Title: Clinical perspective of vedolizumab (Entyvio) use in the Drug Program "Vedolizumab in the treatment of ulcerative colitis".

Protocol Approve Date: 03/08/2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

NON-INTERVENTIONAL STUDY

PROTOCOL

Study Title:

Clinical perspective of vedolizumab (Entyvio) use in the Drug Program "Vedolizumab in the treatment of ulcerative colitis". Study POLONEZ.

Study Number: "Vedolizumab-5050"

Study Protocol Number: 1.0

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: version 1.0 (03/08/2018)

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2.0 LIST OF ABBREVIATIONS

5-ASA 5 aminosalicylate

6-MP 6-mercaptopurine

AE adverse event

AESI adverse event(s) of special interest

CD Crohn's disease

COF contact order form

DTPC direct-to-patient contact

eCRF electronic case report form

EDC electronic data capture

GALT gut-associated lymphoid tissue

GCP Good Clinical Practices

GEP Good Epidemiology Practices

GI gastrointestinal

GPP Good Pharmacoepidemiology Practices

GVP Good Pharmacovigilance Practices

IBD inflammatory bowel disease

ICF Informed Consent Form

ICH International Conference on Harmonisation

IEC Independent Ethics Committee

IgG1 immunoglobulin G1

mAb monoclonal antibody

MAdCAM-1 mucosal addressin cell adhesion molecule-1

MOA mechanism of action

PML progressive multifocal leukoencephalopathy

PPD purified protein derivative

QoL quality of life

SAE serious adverse event

SAP statistical analysis plan

SD standard deviation

SF-12 12-Item Short Form Health Survey

SIBDQ Short Inflammatory Bowel Disease Questionnaire

SOC system organ class

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.

Issue	Poland Contact
Adverse event reporting according to section 9	
Data Management, CRO (advice on e-CRF)	PPD
Study coordination, Sponsor (medical advice on compound)	
Responsible Medical contact (carries overall responsibility for the conduct of the study)	

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 also 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

PPD

4.0 SUMMARY

The aim of this non-interventional study (NIS) is to gain knowledge on the outcomes of routine use of vedolizumab (Entyvio®)in patients with Ulcerative Colitis eligible for Drug Program in Poland.

4.1 Title

Clinical perspective of vedolizumab (Entyvio) use in the Drug Program "Vedolizumab in the treatment of ulcerative colitis".

4.2 Rationale and Background

This study is designed as a Non-Interventional Study to evaluate the effectiveness of treatment with vedolizumab (VDZ) in UC in patients who are administered VDZ in the scope of the Drug Program (DP). Currently Crohn's Disease is not in the scope of DP.

DP is a reimbursement program authorized by Ministry of Health in Poland to grant the patients access to highly specialized therapies, eg. biologics such as VDZ

Inclusion criteria of DP with VDZ are in accordance with approved Entyvio label.

According to the DP conditions, the treatment of the individual patient must be ceased after 54 weeks of therapy, regardless of patient actual response or remission status. There is a data gap in regards to such real-life population characteristics and, in consequence, a data gap in regards to VDZ efficacy and durability of outcomes in the setting outlined by DP in Poland.

4.3 Study sites

Previewed number is approximately 20 GI centers in Poland where DP is applicable will participate in the study. The number of sites may, however, vary and depend on the investigators' (gastroenterologists) willingness to provide the data. One or more investigators (gastroenterologist) per site are expected to participate in the study.

4.4 Objectives

Primary objective:

1. to assess the clinical data for effectiveness (response rate and remission rate) of VDZ in patients with UC administered the drug in the scope of DP.

Secondary objectives:

1. to characterize real-world UC patients population administered the drug in the scope of DP in particular disease phenotype and previous therapies.
2. In responder sub-group to evaluate durability rates of response and remission at 26 weeks after forced discontinuation of the drug administration in the scope of DP

3. to assess the real-world safety of VDZ in UC patients administered the drug in the scope of DP

CCI

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 Regulatory Authorities and Independent Ethics Committee (IEC).

4.5.2 Contract Research Organisation (CRO)

The CRO, PPD 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 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

It is planned that 100 patients will be qualified to participate in the study. The study population includes consecutive patients aged 18 years or older with UC who are initiating VDZ treatment in DP and are enrolled from study start onwards

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

Table 1.

Milestone	Planned Date	Comments
Start of data collection	September 2018	Depends on final internal approval
End of enrollment	Dec 2018	After 6 months since data collection started
End of data collection	Dec 2019	After 26 weeks after last patient ended DP
End of patient observation	June 2020	After 6 months (26 weeks) after termination of DP
Interim report	Nov-Dec 2018	
Final report of the study	Mid 2020	

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:

1) notification of substantial changes of the study documents
2) notification of the end-of-study
3) 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 oral and written information about the study in a form that the patient can understand, and obtain the patient's written consent 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.

For details, see the Patient Information Sheet and Informed Consent Form.

7.0 RATIONALE AND BACKGROUND

Ulcerative colitis (UC) is a chronic, relapsing, remitting inflammatory bowel disease (IBD) that causes long-lasting inflammation and ulcers in the digestive tract. UC affects the innermost lining of the large intestine (colon) and rectum. [1]

Patients with UC are usually diagnosed in their 20s and 30s; however, diagnosis can be made at any age. [2]

Although the etiology of IBD remains unclear, it is strongly suggested that deregulated immune responses play an important role in the development of IBD.[3] After exposure to the abundant intestinal bacterial antigens or environmental factors, innate immune cells such as dendritic cells and macrophages in intestinal mucosa are activated, leading to the overproduction of chemokines and proinflammatory cytokines such as TNF, IL-12 and IL-23.[4; 5] Innate immune cells, together with these proinflammatory cytokines, including IL-12 and IL-23, stimulate T-helper (Th) cell activation and differentiation into Th1 cells and IL-17-producing Th17 cells.[6] Both of these T cells are highly expressed in the inflamed mucosa of IBD patients.[7; 8] Meanwhile, these cytokines induce the expression of adhesion molecule receptors in endothelial cells, which together with chemokines, further initiate leukocyte migration to sites of inflammation.[9] Thus, the aggregated leukocytes and cytokines contribute in maintaining the uncontrolled inflammatory response, eventually leading to the intestinal tissue damage found in IBD.[10, 11] Down regulating over activated innate and adaptive immune responses can successfully ameliorate IBD, as indicated by clinical and experimental research.[12–15]

Treatment can greatly reduce signs and symptoms of the diseases and even bring about long-term remission. UC is relapsing and remitting disease and it is estimated that approximately 50% of patients will have inadequate response with, lost response to, or become intolerant to either conventional therapy or a TNFα antagonist at some point during their lifetime. [16]

Treatments for UC usually involves drug therapy or, in certain cases, surgery. There is currently no cure for these diseases, and there is no one treatment that works for everyone. There are two approaches to treatment, either `step-up`, which starts with milder drugs first, or `top-down`, which gives patients stronger drugs earlier in the treatment process. [17] In recent years, many new biological therapies have been developed. These therapies are shown to be effective for inducing remission, preventing complications, improving life quality of the patients, and reducing hospitalization and surgical rates.

Current nonsurgical treatments of IBD mainly include the administration of corticosteroids, 5-aminosalicylic acid (5-ASA) preparations, and immune-suppressive drugs such as azathioprine. However, only 50% of patients achieve sustained remission with these drugs and the treatment may cause many side effects, including the well-known toxicity of corticosteroids and cytopenia caused by azathioprine.[18, 19] Biological therapies that target immune pathways have been emerged as a new and effective therapeutic approach for the treatment of immune dysfunction-mediated diseases. They include administration of monoclonal antibodies (mAbs) against cytokines and those that influence immune responses such as certain small molecules.. As IBD is an immunological disease, biological therapy targeting excessive cytokines and immune responses in inflamed mucosa should be a highly

promising approach to treatment. To date, many new biological agents acting as therapeutic modifiers have emerged as important new treatments. Among biological therapies of IBD, only mAbs, including infliximab, certolizumab, adalimumab, golimumab and vedolizumab, are approved by the FDA and EMA for clinical treatment of IBD. [20 - 22]

The current treatments do not sufficiently address the unmet need in this population. Many patients still require frequent hospitalization, serial bowel resections, colectomies, and enteral nutrition, and regularly experience fistulae, GI abscesses, refractory diarrhoea, and rectal bleeding. These patients are often unable to function normally in society by virtue of having uncontrolled disease. Therefore, there is a pressing need for a therapy that functions via a mechanism of action (MOA) distinct from existing agents.

Vedolizumab is a humanized immunoglobulin G1 (IgG1) mAb directed against the human lymphocyte integrin α4β7. The α4β7 integrin mediates lymphocyte trafficking to GI mucosa and gut-associated lymphoid tissue (GALT) through adhesive interactions with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), which is expressed on the endothelium of mesenteric lymph nodes and GI mucosa. Vedolizumab exclusively targets the α4β7 integrin, antagonizing its adherence to MAdCAM-1 and thus impairing the migration of leukocytes into GI mucosa. By virtue of its gut-selective MOA, vedolizumab is expected to have anti-inflammatory activity without the generalized immunosuppression found with current treatments for IBD. [27]

7.1 Ulcerative Colitis

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

Vedolizumab patients had a statistically significant improvement in clinical response, clinical remission, mucosal healing, durable clinical response, durable clinical remission, and corticosteroid-free remission compared to placebo. The beneficial effect of vedolizumab on clinical remission was observed both in patients with no prior TNF-α antagonist exposure, as well as in those who had failed prior TNF-α antagonist therapy. The exploratory analysis of both GEMINI trials showed that vedolizumab achieved better results in the patient group with no prior TNF-α antagonist exposure than in patients who had failed prior TNF-α antagonist therapy.

7.2 Study Rationale

First of all this study is designed as a Non-Interventional Study to evaluate the effectiveness of treatment with VDZ in UC in patients who are administered VDZ in the scope of the DP

DP is a reimbursement program authorized by Ministry of Health in Poland to grant the patients access to highly specialized therapies, eg. biologics such as VDZ

Currently Crohn's Disease is not in the scope of Drug Program.

Inclusion criteria of DP with VDZ for patients with ulcerative colitis are in general accordance with approved VDZ label but impose some additional and strict criteria..

Also according to DP conditions, the treatment of each individual patient must be ceased after 54 weeks of therapy, regardless of patient actual response or remission status. There is a data gap in regards to such real-life population characteristics and, in consequence, a data gap in regards to VDZ effectiveness and durability of outcomes in the setting outlined by DP. Also all adverse reactions and SAEs will be collected and reported.

Secondly the prospective, observational design of the study gives the opportunity to document concomitant medication such as use of steroids and its discontinuation rate in due course of DP treatment with VDZ.

Prospective design of the study allows also prospective evaluation of appearing EIMs eg. arthropaty, arthralgia, skin lesions and ocular symptoms since patient inclusion date till VDZ treatment termination within 54 weeks. (For details see Appendix A)

Mandatory termination of DP after maximum 54 weeks of treatment, irrespective from the response status raises the question whether this formally forced approach influences disease course and patients fate. Follow up visit in 6-month time will allow fill the information gap with respect to this issue.

8.0 RESEARCH QUESTION AND OBJECTIVES

Primary objectives

1. to assess the clinical data for effectiveness (response rate and remission rate) of VDZ in patients with UC administered the drug in the scope of DP.

Secondary objectives:

1. to characterize real-world UC patients population administered the drug in the scope of DP in particular disease phenotype and previous therapies.
2. In responder sub-group to evaluate durability rates of response and remission at 26 weeks after forced discontinuation of the drug administration in the scope of DP
3. to assess the real-world safety of VDZ in UC patients administered the drug in the scope of DP

CCI

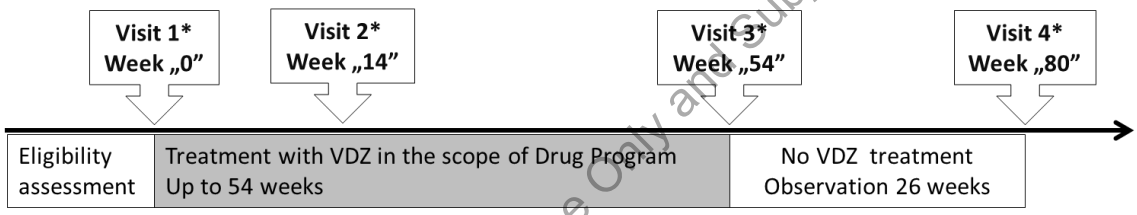
[redacted]

9.0 RESEARCH METHODS

9.1 Study Design

This is a prospective, non-interventional, national, multi-center study, to be conducted in Poland designed to assess 54-week safety and effectiveness in patients with ulcerative colitis who are eligible for DP treatment with VDZ (Fig.1) .

Fig.1 Study design



*- detailed data collection overview see Appendix A.

Physicians will prescribe vedolizumab according to the local prescribing information and DP inclusion and exclusion criteria and there will be no restrictions on the use of commercially available medications.

As a non-interventional study, this study will not change the patient/physician relationship, nor influence the physician's drug prescribing or the therapeutic management of the patient.
After eligible patients will be enrolled where baseline data will be collected.

Patients will be followed in accordance with schedule presented in Fig. 1 and Table 2 until termination of the treatment in week 54 and follow up visit in week 80 will be performed in patients who completed the full treatment schedule within DP.

Table 2.

Study visits	Study procedure	Procedures in non-responders or in cases losing response
Eligibility for DP Week 0 infusion	eCRF (details see App A):: Baseline assessment, Mayo Score (0-12) to confirm eligibility for DP	
Week 2 infusion	-	
Week 6 infusion	-	
Week 14 assessment & infusion	eCRF (details see App A): Mayo Score (0-12) to assess treatment effectiveness, AEs/SAEs CRP, current non-biological treatment, EIMs presence	If no response - Exclusion from study
Week 22 infusion	-	Possible dose escalation in accordance with SmPC
Week 30 infusion	-	Possible dose escalation in accordance with SmPC
Week 38 infusion	-	Possible dose escalation in accordance with SmPC
Week 46 infusion	-	Possible dose escalation in accordance with SmPC
Week 54 assessment & infusion	eCRF (details see App A):: partial Mayo Score (0-9) to assess treatment effectiveness /response durability, AEs/SAEs, CRP, current non-biological treatment, EIMs presence	If early termination occurs: eCRF: partial Mayo Score (0-9), treatment effectiveness /response durability, AEs/SAEs
Week 80 follow up visit	eCRF (details see App A): partial Mayo Score (0-9) to assess response durability; CRP, current non-biological treatment, EIMs presence	

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

Inclusion Criteria

The patient must meet all of the following criteria to be eligible for recruitment in the study:

1. Informed consent signed by the patient, obtained before any study-related activities are undertaken
2. Age 18 years or more at the time of firs VDZ infusion
3. Moderate to severe UC, Mayo Score > 6 (range 0-12)
4. Insufficient response to conventional therapy, including steroids and mercaptopurine or azathioprine, or
    a. intolerant to conventional therapy, including steroids and mercaptopurine or azathioprine, or
    b. existing contraindication to conventional therapy, including steroids and mercaptopurine or azathioprine, or
    c. TNF-α inhibitor failure, defined as primary lack of response or loss of response to TNF-α inhibitor (lack of improvement in partial Mayo score (0-9) of at least 3 or 30% from baseline with concomitant lack of improvement in bleeding in partial Mayo score of at least 1or lack of improvement in residual bleeding of at least 2), or
    d. adverse drug reactions to TNF-α inhibitor with imply inability to continue the treatment

Exclusion Criteria

The patient will not be allowed to enter the study when at least one of the following criteria is met:

1. hyperreactivity to vedolizumab or excipients,
2. severe active infections, ie. tuberculosis, sepsis, CMV infection, listeriosis,
3. opportunistic infections, eg. PML,
4. pregnancy or breastfeeding

9.4 Variables

- Disease Activity
  Mayo Score or Partial Mayo Score (See Appendix A and C)

- Disease extent (Appendix B)

- EIMs Concomitant treatment
- Steroids and its discontinuation
- Immunomodulators
- Past biological therapies – its number and outcomes (e.g. effectiveness, reasons for discontinuation if occurred)
- Past hospitalization due to UC – number and duration
- Comorbidities

Safety

1) 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
   - Malignancies
   - Infusion-related reactions
   - All other AEs, SAEs and adverse reactions
   - Pregnancy outcomes

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:

An initial Baseline Visit will be scheduled for patients who are considered for study participation in due course of eligibility assessment for biological treatment on routine clinical basis.

After written informed consent is obtained, each screened patient will be assigned a unique study identification number.

Study eligibility will be determined by review of the inclusion/exclusion criteria. Patients who are enrolled in the study will then have the following information recorded and undergo the baseline assessments.

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

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 (infliximab, including specific drug used, dose received, efficacy, reason for discontinuation)
   - Current use of the following categories of drugs, including specific drug used, dose received for:
     (a) Immunomodulators: azathioprine, 6-mercaptopurine (6-MP)
     (b) Corticosteroids
4. Co-morbidities (eg. autoimmune, metabolic, malignancies)
5. Health care resource use (ie. prior hospitalizations and surgeries for UC , time spent in hospital)
6. IBD activity assessment: Mayo Score (0-12)
7. CRP/hsCRP

Prospective Data Collection

The sites will record the following data with regards to VDZ treatment:

1. UC activity assessment:
   - Mayo Score or Partial Mayo Score
2. CRP / hsCRP
2. No. of vedolizumab infusions
3. Treatment discontinuation (if applicable): reason (e.g., AEs, death, loss of efficacy)
4. Use of systemic corticosteroids, immunomodulators, including specific drug used, dose
5. EIMs presence
6. Hospitalization for surgery if occurs
7. Hospitalizations due to UC deterioration
8. ER visits due to UC deterioration
9. The following safety data will be recorded:
   - All SAEs and adverse reactions
   - Infusion-related reactions

Female patients are required to report any pregnancy occurring during the study, along with a select set of information regarding the outcome of pregnancy and neonatal condition:

- Pregnancy history (date confirmed)
- Pregnancy outcome (full-term, pre-term, fetal loss/stillbirth, miscarriage, induced
- abortion)

- Neonatal characteristics

9.7 Study Size

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It is planned that 100 patients will be qualified to participate in the study. Sample size was decided based on clinical considerations, (100 consecutive patients fulfilling DP criteria after study initiation) as well as on financial ones, . Nevertheless taking into account primary endpoints of the study - proportion of patients achieving response or remission on week 54, confidence intervals can be determined for observed proportion. For a situation in which precision of estimation is the worst – that is percentage of patients meeting primary endpoints is equal to 50% the width of 95% confidence interval would not be greater than 19,2 percentage points. The study population includes consecutive patients aged 18 years or older with UC who are initiating vedolizumab treatment in DP and are enrolled from study start onwards

Table 3 95% Confidence interval width, assuming qualification of 100 patients

Observed percentage	Lower 95% CI	Higher 95% CI	Width of confidence interval
5	2,2	11,2	9
10	5,5	17,4	11,9
15	9,3	23,3	14
20	13,3	28,9	15,5
25	17,5	34,3	16,8
30	21,9	39,6	17,7
35	26,4	44,7	18,4
40	30,9	49,8	18,9
45	35,6	54,8	19,1
50	40,4	59,6	19,2
55	45,2	64,4	19,1
60	50,2	69,1	18,9
65	55,3	73,6	18,4
70	60,4	78,1	17,7
75	65,7	82,5	16,8
80	71,1	86,7	15,5
85	76,7	90,7	14
90	82,6	94,5	11,9
95	88,8	97,8	9

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 PPD 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.

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 e-CRF it is not expected that there will be missing data or invalid numeric entries, nevertheless data management team will validate database integrity independently of the pre-programmed e-CRF quality checks and create queries if necessary.

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. Selected endpoints pertaining to secondary and exploratory objectives will be tested. In particular a difference in proportion of response and remission rates after 54 weeks of treatment and subsequently after 6 months of forced discontinuation of the drug administration will be statistically compared.

CCI

CCI

[redacted]

Scope and methodology of statistical tests will be described in the statistical analysis plan (SAP), a separate document provided by the CRO.

The safety endpoints will be presented as incidence rate calculated using person-time analyses. The safety analysis set will include all subjects treated with VDZ. Reported adverse events will be coded using MedDRA dictionary and all adverse event summaries will present preferred terms and System Organ Class. Where appropriate 95% confidence intervals will be provided.

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 Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [R5].

Statistical analyses will be performed using R (version 3.4 or higher) – a validated statistical package..

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 adverse event (AE) is any untoward medical occurrence in a patient or clinical trial 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 (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered causally related to the medicinal product.

10.1.2 Adverse Reactions

An adverse reaction is an AE for which there is at least a reasonable possibility of a causal relationship between an AE and a medicinal product.

10.2 Classification

10.2.1 Causality

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

Related: There is a reasonable possibility that the drug caused the event.

Not related: There is not a reasonable possibility that the drug caused the event.
For the purposes of this study, an adverse reaction is an AE that is considered related to VDZ® according to the definition above.

10.2.2 Severity

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

1. Mild: An AE that is easily tolerated and does not interfere with daily activities.
2. Moderate: An AE that is sufficiently discomforting so as to interfere with daily activities.
3. Severe: An AE that prevents normal everyday activity.

Note that “severe is not synonymous with “serious”: an AE may be assessed as severe without meeting the criteria for an SAE (see above).

10.2.3 Seriousness

A serious Adverse Event (SAE) is an AE that meets any of the following criteria:

1. Is fatal of life threatening, i.e., in the view of the investigator, places the patient at immediate risk of death from the reaction as it occurred. An event would not be classified as life threatening solely because, had it occurred in a more serious form, it might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis can be fatal.
2. Results in persistent or significant disability or incapacity. Disability is defined as a substantial disruption of a person´s ability to conduct normal life functions.
3. Requires inpatient hospitalization or prolongation of an existing hospitalization.
4. Is a congenital anomaly/birth defect.

5. Any other important medical event that may not result in death, be life-threatening or require hospitalization, but based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

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

10.2.4 Outcome

1. **Fatal:** The patient died due to the event. If the patient died due to other circumstances than the event the outcome should be stated as “Not recovered” or “Recovering”.
2. **Recovered/Resolved:** The patient has fully recovered from the event or the condition has returned to the level observed at baseline.
3. **Recovering/Resolving:** The event is improving but the patient is still not fully recovered.
4. **Not Recovered/Not Resolved:** The event is ongoing at the time of reporting and the patient has still not recovered.
5. **Recovered with Sequelae/Resolved with Sequelae:** As a result of the event, the patient suffered persistent and significant disability /Incapacity (e.g. became blind, deaf of paralyzed)
6. **Unknown:** If Outcome is not known or not reported.

10.3 Collection and Recording of Adverse Events

Collection and recording of AEs will commence after the study participant has provided informed consent.

AEs and SAEs (which include all deaths) must be reported to the sponsor, whether or not considered causally related to VDZ®.

In case of an AE and SAE, the investigator will notify the sponsor through the use of the e-CRF AE and SAE form, within 24 hours after the investigator becomes aware of the event. The event must be documented in source documentation. The data of AEs and SAEs that have been documented in the e-CRF will be sent automatically per e-mail to the Sponsor´s Drug Safety department immediately after saving the data in the e-CRF.

Follow-up information

After receipt of the initial e-CRF AE and SAE form, the investigator may be contacted by the sponsor to obtain additional information on the event or for data clarification. The investigator shall make best effort to obtain the requested additional information. All new additional information obtained on the event should be sent to the designated contact of the sponsor within 24 hours after the investigator becomes aware of additional information.

10.4 Reporting of Adverse Reactions

The Sponsor is responsible for submission of adverse reactions to regulatory authorities in accordance with local reporting requirements or the Sponsor's post marketing commitments.

10.5 Other Safety Information

If the investigator becomes aware of any of the following events during the study, whether or not associated with an AE, the event should be recorded on the e-CRF AE and SAE form and submitted to the Sponsor within 24 hours of investigator awareness.

1. **Use during pregnancy and breastfeeding**
2. **Medication error:** This refers to any unintentional error in the prescribing, dispensing, or administration of a drug while in the control of the healthcare professional or patient.
3. **Lack of Effect**
4. **Overdose:** administered dose exceeds the maximum recommended dose according to authorized product information.
5. **Occupational Exposure:** This refers to exposure to a drug, as a result of one´s professional or non-professional occupation.
6. **Suspected transmission of an infectious agent via a medicinal product.**

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 course of 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

1. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012 Jan;142(1):46-54.e42; quiz e30. Epub 2011 Oct 14.

2. Carter MJ, Lobo AJ, Travis SPL (2004) Guidelines for the management of inflammatory bowel disease in adults. Gut, 53, Suppl 5, V1–16 <DOI>10.1136/gut.2004.043372</DOI>

3. Xavier RJ, Podolsky DK: Unravelling the pathogenesis of inflammatory bowel disease. Nature 448(7152), 427–434 (2007).

4. Kamada N, Hisamatsu T, Okamoto S et al.: Abnormally differentiated subsets of intestinal macrophage play a key role in Th1-dominant chronic colitis through excess production of IL-12 and IL-23 in response to bacteria. J. Immunol. 175(10), 6900–6908 (2005).

5. Bai AP, Ouyang Q: Probiotics and inflammatory bowel diseases. Postgrad. Med. J. 82(968), 376–382 (2006).

6. Ahern PP, Izcue A, Maloy KJ et al.: The interleukin-23 axis in intestinal inflammation. Immunol. Rev. 226, 147–159 (2008).

7. Kobayashi T, Okamoto S, Hisamatsu T et al.: IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. Gut 57(12), 1682–1689 (2008).

8. Fujino S, Andoh A, Bamba S et al.: Increased expression of interleukin 17 in inflammatory bowel disease. Gut 52(1), 65–70 (2003).

9. Wittchen ES: Endothelial signaling in paracellular and transcellular leukocyte transmigration. Front. Biosci. 14, 2522–2545 (2009).

10. Mahida YR: The key role of macrophages in the immunopathogenesis of inflammatory bowel disease. Inflamm. Bowel Dis. 6(1), 21–33 (2000).

11. Ogata H, Hibi T: Cytokine and anti-cytokine therapies for inflammatory bowel disease. Curr. Pharm. Des. 9(14), 1107–1113 (2003).

12. Mannon PJ, Fuss IJ, Mayer L et al.: Anti-interleukin-12 antibody for active Crohn's disease. N. Engl. J. Med. 351(20), 2069–2079 (2004).

13. Andou A, Hisamatsu T, Okamoto S et al.: Dietary histidine ameliorates murine colitis by inhibition of proinflammatory cytokine production from macrophages. Gastroenterology 136(2), 564–574 e2 (2009).

14. P 0963 A Multinational Study to Determine Indicators of Suboptimal Therapy Among Ulcerative Colitis Patients Treated With Tumour Necrosis Factor Antagonists, J.O.Lindsay et al. UEGW 2015

15. Management of Crohn's disease in adults. Bethesda, Md.: American College of Gastroenterology. http://gi.org/guideline/management-of-crohn%e2%80%99s-disease-in-adults/. Accessed March 04 2016

16. Kamada N, Hisamatsu T, Okamoto S et al.: Unique CD14 intestinal macrophages contribute to the pathogenesis of Crohn disease via IL-23/IFN-γ axis. J. Clin. Invest. 118(6), 2269–2280 (2008).

17. Mucida D, Park Y, Kim G et al.: Reciprocal Th17 and regulatory T cell differentiation mediated by retinoic acid. Science 317(5835), 256–260 (2007).

18. Sandborn WJ: Current directions in IBD therapy: what goals are feasible with biological modifiers? Gastroenterology 135(5), 1442–1447 (2008).

19. Katz S: Update in medical therapy of ulcerative colitis: a practical approach. J. Clin. Gastroenterol. 34(4), 397–407 (2002).

20. S.Danese et al.:Biologic agents for IBD: practical insights Nat. Rev. Gastroenterol. Hepatol. 12, 537–545 (2015); published online 18 August 2015; doi:10.1038/nrgastro.2015.135

21. J.P Gisbert et al.: Loss of Response and Requirement of Infl iximab Dose Intensification in Crohn ' s Disease: A Review Am J Gastroenterol 2009; 104:760–767; doi: 10.1038/ajg.2008.88 ; published online 27 January 2009

22. S. Ben-Horin et al.: Review article: loss of response to anti-TNF treatments in Crohn's diseaseAliment Pharmacol Ther 2011; 33: 987–995 doi:10.1111/j.1365-2036.2011.04612.x

23. SmPC Vedolizumab as of August 2015

24. Harvey RF, Bradshaw JM. A simple index of Crohn´s-disease activity. Lancet 1980 Mar 8; 1(8167): 514.

25. Lewis JD, Chuai S, Neddel L, Lichtenstein GR, Aberra FN, Ellenberg JH. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. Inflamm Bowel Dis. 2008; 14(12): 1660-6.

13.0 Appendices

13.1 Appendix A

Data collection overview

Visit	Visit 1	Visit 2	Visit 3	Early termination	Visit 4 (Follow-up)
Week	0	14	54		80
Informed consent	x				
Inclusion and exclusion criteria for DP	x				
Subject demographics[1]	x				
Clinical characteristics and history of UC[2]	x				
Comorbidities[3]	x				
History of biologic UC treatment[4]	x				
Current treatment with vedolizumab in DP overview [5]		x	x		
Assessment of vedolizumab effectiveness in MS (0-12)[6]	x	x			
Assessment of vedolizumab effectiveness in pMS (0-9)[6]			x	x	x
Current non-biologic treatment[7], biomarkers[8] and presence of EIMs	x	x	x	x	x
Adverse events		x	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 (see Appendix B)
   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 and cumulative number of days spent in hospital

e. Course of disease treatment (steroid resistant, steroid dependent, steroid intolerance)
f. Current treatment with steroids and immunomodulators (substance and daily dose)

3. Comorbidities if present
   a. Autoimmune such as: RA, psoriasis, PSA, LE, autoimmune hepatitis, G-B disease, Hashimoto thyroiditis, multiple sclerosis, if any other - may be specified;
   b. Metabolic such as diabetes, if any other – may be specified,
   c. Any other comorbidity - may be specified

4. History of biologic treatment due to UC with infliximab or its similars and its outcomes -
   a. specific drug used,
   b. dose received,
   c. effectiveness,
   d. dose escalation if occurred
   e. reason for discontinuation if occurred

5. Current treatment with vedolizumab in DP - overview
   a. Number of dose received so far,
   b. Reason for dose delay if occurred
   c. Infusion reaction if occurred
   d. AE/SAE if occurred

6. Assessment of vedolizumab effectiveness in MS or pMS (see Appendix C)

7. Current non-biologic treatment includes following categories of drugs, including specific drug used, dose received:
   a. Immunomodulators: azathioprine or 6-mercaptopurine (6-MP)
   b. Corticosteroids (Prednizon or Metylprednizolon or Budesonid)

8. Biomarkers (CRP/hsCRP)

13.2 Appendix B

Montreal classification of extent of ulcerative colitis (UC)

Extent		Anatomy
E1	Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2	Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3	Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

13.3 Appendix C

Components of the Mayo Score

Stool Frequency

0 = Normal
1 = 1–2 stools/day more than normal
2 = 3–4 stools/day more thannormal
3 = >4 stools/day more than normal

Rectal bleeding[*]

0 = None
1 = Visible blood with stool less than half the time
2 = Visible blood with stool half of the time or more
3 = Passing blood alone

Mucosal appearance at endoscopy[†]

0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

Physician rating of disease activity

0 = Normal
1 = Mild
2 = Moderate
3 = Severe

[*]A score of 3 for bleeding required patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.

[†]**The mucosal appearance at endoscopy is not included in the Partial Mayo Score**