v. pyoderma,
        vi. ocular symptoms (uveitis, scleritis),
        vii. PSC,

viii. aphtous stomatitis.

d. Hospitalizations in last 12 months due to UC before enrollment to DP
e. Biological treatment before enrolment to DP
f. Course of disease treatment (steroid resistant, steroid dependent, steroid intolerance)
g. Steroids and immunomodulators use (substance and daily dose)

3. Treatment with vedolizumab and infliximab in DP
    a. Number of dose received,
    b. Infusion reaction if occurred
    c. AE/SAE if occurred
    d. Response and remission

4. Assessment of vedolizumab effectiveness in MS or pMS
5. Non-biologic treatment includes following categories of drugs, including specific drug used, dose received:
    a. Immunomodulators such as azathioprine, 6-mercaptopurine, methotrexate, ciclosporin or tofacitinib.
    b. Corticosteroids (Prednizon or Metylprednizolon or Budesonid)

6. Biomarkers (CRP/hsCRP)
7. Relapse after treatment cessation