Clinical Study Protocol

EU PAS Number: EUPAS23580

Title: Observational Study of the Effectiveness of Vedolizumab on Treatment Outcomes and HRQoL in biologic naïve Patients with Inflammatory Bowel Diseases in Greece (TROVE)

Study Number: Vedolizumab-4018

Document Version and Date: Version 1.1, 28 May 2018

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

Short Title: Vedolizumab in biologic naïve patients with IBD in Greece

Title: Observational Study of the Effectiveness of Vedolizumab on Treatment Outcomes and HRQoL in biologic naïve Patients with Inflammatory Bowel Diseases in Greece – the TROVE Study

Study ID: Vedolizumab-4018

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Study Phase: Medical Affairs, Non-registration Company Sponsored (Observational)

Date of Version 1.1 of Protocol: 28 May 2018

1 Administrative Information

1.1 Contacts

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

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1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good Pharmacoepidemiology practices (GPP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws and regulations.

SIGNATURES

[redacted] MD., Ph.D., FEBG&H
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Others as identified

Summary

Short Title of Study

Vedolizumab treatment in biologic naïve patients with IBD in Greece

Study Sites

The study is planned to be conducted in approximately 20 hospital/clinics in Greece.

Objectives

The primary objective of the study is to assess long term clinical benefit for the biologic naïve patients with Inflammatory Bowel Disease on treatment with Vedolizumab.

The secondary objectives of the study are

- to assess the effectiveness of Vedolizumab on health related quality of life (HRQoL)
- to evaluate clinical and endoscopic remission in patients on treatment with Vedolizumab in real world clinical practice
- to evaluate patient satisfaction with treatment
- to evaluate the role of laboratory tests (biological activity markers as CRP and faecal calprotectin) as adjunctive measure in disease management and Vedolizumab treatment in clinical practice
- to assess safety of Vedolizumab

Methodology

This is a prospective, observational, multi-centre, cohort study, designed primarily to assess long-term clinical benefit in patients who are initiating Vedolizumab for UC or CD.

Physicians will prescribe Vedolizumab according to the local prescribing information in Greece, and there will be no restrictions on the use of commercially available medications. As an observational study, this study will not change the patient/physician relationship, nor influence the physician's drug prescribing or the therapeutic management of the patient.)

Biologic naïve patients with UC or CD who are initiating treatment with Vedolizumab will be recruited and screened to determine eligibility. Recruitment period will last for 2 years. After eligible patients are enrolled, baseline data will be collected. Patients will be followed for two years or until discontinuation of Vedolizumab treatment, whichever occurs earlier. For patients that will discontinue Vedolizumab treatment, every effort should be made for discontinuation reason, IBD activity and QoL as well as information on new therapy to be collected as they become available and to be recorded in eCRF under the premature discontinuation visit. For cases where this information is not available at the time of discontinuation, data may be collected at the earliest as they become available to the investigator by phone communication. Data on possible new treatment after Vedolizumab discontinuation might be collected and recorded in the eCRF within 12 months from the date of discontinuation.

Completion of questionnaires by patients will be optional.

Number of Subjects

In total approximately 200 patients will be enrolled in the study: 100 adult patients with moderately to severely active ulcerative colitis and 100 adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy, naïve to biologic treatments. These numbers (per group) are expected according to the current epidemiology for both indications in Greece.

Diagnosis/Disease/Condition and Main Criteria for Inclusion

Inclusion criteria for the study are:

1. Male or female, aged 18 years or older patients with moderately to severely active ulcerative colitis or Crohn's disease, naïve to biologic treatments, initiating treatment with Vedolizumab under normal clinical practice according to the approved SmPC in the European Union.
2. Informed consent to study participation and to data being collected and provided to Takeda Hellas.

Exclusion criteria are:

1. Contraindications according to the SmPC.
2. Patients not willing to consent to study participation and to data being collected and provided to Takeda Hellas.
3. Current or planned participation in any interventional clinical trial.
4. Presence of mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
5. Treatment with any biologic therapies in the past (including Vedolizumab).

Duration of Data Collection per Subject

Patients will be followed-up for two years after enrollment in the study.

Criteria for Evaluation

Population descriptors

Adult patients with moderately to severely active ulcerative colitis or Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy, naïve to biologic treatments, will be enrolled in the study.

Main outcome variables

The primary outcome of the study is the drug discontinuation rate in UC patients and in CD patients under treatment with Vedolizumab in the two years follow-up period. Reasons for discontinuation will be collected.

The secondary outcomes of the study are:

- Changes in partial Mayo score for UC patients and Harvey-Bradshaw Index for CD patients, as assessed per clinical practice (where data are available) at baseline and at 14, 30, 46(optional), 54, 78 and 102 weeks of treatment and their correlation with the Vedolizumab treatment.

- Changes in Short Inflammatory Bowel Disease Questionnaire (SIBDQ) score and EQ-5D Questionnaire measured at baseline, and at 30, 46(optional), 54, 78 and 102 weeks in UC and in CD patients' treatment and their correlation with the Vedolizumab treatment.
- Rate of dose intensification (from Q8W to Q6W or to Q4W) in UC and in CD patients in the two years follow up period.
- Rate of UC and CD patients under steroids (Steroid sparing effect) at Baseline, week 6 and week 14.
- Impact of treat to target treatment with Vedolizumab assessing Clinical/PROs (Rectal bleeding and diarrhea/altered bowel habit for UC. Pain and diarrhea/altered bowel habit for CD) measured by the clinicians according to clinical practice, at baseline, and at 14, 30, 46(optional), 54, 78 and 102 weeks of treatment taking in consideration the average of the last 3 days by means of partial Mayo score for UC patients and Harvey-Bradshaw Index for CD patients.
- Endoscopic disease activity at baseline and week 52 using the simple endoscopic score (SES) in CD and MAYO score in UC. (Regarding UC, the majority of clinical trials define endoscopic remission and mucosal healing as a Mayo score equal to 0 or 1. Regarding CD, endoscopic remission is defined as a SES-CD score (Simplified Endoscopic Score for Crohn's Disease) of between 0 and 2).
- Changes in Treatment Satisfaction Questionnaire for Medication (TSQM-9) in UC and in CD patients, measured at baseline, and at 14, 30, 46(optional), 54, 78 and 102 weeks of treatment and their correlation with the Vedolizumab treatment.
- Effects of biological parameters (CRP and faecal calprotectin) as adjunctive measure of inflammation monitoring in UC and CD used as exploratory parameter by the clinicians when applicable/available.
- Collection of Nr of SAEs, Nr of non-serious related AEs, Nr of SSRs.

Data will be collected at follow-up visits closest to the aforementioned time points.

Statistical Methods

The analysis will be descriptive; all categorical variables will be listed and illustrated by absolute and relative frequencies.Continuous variables will be expressed as as means, standard deviation, median and range

Table of Contents

List of Abbreviations and Definition of Terms

AE:	Adverse Event
ADR:	Adverse Drug Reaction
CA:	Competent Authority
CD:	Crohn's Disease
CRF:	Case Report Form
CRO:	Contract Research Organisation
CV:	Curriculum Vitae
EQ-5D:	EuroCol Group health related quality of life questionnaire
FPI	First Patient In
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
HRQoL:	Health Related Qualtiy of Life
IBD:	Inflammatory Bowel Disease
ICH:	International Conference on Harmonisation
GPV:	Global Pharmacovigilance
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
PSUR:	Periodic Safety Update Report
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SIBDQ:	Short Inflammatory Bowel Disease Questionnaire
SMPC:	Summary of Product Characteristics
SSR:	Special Situation Report
TNF:	Tumor Necrosis Factor
TSQM-9:	Treatment Satisfaction Questionnaire for Medication
UC:	Ulcerative Colitis

2 Introduction

Inflammatory Bowel Disease (IBD) is an umbrella term given to the life-long ('chronic') bowel diseases of which Crohn's disease (CD) and ulcerative colitis (UC) are the predominant forms. Although the causes of IBD are unknown, it is recognised as an immune-mediated disease, possibly precipitated by a mixture of genetic and environmental factors which may include fastidious childhood hygiene, smoking, or drugs (such as anti-inflammatories, the contraceptive pill, or antibiotics) . IBD commonly presents in adolescence or young adulthood, and follows a currently unpredictable relapsing and remitting course.

The worldwide prevalence of IBD is estimated to be as high as 396 per 100,000 persons (Lakatos 2006); however, there is wide geographic variance. The incidence and prevalence of UC and CD are highest in Europe and North America, with rates increasing over time in both industrialized and developing nations (Lakatos 2006; Molodecky 2012). Although determining the precise incidence and prevalence of UC is limited by the lack of standardised criteria for diagnosis, inconsistent new case assessment methodology, and issues of disease misclassification, existing epidemiologic data suggest worldwide incidence rates of UC between 0.5 and 24.5 per 100,000 individuals (Lakatos 2006; Molodecky 2012). For CD, incidence estimates range from 0.3 to 12.7 per 100,000 person-years in Europe, 0.04 to 5.0 per 100,000 person-years in Asia and the Middle East, and 0 to 20.2 per 100,000 person-years in North America (Molodecky 2012). In Greece, the incidence of IBD is comparable to other European countries (Ladas, 2005), but differences are noted in the incidence and prevalence of the disease as well as the UC/CD ratio that decreases over time among different parts of the country (Ladas, 2005; Tsianos, 2005; Manousos, 1996). The highest incidence of UC has been reported in Central Greece (11.2 per 100,000 population) and the lowest in northwestern Greece (4 per 100,000 population)(Ladas, 2005; Tsianos, 2005). It is estimated that approximately 15,000 patients are diagnosed with IBD in Greece.

Available pharmacologic treatments for IBD include conventional agents (i.e., aminosalicylates, corticosteroids, immunosuppressants) and biologic therapies (i.e. tumour necrosis factor [TNF]-α antagonists and natalizumab) (McLean 2012). The selection of treatment depends on symptom severity, location and extent of disease, goal of treatment (induction or remission), disease course and disease-related complications and patient preferences (Danese 2011). Surgery is generally reserved for patients with severe disease not amenable to medical management, those intolerant to medical therapies, or those with certain disease-related complications (McLean 2012; Ford 2013).

Vedolizumab is a novel integrin receptor antagonist for induction and maintenance treatment in adult patients with moderately to severely active UC and CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist. Vedolizumab exclusively binds the α4β7 heterodimer on leukocytes, selectively blocking interaction with gastrointestinal (GI)-specific cellular adhesion molecules.

A Phase III, multicenter, randomized, double-blind, placebo-controlled study (GEMINI I) has evaluated the safety and efficacy of Vedolizumab as induction treatment in 895 patients and as maintenance

treatment in 373 patients with moderate to severe UC (Feagan 2013). Compared to placebo, Vedolizumab induction treatment resulted in significantly greater rates of clinical response, clinical remission, and mucosal healing at Week 6:

Clinical response: Vedolizumab – 47.1% vs placebo – 25.5%; difference – 21.7%, p<0.001

Clinical remission: Vedolizumab – 16.9% vs placebo – 5.4%; difference – 11.5%, p=0.001

Mucosal healing: Vedolizumab – 40.9% vs placebo – 24.8%; difference – 16.1%, p=0.001.

Vedolizumab efficacy was not substantively affected by concomitant use of glucocorticoids or immunosuppressants or previous treatment with TNF-α antagonists.

Patients receiving Vedolizumab maintenance treatment either every 4 weeks (44.8%) or every 8 weeks (41.8%) were significantly more likely to achieve clinical remission at Week 52 compared to placebo-treated patients (15.9%); p<0.001 for both Vedolizumab regimens vs placebo (Feagan 2013). Compared to placebo, Vedolizumab maintenance treatment was associated with significantly higher rates of all secondary endpoints, including durable clinical response, durable clinical remission, mucosal healing, and glucocorticoid-free remission (Feagan 2013).

A Phase III, multicenter, randomized, double-blind, placebo-controlled study (GEMINI II) evaluated the safety and efficacy of Vedolizumab as induction treatment in 1115 patients and as maintenance treatment in 461 patients with moderate to severe CD (Sandborn 2013). At Week 6, clinical remission rates were significantly higher in the patients receiving Vedolizumab (14.5%) vs patients receiving placebo (6.8%); p=0.02 (Sandborn 2013). There was a positive trend favouring Vedolizumab over placebo in the number of patients achieving a CDAI-100 response at Week 6 (31.4% vs 25.7%; p=0.23) (Sandborn 2013). In the maintenance study, significantly more Vedolizumab-treated patients in the every-8-weeks (39.0%) and every-4-weeks (36.4%) groups achieved clinical remission at Week 52 vs placebo-treated patients (21.6%; p<0.001 and p=0.004, respectively) (Sandborn 2013). Patients receiving Vedolizumab every 4 or 8 weeks were significantly more likely to achieve a CDAI-100 response and have a glucocorticoid-free remission at Week 52 compared to patients receiving placebo, although there was no significant difference between the treatment groups in the number of patients with a durable clinical remission (Sandborn 2013).

A Phase III, multicenter, randomized, double-blind, placebo-controlled study (GEMINI III) evaluated the safety and efficacy of Vedolizumab as induction treatment in 416 patients with moderate to severe CD who had failed prior anti TNF therapy (Sands B 2014). For the primary endpoint, no statistically significant difference was observed between the Vedolizumab (15.2%) and placebo (12.1%) groups for the number of patients in clinical remission at Week 6 in the TNF-α antagonist failure group (p=0.4332) (Sands B 2014). In exploratory analyses, compared to placebo Vedolizumab was associated with a higher number of patients achieving clinical remission at Week 10 (26.6% vs 12.1%, p=0.0012) and a CDAI-100 response at Week 6 (39.2% vs 22.3%; p=0.0011) in the TNF-α antagonist failure population, suggesting a potential treatment benefit for Vedolizumab in this population beyond the 6-week period (Sands B 2014). In the overall population, Vedolizumab-treated patients had higher rates of clinical remission at Weeks 6 and 10, sustained remission, and CDAI-100 response at Week

6 compared to placebo-treated patients (Sands B 2014).

Health related quality of life (HRQoL) is influenced by IBD in both remission and relapse, although perhaps more so in the latter (Casellas 2005; Cohen 2002). Psychological wellbeing can be significantly impaired regardless of disease type or status, possibly attributable to sustained psychological distress. Psychological intervention or counselling support may be appropriate for patients demonstrating higher levels of concern although the benefits have not been fully demonstrated (Irvine 1997; Turnbull 1995). Even in remission, background persistent disease-related issues such as fatigue, extra-intestinal manifestations and sleep difficulties can also affect HRQoL. Individuals with IBD often find that their disease impacts on many aspects of daily life, affecting relationships, schooling, socialising and work life. In a large European study undertaken in collaboration with patient associations, 75% of patients with IBD had taken time off work in the last year owing to their IBD and 35% reported that their IBD had prevented an intimate relationship (Lönnfors 2014). Furthermore in this study, patients often felt that their HRQoL is not explored or discussed properly with them during healthcare consultations, as 54% reported that they were unable, during a consultation to discuss something important to them.

In addition, data for the Greek population to describe the 'real world' effectiveness of the Vedolizumab with regards to improvement in patient quality of life as well as improvement in the control of the disease are lacking.

The aim of this study is to assess long term clinical benefit for the patients by means of drug discontinuation rate and to evaluate the effectiveness of Vedolizumab on disease control by means of partial Mayo Score in UC patients and Harvey-Bradshaw Index in CD patients through the course of their treatment as well as its impact on patient satisfaction and HRQoL.

3 Study Objectives

3.1 Primary Objective

The primary objective of the study is to assess long term clinical benefit for the biologic naïve patients with Inflammatory Bowel Disease on treatment with Vedolizumab.

3.2 Secondary Objectives

The secondary objectives of the study are:

- to assess the effectiveness of Vedolizumab on health related quality of life (HRQoL)
- to evaluate clinical and endoscopic remission in patients on treatment with Vedolizumab in real world clinical practice
- to evaluate patient satisfaction with treatment
- to evaluate the role of laboratory tests (biological activity markers as CRP and faecal calprotectin) as adjunctive measure in disease management and Vedolizumab treatment in clinical practice
- to assess safety of Vedolizumab

3.3 Primary Outcome

The primary outcome of the study is the drug discontinuation rate in UC patients and in CD patients under treatment with Vedolizumab in the two years follow-up period. Reasons for discontinuation will be collected.

3.4 Secondary Outcomes

The secondary outcomes of the study are:

- Changes in partial Mayo score for UC patients and Harvey-Bradshaw Index for CD patients, as assessed per clinical practice (where data are available) at baseline and at 14, 30, 46(optional), 54, 78 and 102 weeks of treatment and their correlation with the Vedolizumab treatment
- Changes in Short Inflammatory Bowel Disease Questionnaire (SIBDQ) score and EQ-5D Questionnaire measured at baseline, and at 30, 46(optional), 54, 78 and 102 weeks in UC and in CD patients treatment and their correlation with the Vedolizumab treatment
- Rate of dose intensification (from Q8W to Q6W or to Q4W) in UC and in CD patients in the two years follow up period
- Rate of UC and in CD patients under steroids (Steroid sparing effect) at Baseline, week 6 and week 14
- Impact of treat-to-target treatment with Vedolizumab assessing Clinical/PROs (Rectal bleeding and diarrhea/altered bowel habit for UC. Pain and diarrhea/altered bowel habit for CD) measured by the clinicians according to clinical practice, at baseline, and at 14, 30, 46(optional), 54, 78 and 102 weeks of treatment taking in consideration the average of the last 3 days by means of partial Mayo score for UC patients and Harvey-Bradshaw Index for CD patients
- Endoscopic disease activity at baseline and week 52 using the simple endoscopic score (SES) in CD, and MAYO score in UC. (Regarding UC, the majority of clinical trials define endoscopic remission and mucosal healing as a Mayo score equal to 0 or 1. Regarding CD, endoscopic remission is defined as a SES-CD score (Simplified Endoscopic Score for Crohn's Disease) of between 0 and 2)
- Changes in Treatment Satisfaction Questionnaire for Medication (TSQM-9) in UC and in CD patients, measured at baseline, and at 14, 30, 46(optional), 54, 78 and 102 weeks of treatment and their correlation with the Vedolizumab treatment
- Effects of biological parameters (CRP and faecal calprotectin) as adjunctive measure of inflammation monitoring in UC and CD used as exploratory parameter by the clinicians when applicable/available
- Collection of Nr of SAEs, Nr of non-serious related AEs, Nr of SSRs

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in approximately 20 hospital/clinics in Greece. Primary Investigators/Sites will be selected based on their experience in treating IBD patients, their scientific expertise and their research facilities in order to assure high quality data collection. The sites distribution will be broad enough to ensure adequate geographical representation (more site representation in regions with high numbers of IBD patients) *(where possible)*.

4.2 Sponsor Personnel

Takeda Hellas will keep a record of all relevant sponsor and vendor personnel. This record should include Study Managers and other medical staff (medical and/or drug safety responsible for the study).

4.3 Essential Documents

The following essential documents must exist before the study is initiated at a site:

- Written agreement between Takeda or their representative and the Study Site Responsible.
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible.
- Subject Information Sheet and Informed Consent Form in Greek (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required).
- Written IEC / IRB approval / vote according to local regulations.
- Authority approval according to local regulations.

5 Ethics

This study is an observational study where the conduct of the study has no impact on the subject and on the way he/she will be treated and managed by their clinicians, except for collection of informed consent to use the subject's data.

5.1 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 any local regulations. Special attention will be paid to data protection in accordance with the EU directive on data protection (95/46/EC).

Takeda/the appointed CRO will ensure that the protocol, any amendments and the Subject Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

Takeda as the sponsor is responsible for meeting the ICH requirement for yearly updates to the

IECs/IRBs, if applicable.

5.2 Independent Ethics Committee/Institutional Review Board and Authorities IEC/IRB

According to applicable regulations, the appointed CRO or the Site Study Responsible will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Subject Information Sheet / Informed Consent Form and all other study-related documents, e.g. Questionnaires
- The appointed CRO or the Site Study Responsible will submit required documents to the IEC / IRB, such as:
- periodic updates on the progress of the study
- notification of the end-of-study
- a summary of the study results

Authorities: The appointed Contract Research Organisation (CRO) will submit all required documents to the Independent Ethics Committees of particiating investigational sites as well as to corresponding Financial Authorities. An updated list of submission and approval dates and a copy of all documents submitted will be kept.

5.3 Subject Information and Written Informed Consent

The Site Study Responsible must give the subject (and if applicable, or legal guardian) oral and written information about the study in a form that the subject (or legal guardian) can understand, and obtain the subject's (and if applicable, the legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and if applicable, legal guardian) must be left with ample time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment.

The subject must agree that sponsor personnel, their representatives, IEC/IRB and/or CA personnel (national or other) may require direct access to the subject's data/personal records which were collected, processed and stored in an anonymous form.

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g. other companies or authorities, that may be located in other countries with potentially different regulations for data.

The subject or legal guardian, if applicable, 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. The original, signed Informed Consent Forms must be kept on the Site.

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

6 Study Design and Plan

This study is a 'non-interventional study' as defined in: Directive 2001/20/EC and will follow the guidelines for GPP.

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice
- No additional diagnostic or monitoring procedures shall be applied to the subjects
- Epidemiological methods shall be used for the analysis of collected data
- Vedolizumab will be prescribed in accordance with the terms of the marketing authorisation(s)
- The prescription of Vedolizumab will be clearly separated from the decision to include the subject in the study

6.1 Study Schedule

Based on upcoming knowledge, Takeda might choose to terminate the study prematurely. In such case the Committee(s), study sites, IECs/IRBs and authorities will be informed promptly.

6.2 Discussion of Study Design

This is a prospective, observational, multi-center, cohort study, to be conducted in Greece, designed primarily to assess long-term clinical benefit in patients who are initiating Vedolizumab for UC or CD.

Physicians will prescribe Vedolizumab according to the local prescribing information in Greece, and there will be no restrictions on the use of commercially available medications. As an observational study, this study will not change the patient/physician relationship, nor influence the physician's drug prescribing or the therapeutic management of the patient.

Patients with UC or CD who are initiating Vedolizumab will be recruited continuously and screened to determine eligibility within the 2 years recruiting period.After eligible patients are enrolled, baseline data will be collected. Patients will be followed for two years. Completion of questionnaires by patients will be optional.

Study visits, procedures, and evaluations are summarized in Section 7 in detail.

6.3 Selection of Study Population

Adult patients with moderately to severely active ulcerative colitis or Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy, naïve to biologic treatments, will be enrolled in the study.

6.3.1 Inclusion Criteria

1. Male or female, aged 18 years or older Patients with moderately to severely active ulcerative colitis or Crohn's disease, naïve to biologic treatments, initiating treatment with Vedolizumab under normal clinical practice according to the approved SmPC in the European Union.

2. Informed consent to study participation and to data being collected and provided to Takeda Hellas.

6.3.2 Exclusion Criteria

1. Contraindications according to the SmPC.
2. Patients not willing to consent to study participation and to data being collected and provided to Takeda Hellas.
3. Current or planned participation in any interventional clinical trial.
4. Presence of mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
5. Treatment with any biologic therapies in the past (including Vedolizumab).

6.3.3 Number of Patients to be Enrolled

In total, approximately 200 adult patients will be enrolled in the study. 100 with moderately to severely active ulcerative colitis and 100 with Crohn's disease, naïve to biologic treatments. From each study site, sequential patients with Ulcerative Colitis or Crohn's disease will be enrolled; recruitment is repetitive in this study. Subjects should be included in the study only once. These numbers (per group) are expected according to the current epidemiology for both indications in Greece.

Data erroneously collected from subjects at baseline or/and for which written consent is not available, will not be included in or will be deleted from the database and they will be replaced.

6.4 Treatments

This is a non-interventional, observational study. Therefore, no investigational treatment exists. Patients with moderately to severely active IBD, unresponsive, inadequately responsive or intolerant to conventional treatment, naïve to biologic treatments, that are committed to receive Vedolizumab according to treating physician's best clinical judgement and the approved SmPC of the drug will be included in the study.

6.5 Treatment Discontinuation

Patients that discontinue treatment with Vedolizumab prior to the completion of two years of follow up after study entry will be permanently discontinued from this observational study. For patients that will discontinue Vedolizumab treatment, every effort should be made for discontinuation reason, IBD activity and QoL as well as information on new therapy to be collected as they become available and to be recorded in eCRF under the premature discontinuation visit. For cases where this information is not available at the time of discontinuation, data may be collected at the earliest as they become available to the investigator by phone interview. Data on possible new treatment after VDZ discontinuation might be collected and recorded in the eCRF within 12 months from the date of discontinuation (where data are available).

7 Conduct

Data collection overview:

	Baseline	Week 14	Week 30	Week 46(optional)	Week 54	Week 78	Week 102	Premature Treatment Discontinuation Visit
Demographics	X							
Informed Consent	X							
Inclusion & Exclusion Criteria	X							
Medical History	X							
Endoscopy	X[a]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	
Other Tests	X[c]	X[c]	X[c]	Xc	X[c]	X[c]	X[c]	
Previous/Concomitant Medications	X	X	X	X	X	X	X	
Partial Mayo Score	X	X	X	X	X	X	X	X
Harvey-Bradshaw Index	X	X	X	X	X	X	X	X
SIBDQ	X		X	X	X	X	X	X
TSQM-9	X	X	X	X	X	X	X	X
EQ-5D	X		X	X	X	X	X	X
Reason for discontinuation								X

[a] Endoscopic data at baseline will be collected if endoscopy has been performed within 3 months of Vedolizumab treatment initiation

[b] Endoscopic data will be collected during study observational period, if and when endoscopy has been performed as per routine clinical practice

[c] Other tests that used by the HCP for supporting evaluation of disease activity (e.g. faecal calprotectin and CRP, or CT scan)

Data will be collected at follow-up visits closest to the aforementioned time points.

7.1 Data to be collected at Baseline

7.1.1 Demographics

The physician will determine the patient demographic information at the Baseline visit and record it in the Baseline Case Report Form (CRF). The demographic information will include gender, date of birth, height, weight and ethnicity.

7.1.2 Patient History

The physician will determine the patient's history and current status at the Baseline visit and record it in the Baseline Case Report Forms (CRFs). The patient's status will also include smoking status (never, former, current, unknown, including number of years smoked, number of cigarettes smoked per day), comorbidities and whether or not these conditions are currently treated.

UC/CD history will be captured, including:

- Dates and age of onset / diagnosis

Disease location(s) in GI tract and mucosal status (descriptive analysis: Normal or inactive disease, Mild disease (erythema, decreased vascular pattern, mild friability); Moderate disease (marked erythema, absent vascular pattern, friability, and erosions); Severe disease (spontaneous bleeding, ulcerations)

- Presence of extraintestinal manifestations
- Surgical history / disease management
- Recent endoscopy (with or without any biopsies) if performed within 3 months of initiating treatment with Vedolizumab
- Past medications used to treat IBD will be recorded in the CRF

7.1.3 Patient Current Status

IBD activity will be assessed by means of:

- Partial Mayo Score for patients with UC
- Harvey-Bradshaw Index (HBI) for patients with CD

HRQoL will be assessed by means of:

- Short Inflammatory Diseases Questionnaire (SIBDQ)
- EQ-5D

Patient satisfaction with treatment medication will be assessed by means of the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9)

Concomitant medications used to treat IBD will be recorded in CRF.

7.2 Data to be collected from patient's next visits

Treatment and/or study discontinuation: date, reason.

Vedolizumab infusions, including dose and dates

Concomitant drugs

Endoscopy (colonoscopy, sigmoidoscopy) +/- Biopsies performed as per clinical practice

IBD activity by means of:

- Partial Mayo Score for patients with UC
- Harvey-Bradshaw Index (HBI) for patients with CD
- Assessing Clinical/PROs (Rectal bleeding and diarrhea/altered bowel habit for UC. Pain and diarrhea/altered bowel habit for CD) measured by the clinicians according to clinical practice, at baseline, and at 14, 30, 46(optional), 54, 78 and 102 weeks of treatment taking in consideration the average of the last 3 days by means of partial Mayo score for UC patients and Harvey-Bradshaw Index for CD patients
- Assessing CRP and faecal calprotectin as adjunctive measure of inflammation for monitoring in UC and CD used as exploratory parameter by the clinicians when applicable.

HRQoL by means of:

- Short Inflammatory Diseases Questionnaire (SIBDQ)
- EQ-5D

Patient satisfaction with treatment medication by means of:

- the 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9)

7.3 Patient Questionnaires

The following patient reported outcome (PRO) questionnaires will be used during the study visits. Completion of the questionnaires will be optional.

The Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The IBDQ is a validated and reliable tool to measure health-related quality of life in adult patients with inflammatory bowel disease, ulcerative colitis, or Crohn's disease. The questionnaire consists of 32 questions scored in four domains: bowel symptoms, emotional health, systemic systems, social function. The IBDQ is a respected quality of life questionnaire used extensively in academic research and clinical trials (Pallis 2001). The Short Inflammatory Bowel Disease Questionnaire (SIBDQ) is a simple, validated, 10 item questionnaire, taken from the original 32 question IBDQ that can be easily scored and interpreted by clinicians (Irvine 1996).

The EQ-5D

The EQ-5D is one of the most commonly used generic health-related quality of life questionnaire in adults. It consists of five questions that assess function in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with five level classification system (no problems, slight problems, moderate problems, severe problems and extreme problems). The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state.

Moreover, the EQ-5D includes a Visual Analogue Scale (VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health) (Euroqol Group 1990; Brooks 1996). The EQ-5D is self-administered and takes three to five minutes to complete, while it has been translated and validated for the Greek population by Yfantopoulos J (Yfantopoulos J., 1998).

The 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The TSQM Version 1.4 is a 14-item psychometrically robust and validated instrument consisting of four scales (Atkinson 2004). The 14 questions were selected from an original set of 55 questions obtained from literature review and focus groups. The four scales of the TSQM include the effectiveness scale (questions 1 to 3), the undesirable effects scale (questions 4 to 8), the convenience scale (questions 9 to 11) and the global satisfaction scale (questions 12 to 14). In naturalistic studies, administering the TSQM with the undesirable effects domain could provoke the physician to assess the presence or absence of adverse events in a way that is clinically atypical, carrying the potential to interfere with routine medical care. As a result, an abbreviated 9-item TSQM (TSQM-9), derived from the TSQM Version 1.4 but without the five items of the undesirable effects domain was created.

8 Safety Reporting

8.1 Definitions

Adverse Event

An adverse event (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 adverse event can therefore be any unfavourable and unintended sign (e.g. 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 considered related to the medicinal product.

Adverse Drug Reaction

An adverse 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.

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 authorisation, also known as "off-label" use

• Use of a 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, labelling, or design of the product

8.2 Classifications

Seriousness

A serious ADR or AE (SADR/SAE) is any ADR or AE which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Life-threatening in this context refers to a reaction/event in which the subject was at risk of death at the time of the reaction/event. It does not refer to a reaction/event that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of dependency or abuse.

Any suspected transmission of an infectious agent via a medicinal product is considered a serious adverse reaction.

Causality

- Related (Yes): An AE that follows a reasonable temporal sequence from administration of the medication, vaccine or device (including the course after withdrawal of the medication), or for which a causal relationship is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the medication, vaccine or device, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible
- Not related (No): An AE that does not follow a reasonable temporal sequence from administration of the medication, vaccine or device and/or that can reasonably be explained

by other factors, such as underlying disease, complications, concomitant drugs and concurrent treatments. The investigator must make an assessment of causality using the above definition. Causality cannot be assumed in the absence of the investigator's assessment

Outcome

- Fatal: The subject died due to the event. If the subject died due to other circumstances than the event the outcome should be stated as 'Not recovered' or 'Recovering'
- Recovered/Resolved: The subject has fully recovered from the event or the condition has returned to the level observed at baseline
- Recovering/Resolving: The event is improving but the subject is still not fully recovered
- Not Recovered/Not Resolved: The event is ongoing at the time of reporting and the subject has still not recovered
- Recovered with Sequelae/Resolved with Sequelae: As a result of the event, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf or paralysed)
- Unknown: If Outcome is not known or not reported

8.3 Collection and Recording of Adverse Events, Special Situation Reports and Product Quality Issues

• All Serious AEs (including deaths), non-serious related AEs, SSRs including product quality issues that an investigator becomes aware of should be collected and notified to the Sponsor.

• Collection and recording of SAEs, non-serious related AEs, SSRs including product quality issues will commence once the study participant has provided informed consent. Each individual report concerning a serious adverse event, a non-serious related adverse event, a special situation or a product quality issue will be transmitted to the Sponsor within 1 calendar day from the awareness day. The awareness day will be stated in the report. The reports will be transmitted by email to the electronic address DSO-GR@takeda.com.

Follow-up information

After notification of the initial report, 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. The obtained follow-up information will be transmitted to the Sponsor within 1 calendar day from the day of awareness. The follow-up information will be transmitted by email to the electronic address DSO-GR@takeda.com.

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

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

9 Data Quality Control and Assurance

9.1 Quality Control

The study will be monitored according to the details specified in the Study Plan. The Investigator will be contacted by the study monitor on a regular basis. The monitor will have the responsibility of reviewing the ongoing study with the Investigator to verify adherence to the protocol and to deal with any issues/deviations. CRFs will be checked for completeness and consistency with the source data and special attention should be dedicated to the following items: patient enrolment, obtaining of the signed informed consent. At all times, the confidentiality of study related documents will be maintained. The Investigator agrees to allow access to all study materials needed for the proper review of study conduct. The Investigator agrees to assist the monitor in resolving any issue that may be detected during the monitoring visit or data cleaning process. The Sponsor or CRO will perform all monitoring activities.

9.2 Audit from Quality Assurance Function

The Quality Assurance (QA) function 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.

9.3 Inspection by IRB/IEC or Competent Authority

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

9.4 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 finalised. The data management provider should approve all data formats before the data collection tools are made available to the sites. If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database.

If a subject 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 subject is included in the study in spite of being treated off-label (not according to the SMPC), data is kept in the database and analysed separately and as part of the overall analyses as described in the Statistical Analysis Plan. The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), concomitant medication (WHO-Drug) and adverse events/reactions (MedDRA) must be followed.

9.4.1 Data Collection Tools and Flow

The Study Site will receive data collection tools (CRFs, access to electronic data capture etc) from Takeda. 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 Study Site Responsible must sign off the complete data set for each subject, confirming the collected data.

Data collected during the study will be recorded in the CRF, which is confidential. Data reported on the CRF have to be consistent with the source documents. The Investigator must ensure the accuracy, the completeness and the consistency of the data entered in the CRF. On the CRF, patients will be identified by the patient number, assigned at the Study Visit. During the conduct of the clinical part of the study, the CRF must be available and up-to-date, so that it always reflects the latest observations on the respective patient. The Investigator will be responsible for entering study data into the CRF in accordance to the CRF user guidelines.

10 Statistical Methods and Determination of Sample Size

Statistical analysis will be performed according to the Statistical Analysis Plan that will be formed upon completion of data collection. The analysis will be descriptive; all variables will be listed and illustrated by frequency or parameter tables. Continuous variables will be expressed as median, as percent where appropriate, as means (SD), and prevalence rates as crude and standardized gender-adjusted, and age-adjusted values.

10.1 Statistical Analysis

This study is observational and epidemiological methods will be employed for data analysis and therefore no inferential statistics will be considered with respect to primary and secondary endpoints. A detailed statistical analysis plan will be developed prior to the data base lock.

Summary statistics for continuous variables will include mean, standard deviation, median and range. For categorical variables the number and percentage of subjects in each category will be presented.

Analysis of primary outcome

The percentage of patients among biologic naïve UC patients and among biologic naïve CD patients that discontinue treatment with Vedolizumab within the two years follow up period will be reported, followed by the corresponding 95% confidence interval.

Analysis of secondary outcomes

- The reasons for drug discontinuation in the two populations will be listed in a frequency distribution table.
- The percentage of UC and CD patients with dose intensification (from Q8W to Q6W or to Q4W) in the two years follow up period will be provided
- The percentage of UC and CD patients under steroids at Baseline, week 6 and week 14

(Steroid sparing effect) will be provided

- Summary statistics of partial Mayo score for UC patients and Harvey-Bradshaw Index for CD at each visit assessed as well as the mean change from baseline will be provided for each population
- Summary statistics of SIBDQ score and EQ-5D-5L score at each visit assessed as well as the mean change from baseline will be provided for both UC and CD patients
- Table of absolute and relative frequencies for each item of EQ-5D-5L score for each visit assessed will be provided for each population for both UC and CD patients. Summary statistics of each domain of TSQM-9 score at each visit assessed as well as the mean change from baseline will be provided for both UC and CD patients
- Summary statistics of Clinical/PROs (Rectal bleeding and diarrhea/altered bowel habit for UC, Pain and diarrhea/altered bowel habit for CD) at each visit assessed as well as the mean change from baseline will be provided, taking in consideration the average of the last 3 days by means of partial Mayo score for UC patients and Harvey-Bradshaw Index for CD patients
- Summary statistics of endoscopic disease activity assessed at baseline and at week 52 using the simple endoscopic score (SES) in CD and MAYO score in UC. The rate of Endoscopic Mucosal Healing for UC and CD patients. In clinical practice, we consider endoscopic Mucosal Healing (MH) the absence of friability (for UC), ulcerations and erosions (UC and CD). The mean change from baseline will be provided for both UC and CD patients, also.
- Summary statistics of biological parameters (CRP and faecal calprotectin) at each visit assessed as well as the mean change from baseline will be provided for both UC and CD patients

Analysis of safety outcomes

Treatment emergent adverse events (TEAEs) will be presented by preferred terms and primary system organ class separately for both CD and UC patients. Separate summaries will be employed for serious TEAEs, for deaths, for TEAEs causing treatment discontinuations and for drug related TEAEs.

All adverse events will be coded according to MedDRA.

10.2 Interim Analyses

An interim analysis will be performed when 50% of the UC and 50% of the CD enrolled patients will have completed approximately one year of follow-up from FPI date, depending in the recruitment rate per group.

10.3 Determination of Sample Size

Assuming that the expected discontinuation rate is no more than 10% among IBD patients, then 196 patients are need to estimate the corresponding percentage within 4.2% of the true value with 95% confidence (based on the normal approximation). Therefore, 200 patients should be enrolled in the study.

11 Reports

A Non-Interventional Study Report based on the results obtained will be prepared. The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalised.

12 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.

13 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the essential documents (Section 3.5), the protocol, any amendments, the list of participating subjects, the written informed consents, the CRFs and the progress reports in the Study Site File. After final database lock the Site Responsible must as a minimum store the list of participating subjects and the signed Informed Consent Forms on site for 25 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

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