CLINICAL STUDY PROTOCOL

NCT Number: NCT04567628

Study Title: The Relationship Between Vedolizumab Therapeutic Drug Monitoring, Biomarkers of Inflammation and Clinical Outcomes in the Real World Setting (VEDO TDM RWE)

Study Number: Vedolizumab-5062

Protocol Version and Date:

Version 1.0: 18-August-2020

Non-Interventional Study Protocol

Title: The Relationship Between Vedolizumab Therapeutic Drug Monitoring, Biomarkers of Inflammation and Clinical Outcomes in the Real World Setting (VEDO TDM RWE)

Short title: VEDO TDM RWE

Study ID: Vedolizumab-5062

Sponsor: Takeda Canada Inc.
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Study phase: Medical Affairs, Post-Approval Company Sponsored (Observational)

Date of draft version 1.0 of protocol: 22-July-2020

1 Administrative information

1.1 Contacts

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

[Delete columns that are not needed and specify telephone and fax contact numbers for the appropriate department, not an individual person, in completed protocol.]

Issue	Takeda Canada Contact
Serious adverse event and pregnancy reporting	PPD PPD *Medical Information and Pharmacovigilance,* *Takeda Canada Inc.,* ***Phone:*** PPD *Email:* PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	*Takeda Medical Information – Canada* ***Phone:*** *1 866 295 4636* *Email: canmedinfo@takeda.com*
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD *, PhD* PPD *, Medical,* *Takeda Canada Inc.,* ***Phone:*** PPD *Email:* PPD

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 Harmonisation 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 *[If the protocol is signed off electronically, this page should be kept (to identify why the electronic signatories are signing)]*

DocuSigned by: PPD AB6631DE2EF1417...

8/17/2020

PPD , PhD Date Date

PPD , Gastroenterology

Takeda Canada Inc.

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8/18/2020

PPD Date Date

PPD , Medical Information and Pharmacovigilance,

Takeda Canada Inc.

<Others as identified>

INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

Signature of Investigator Date

<Investigator Name (print or type)>

<Investigator's Title>

<Location of Facility (City, State/Provence)>

<Location of Facility (Country)>

STUDY SUMMARY

Name of Sponsor(s): Takeda Canada Inc.	**Compound/Product:** Vedolizumab (ENTYVIO®)
Title of Protocol: The Relationship Between Vedolizumab Therapeutic Drug Monitoring, Biomarkers of Inflammation and Clinical Outcomes in the Real-World Setting (VEDO TDM RWE)	
Study Number: Vedolizumab-5062	**Phase:** N/A

Study Design:

The proposed study is a retrospective, longitudinal analysis of data collected in a subset of Takeda Canada PSP, specifically those patients on vedolizumab, some of which received biomarker testing and Therapeutic Drug Monitoring (TDM) at pre-specified intervals during their treatment.

Primary Objectives:

To determine if a relationship exists between week 6 vedolizumab TDM and week 30 Faecal calprotectin (FCP).

Secondary Objectives:

- To assess the longitudinal relationship between TDM at week 6, week 14, week 22, and week 30 with baseline characteristics (albumin, CRP, FCP, line of therapy, disease subtype, disease duration, concomitant immunomodulator use).
- To assess the relationship between week 6 TDM and week 30 CRP, disease scores, dose escalation, and treatment persistence.
- To assess the relationship between week 14 TDM and week 30 FCP.
- To assess the relationship between week 14 TDM and week 30 CRP, disease scores, dose escalation, and/or treatment persistence.
- To assess the longitudinal relationship between TDM at week 6, week 14, week 22 and week 30 and week 30 FCP, CRP, disease scores, dose escalation and treatment persistence.
- To assess vedolizumab drug concentration by quartile analysis, at week 6, 14, 22 and 30.
- To assess relationships between therapy discontinuation and baseline characteristics (albumin, CRP, FCP, line of therapy, disease subtype, disease duration, concomitant immunomodulator use).
- To assess relationships between dose escalation and baseline characteristics (albumin, CRP, FCP, line of therapy, disease subtype, disease duration, concomitant immunomodulator use).
- To assess the longitudinal relationships of FCP, CRP, disease scores, therapy discontinuation, dose escalation with baseline characteristics (albumin, disease subtype, disease duration, line of therapy).
- To assess the relationship between TDM (at week 6 and longitudinally) and therapy discontinuation.
- To assess the relationship between TDM (at week 6 and longitudinally) and dose escalation.
- To assess the relationship between any primary or secondary endpoint in patient subgroups, including by disease subtype, disease severity, disease localization/extension (if provided), line of therapy, line of therapy by disease subtype, and by baseline disease characteristics (albumin, CRP, FCP, disease duration, concomitant immunomodulator use).

Exploratory Objectives:

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Subject Population: Subjects aged ≥18 years, with Inflammatory Bowel Disease (IBD) (Ulcerative colitis (UC) or Crohn's Disease (CD)).

Number of Subjects:	**Study Sites:**
TDM cohort: ~500 Historical cohort: ~5,000	N/A. Data is generated from Takeda Canada Patient Support Program
Dose Level(s):	**Route of Administration:**
Vedolizumab, 300 mg at (induction) week 0, week 2, week 6 and (maintenance) every 8 weeks thereafter as per product Health Canada Product Monograph, or every 4 or 6 weeks thereafter if requested by treating physician as per local practice.	Intravenous (IV) infusion over 30 minutes.

Duration of Study:

Data extract is from the Takeda Patient Support Program from 2015 to 2020. Data analysis and reporting is from August 2020 to March 2021.

Criteria for Inclusion:

Subjects who are:

- Adult patients (≥18 years) diagnosed with IBD (UC or CD)
- Enrolled in the Takeda Canada PSP
- Received or receiving vedolizumab between the years 2015 and 2020
- Provided consent for secondary use of their data

Criteria for Exclusion:

No exclusion criteria were applied.

Criteria for Evaluation and Analyses:

TDM cohort:

The available data include (but are not limited to):

- Baseline characteristics: age, sex, disease type (CD/UC), disease duration, prior immunomodulator therapy, prior biologic therapy, CRP, FCP, albumin and disease scores
- Vedolizumab treatment: Start date, end date, dose, frequency, reason for discontinuation
- Biochemical markers of inflammation: FCP, CRP at week 0, week 6, week 14, week 22, and week 30
- Vedolizumab therapeutic drug monitoring (TDM) at week 6, week 14, week 22 and week 30
- Disease scores (CD:HBI, UC:partial Mayo) at baseline (week 0) and week 6, week 14, week 22 and week 30

CCI [redacted]

Statistical Considerations:

Receiver-operating characteristic (ROC) curve analysis will be used to establish the best cut-off for vedolizumab TDM at week 6 and its corresponding performance for the prediction of Faecal calprotectin (FCP) at week 30. Kaplan-Meier survival curves and the log-rank test will be used to obtain treatment persistence curves. A two-sided p-value of <0.05 will be considered statistically significant.

Sample Size Justification: The retrospective data extraction will include up to 5500 patients (~550 in the TDM cohort and ~5000 in the historical control) with IBD. This study size is based on all patients within the Takeda Canada PSP Group that received vedolizumab between the years 2015 and 2020 and provided consent for secondary data usage.

Table of Contents

List of Abbreviations and Definition of Terms

AE:	Adverse Event
AI:	Artificial Intelligence
ADR:	Adverse Drug Reaction
AUROC:	Area under the Tececiver-operating characteristic curve
CD:	Crohn's Disease
CI:	Confidence Interval
CRP:	C-Reactive Protein
CRO:	Contract Research Organisation
EC:	Ethics Committee
FCP:	Faecal Calprotectin
FTP:	File Transfer Protocol
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
HBI:	Harvey-Bradshaw Index
IBD:	Inflammatory Bowel Disease
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IQR:	Inter-Quartile Range
IRB:	Institutional Review Board
ISPE:	International Society of Pharmacoepidemiology
MAR:	Missing at random
MCAR:	Missing completely at random
MNAR:	Missing not at random
NLP:	Natural Language Processing
PSP:	Patient Support Program
ROC:	Receiver-operating characteristic
RWE:	Real-world evidence
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
TDM:	Therapeutic Drug Monitoring
UC:	Ulcerative Colitis

2 Introduction

Disease background and rationale:

Inflammatory Bowel Disease (IBD) refers to a group of serious, chronic conditions that affect more than five million people worldwide (1,2). Although it can affect people at any age it has a propensity to strike teenagers and those in their twenties with unpredictable symptoms and significant morbidity and mortality (3). Currently the cause for either Ulcerative Colitis or Crohn's Disease are poorly understood, however, significant advances have been made in the treatment of these diseases including the biologic vedolizumab (4-7).

Takeda is conducting a retrospective study which seeks to leverage the data generated as part of the Takeda Canada Patient Support Program to determine the real-world evidence (RWE) of vedolizumab, its relationship with Therapeutic Drug Monitoring (TDM), biomarkers of inflammation, and its effect on clinical outcomes in a real-world setting.

Study design:

The study is retrospective and longitudinal by design, conducted on data collected as part of the cross-Canada PSP group, and will include IBD patients receiving vedolizumab between the years 2015 and 2020.

A total of approximately 5,500 patients will be included. The main study cohort consists of ~500 patients who received TDM during their treatment ("TDM cohort"). The remaining ~5,000 patients received vedolizumab but did not receive TDM during the course of their treatment ("Historical cohort"). CCI [redacted]

The TDM cohort includes the following data points:

- Baseline characteristics: age, sex, disease type (CD/UC), disease duration, prior immunomodulator therapy, prior biologic therapy, CRP, FCP, albumin and disease scores
- Vedolizumab treatment: Start date, end date, dose, frequency, reason for discontinuation
- Biochemical markers of inflammation: FCP, CRP at w0, w6, w14, w22, and w30
- Vedolizumab therapeutic drug monitoring (TDM) at w6, w14, w22 and 30

- Disease scores (CD:HBI, UC:partial Mayo) at baseline and w6, w14, w22 and w30

The Historical cohort includes the following data points:

- Baseline characteristics: age, sex, disease type (CD/UC), disease duration
- Vedolizumab treatment: Start date, end date, dose, frequency, reason for discontinuation

3 Study Objective(s) and Endpoint(s)

3.1 Objective(s)

The goal of the study is to determine whether there is a relationship between TDM of patients on vedolizumab and their clinical outcomes to generate hypotheses for future testing.

3.1.1 Primary Objective

- Determine if a relationship exists between week 6 vedolizumab TDM and week 30 FCP. Subgroup analyses of the primary outcome will include by disease subtype (UC, CD), line of therapy (bionaive, failure on $\geq$ 1 previous biologic therapy), line of therapy by disease subtype, and by baseline disease characteristics (albumin, CRP, FCP, disease duration and concomitant immunomodulator use).

3.1.2 Secondary Objectives

- Assess the longitudinal relationship between TDM at week 6, week 14, week 22, and week 30 with baseline characteristics (albumin, CRP, FCP, line of therapy, disease subtype, disease duration, concomitant immunomodulator use).
- Assess the relationship between week 6 TDM and week 30 CRP, disease scores, dose escalation, and treatment persistence.
- Assess the relationship between week 14 TDM and week 30 FCP.
- Assess the relationship between week 14 TDM and week 30 CRP, disease scores, dose escalation, and/or treatment persistence.
- Assess the longitudinal relationship between TDM at week 6, week 14, week 22 and week 30 and week 30 FCP, CRP, disease scores, dose escalation and treatment persistence.
- Assess vedolizumab drug concentration by quartile analysis, at week 6, 14, 22 and 30.
- Assess relationships between therapy discontinuation and baseline characteristics (albumin, CRP, FCP, line of therapy, disease subtype, disease duration, concomitant immunomodulator use).

- Assess relationships between dose escalation and baseline characteristics (albumin, CRP, FCP, line of therapy, disease subtype, disease duration, concomitant immunomodulator use).
- Assess the longitudinal relationships of FCP, CRP, disease scores, therapy discontinuation, dose escalation with baseline characteristics (albumin, disease subtype, disease duration, line of therapy).
- Assess the relationship between TDM (at week 6 and longitudinally) and therapy discontinuation.
- Assess the relationship between TDM (at week 6 and longitudinally) and dose escalation.
- Assess the relationship between TDM (at week 6 and longitudinally) and treatment duration.
- To assess the relationship between any primary or secondary endpoint in patient subgroups, including by disease subtype, line of therapy, line of therapy by disease subtype, and by baseline disease characteristics (albumin, CRP, FCP, disease duration, concomitant immunomodulator use).

3.1.3 Exploratory Objective(s)

CCI [redacted]

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CCI [redacted]

CCI [redacted]

3.2 Endpoint(s)

3.2.1 Primary Endpoint

The primary endpoint for this study is the correlation between week 6 vedolizumab TDM and week 30 FCP. FCP is being used as a surrogate marker for disease severity, and by extension drug efficacy, with higher levels indicating poor drug efficacy, and low to non-detectable levels indicating increased drug efficacy.

3.2.2 Secondary Endpoints

Secondary endpoints for this study are CRP levels at week 30, disease scores (HBI and Partial Mayo), dose escalation, and treatment persistence, each of which are being used as surrogates for treatment efficacy. Similar to FCP, decreased levels of CRP, HBI and Partial Mayo disease scores, and less dose escalation will each be interpreted to indicate increased drug efficacy. Treatment persistence and longer treatment duration will each be interpreted to indicate drug efficacy.

3.2.3 Exploratory Endpoints

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[redacted]

4 Study Administrative Structure

Takeda Canada Inc. is the study sponsor. They have contracted Pentavere Research Group Inc. (hereafter referred to as Pentavere) to act as CRO and conduct all study activities related to the proposed secondary data analysis, including drafting of protocols, Statistical Analysis Plan (SAP), Data management plans, submission to IRB/IEC, analysis of data and reporting of study results. Pentavere will maintain records of generated study material, excluding patient informed consent, as these were collected by the PSP provider at the time of patient enrollemnt.

4.1 Sponsor Personnel

The Sponsor (Takeda Canada Inc.) will keep a record of all relevant sponsor personnel.

4.2 Contract Research Organisation (CRO)

Pentavere is a Healthcare Technology Research group, which provides CRO services along with proprietary AI and NLP data curation engine DARWEN™, which transforms structured and unstructured healthcare information into analysis-ready structured and curated datasets. Pentavere's clinical, research and data science teams will perform all study-related activities to execute the proposed retrospective, longitudinal analysis of data collected in a subset of Takeda's Canada Patient Support Program. Pentavere will keep a record of all involved Pentavere personnel.

4.3 Steering Committee

Three IBD Thought Leaders, external to Takeda Canada Inc and Pentavere, and practicing gastroenterologists from across Canada, will form the study's Steering Committee and will help guide the research project, ensuring the project outputs are clinically relevant, meaningful and credible.

5 Ethics

This study is a retrospective observational study where the existence of the study has no impact on the subject except for collection of informed consent to use of 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 (8-11). Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data, in accordance with local applicable privacy and confidentiality requirements.

The appointed CRO will ensure that the protocol, any amendments are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

The appointed CRO 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 will:

- notify or obtain approval from the relevant IEC/IRB of the protocol and any amendments

The appointed CRO 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

The appointed CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB. Copies of the documents will be distributed upon request.

5.3 Subject Information and Written Informed Consent

The proposed study is a retrospective, secondary data analysis. Takeda Canada has ensured that the patients in this study have explicitly agreed to any secondary use of their data by following the below guidelines:

The Site Study Responsible must give the subject (and if applicable, parent or legal guardian) oral and written information about the study in a form that the subject (and if applicable, the parent or legal guardian) can understand, and obtain the subject's (and if applicable, the subject's assent and the parent's or legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and if applicable, parent or 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 or IEC/IRB or Competent Authority 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 and parent 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 (9,11).

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 was prescribed in accordance with the terms of the marketing authorisation(s)
- The prescription of vedolizumab is clearly separated from the decision to include the subject in the study

The proposed study is a retrospective, longitudinal analysis of data collected in a subset of Takeda Canada PSP, specifically those patients on vedolizumab, some of which received biomarker testing and TDM at pre-specified intervals during their treatment. This activity aims to investigate whether there are relationships between the proposed variables and clinical outcomes, and whether there is a benefit of early therapeutic drug monitoring for patients receiving vedolizumab.

6.1 Study Schedule

Start of Historical Cohort	May 2015
Start of TDM Cohort	March 2018
Planned Start of Analysis:	August 2020
Planned completion of the Study Report:	November 2020
Planned End of Study:	November 2020

The Start of Study is defined as defined as the date that IRB/IEC was obtained. The End of study is defined as first study publication submitted.

The Sponsor will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB, as locally required.

The Sponsor will ensure that results are posted on "clinicaltrials.gov" and as required by local authorities.

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

6.2 Discussion of Study Design

The proposed study is a retrospective, longitudinal analysis of data collected in a subset of Takeda Canada PSP. A total of approximately 5,500 patients will be included. The main study cohort consists of 500 patients which received TDM during their treatment ("TDM cohort"). The remaining ~5,000 patients received vedolizumab but did not receive TDM during the course of their treatment ("Historical cohort"). CCI [redacted].

In addition, as the TDM and biomarker data comes from only 500 patients, the cohort may not accurately represent the Canadian population, and may be subject to issues in reproducibility. Moreover, treatment is not reflective of the entire care pathway as information may not be linked between healthcare providers. As the data is coming from the Takeda Canada Patient Support Group database, assumptions are based on the PSP's team and are potentially imprecise.

Results from the currently proposed comparison of dose frequency escalations and treatment persistence between cohorts should be interpreted with caution as this is only a proxy of disease severity. Furthermore, bias may exist due to data collection occurring for both cohorts occurred during different periods of time, and thus disease management may have differed. Additionally, there may be selection bias as patients in the TDM cohort agreed to extensive disease monitoring, whereas patients in the Historical cohort were not offered a similar option. Lastly, no causal conclusions will be drawn from the proposed analyses, only correlations will be investigated.

6.3 Selection of Study Population

This is a retrospective longitudinal study being conducted on data collected as part of a cross-Canada PSP group, and will include IBD patients receiving vedolizumab between years 2015 and 2020.

6.3.1 Inclusion Criteria

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

1. The subject or, when applicable, the subject's legally acceptable representative signed and dated a written, informed consent form, which specified secondary use of their data, and any required privacy authorization as part of their enrollment in Takeda Canada's PSP.
2. Adult patients (≥18 years) diagnosed with IBD (UC or CD)
3. Received or receiving vedolizumab between the years 2015 and 2020

6.3.2 Exclusion Criteria

No exclusion criteria were applied.

Subjects should be included in the study only once.

Data erroneously collected from subjects for which written consent is not available, will not be included in or will be deleted from the database.

6.4 Treatments

Non-interventional/observational – no treatments/pharmacotherapy are instructed by the study protocol.

6.5 Criteria for Premature Termination or Suspension of Study

The study will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- If the Sponsor and/or CRO is found in significant violation of GCP/GPP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.5.1 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

6.6 Study Plan

Data collection overview:

Variable	Week 0		Week 6		Week 14		Week 22		Week 30	
Cohort:	**TDM**	**HIST**	**TDM**	**HIST**	**TDM**	**HIST**	**TDM**	**HIST**	**TDM**	**HIST**
Age	x	x								
Sex	x	x								
Disease type (CD/UC) and duration	x	x								
Prior immunomodulator, biologic therapy	x	x								
Vedolizumab start and end dates	x	x								
Vedolizumab dose and frequency	x	x								
Reasons for vedolizumab discontinuation	x	x								
Albumin	x									
CRP	x		x		x		x		x	
FCP	x		x		x		x		x	
TDM			x		x		x		x	
HBI/Partial Mayo	x		x		x		x		x	

HIST, Historical cohort.

The following data has been collected as part of the Takeda Canada PSP and will be analysed for this study:

TDM cohort:

Approximately 500 patients from the Takeda Canada PSP patients receiving vedolizumab with biomarker and TDM data will be analysed.

The available data include (but are not limited to):

- Baseline characteristics: age, sex, disease type (CD/UC), disease duration, prior immunomodulator therapy, prior biologic therapy, CRP, FCP, albumin and disease scores
- Vedolizumab treatment: Start date, end date, dose, frequency, reason for discontinuation
- Biochemical markers of inflammation: FCP, CRP at week 0, week 6, week 14, week 22, and week 30
- Vedolizumab therapeutic drug monitoring (TDM) at week 6, week 14, week 22 and week 30
- Disease scores (CD:HBI, UC:partial Mayo) at baseline (week 0) and week 6, week 14, week 22 and week 30

Historical cohort:

Approximately 5,000 patients from the Takeda Canada Patient Support Program patients who received/are receiving vedolizumab but did not undergo biomarker or TDM monitoring will be analysed.

The available data include (but may not be limited to):

- Baseline characteristics: age, sex, disease type (CD/UC), disease duration
- Vedolizumab treatment: Start date, end date, dose, frequency, reason for discontinuation

7 Safety Reporting

7.1 Definitions

7.1.1 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 AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

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

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

7.1.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

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

of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

7.1.3 Adverse Drug Reactions

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

7.1.4 Product Quality Issues

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

7.1.5 Special Situation Reports

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
- Accidental exposure
- Use outside the terms of the marketing authorization, also known as “off-label”
- Use of falsified medicinal product
- Unintended benefit

A SSR should be reported even if there is no associated AE.

7.2 Collection and notifying of Adverse Events, Special Situation Reports and Product Quality Issues to Takeda Pharmacovigilance

- SAEs, AEs, ADRs, SSRs and PQIs in the healthcare record or other applicable source data that are part of the study objectives or endpoints

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

  Events/Issues which are not part of the study objectives and endpoints will not be abstracted or collected from healthcare records or other applicable source records.

8 Data Quality Control and Assurance

8.1 Quality Control

The proposed study is a secondary data analysis. No Manual Data Monitoring or source data verification will be performed. Informed consent has already been obtained when patients enrolled into the PSP.

Pentavere will comply with Takeda's procedures regarding content, archiving and records management of process documents.

Pentavere shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

8.2 Audit from Quality Assurance Unit

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

8.3 Inspection by IRB/IEC or Competent Authority

Representatives from IRB/IEC or Competent Authority may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact Global Research and must make the records available as requested. The Inspector must be reminded up front that consent to access to personal data has not been obtained from the participants in this study.

8.4 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.

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.

The subjects will be identified in the database only by their unique Takeda Canada Patient Support Program reference number.

8.4.1 Data Flow

Takeda Canada will extract the required data from their PSP Group and provide it to Pentavere. Following the extraction from the data source, anonymized data will be transferred electronically to Pentavere, and Pentavere's standard procedures will be used to handle and process the electronic transfer of these data. The anonymized data will be transferred and stored at Pentavere using a zero-knowledge cloud-based data store which maintains compliance with the strictest standards to ensure privacy and data protection. Access to the data will be restricted to only those members at Pentavere working on the study and who will have access.

Further data management procedures are as follows:

- Pentavere will produce a Quality Assurance Plan that is approved by Takeda and describes the quality checking to be performed on the data. Correction documentation will be maintained following Pentavere's standard procedures.
- System backups for data stored at Pentavere and records retention for the study data will be consistent with Pentavere's standard procedures.

It is assumed that safety reporting of data which are going to be analysed as part of this study have been appropriately performed and documented at the time this data was collected through primary data collection mechanism (PSP).

9 Statistical Methods and Determination of Sample Size

The data will be analysed by Pentavere statisticians and machine learning engineers. The database will be imported into a statistical analysis tool such as SAS (version 9.4), Stata (version 16), or R (version 3.6.3) for data analysis.

This section describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised SAP before starting analysis. All later deviations and / or alterations will be summarised in the Clinical Study Report.

9.1 Statistical Analysis Plan

This study is observational and epidemiological methods will be employed for data analyses. The following statistical analysis plan will be conducted on the TDM cohort only, unless inclusion of the historical cohort has been explicitly stated.

9.1.1 Primary outcome

The primary outcome of the study is Week 30 FCP, which will be defined as the level of FCP detected within patient's stool 30 weeks after the patient's first dose of vedolizumab. This will be measured in the TDM cohort only.

9.1.2 Secondary outcomes

FCP, CRP, HBI/Partial Mayo scores are for the TDM cohort only. The secondary outcomes of the study are:

- Week 30 CRP, which will be defined as the level of CRP detected within patient's blood 30 weeks after that patient's first dose of vedolizumab.
- Week 30 Disease score, which will be defined as the HBI (for CD patients) or Partial Mayo score (for UC patients) measured 30 weeks after the patient's first dose of vedolizumab.
- Dose escalation, which will be defined as a change from doses every 8 weeks to every 6 or 4 weeks.

- Treatment persistence, which will be defined whether the patient is still on the treatment at the end of the TDM study (week 30).
- Treatment duration, which will be defined as the length of time a patient remains on treatment.

9.1.3 Methods for handling missing data

Summary statistics for the interim and entire dataset will be calculated by Pentavere's Biostatistician to identify inconsistent and/or missing data patterns, outliers, and potential selection and information biases. For all numerical features the min, max, median, Q1, Q3 and number missing will be included. For all categorical features the count, % and number missing will be included.

The cause of missing data will be investigated, and Little's test will be used to examine if data is missing completely at random (MCAR). If data is missing completely at random (MCAR) and the percentage of missing data is less than 5% of all observations, complete case analysis will be carried out. If the data is missing at random (MAR) or missing not at random (MNAR), best-worst and worst-best case analyses will be carried out to account for the range of uncertainty due to missing data. The extent of missing data and the limitations will be discussed. No missing data imputation will be performed on patient baseline characteristics.

9.1.4 Data analysis

Data analysis can be split into two major sections:

Cohort characterization and comparisons

We will carry out descriptive statistics to characterize the TDM and Historical cohorts.

- Continuous data (depending on the data distribution) will be described as:
  - median and interquartile range (IQR)
  - mean and 95% confidence interval (CI)
- Discrete data will be described as:
  - frequencies and proportions

Comparisons of TDM and Historical cohort clinico-demographics will be carried out.

- Continuous variables (depending on the data distribution) will be described as:
  - Parametric test (such as ANOVA, t-test)
  - Non-parametric test (such as Kruskall-Wallis test or Wilcoxon rank-sum test)
- Discrete variables (depending on the expected value)
  - χ^2 test
  - Fisher's exact test

Outcome Analyses

The relationship between TDM at week 6 and FCP levels at week 30 will be studied using univariate logistic regression models. Multivariate analyses will be performed to control for confounding factors. Possible confounding factors which will be examined are age, sex, disease type (CD/UC), duration, prior immunomodulator/biologic therapy, vedolizumab start and end dates, vedolizumab dose, vedolizumab frequency, and albumin. Both Univariate and Multivariate logistic regression models will be perfoemed using the SAS GENMOD procedure, or similar package in another software.

For an initial investigation of relationships described in the primary and secondary objectives, correlations will be explored using the following (as appropriate):

- Pearson correlation coefficient
- Spearman's rank test

For the described subgroup analyses, the following tests will be used to compare data within subgroups:

- Continuous variables (depending on the data distribution):
  - Parametric tests (such as ANOVA, t-test)
  - Non-parametric tests (such as Kruskal-Wallis test or Wilcoxon rank-sum test)
- Discrete variables (depending on the expected value):
  - χ^2 test

- Fisher's exact test

Next, to further explore the relationships between TDM intervals and outcomes described in the primary and secondary objectives, the vedolizumab TDM cut-off level that predicts the outcomes will be determined using:

- Receiver-operating characteristic (ROC) curve analysis; the following will be reported:
  - Sensitivity
  - Specificity
  - Area under the curve (AUROC)
  - 95% CI
  - We will also use the SAS procedure GLIMMROC (or similar package in another software) to explore estimating the AUROC for repeated measures analyses with TDM as time-dependent covariate.
- Kaplan Meier survival analysis and Log-Rank test using the SAS procedure PHREG (or similar package in another software) will be done to obtain treatment persistence curves; the following will be reported:
  - Hazard ratios
  - 95% CIs
  - We will also use PHREG (or similar package in another software) to explore survival analyses with TDM as a time-dependent covariate.
- Univariate and multivariate analysis by logistic regression, using the determined cut-off levels, will be carried out using either the SAS procedure GENMOD or GLIMMIX (or similar package in another software). From this analysis, the following will be reported:
  - Odds ratios
  - 95% CIs
- A two-sided p value of <0.05 will be considered statistically significant.
- Benjamini & Hochberg procedure will be applied to correct for multiple testing.

We may leverage the concept of unsupervised clustering of data to find any new patterns which have not yet been explored and are not very obvious in the data set. To do this we will perform:

- Dimensionality reduction (such a principal component analysis) to get a list of linearly uncorrelated features
- Perform clustering (exploring various algorithms) on these features

The entire act of monitoring patients during treatment, instead of any one variable, may actually be related to outcome. To investigate this potential phenomenon, we will first:

- Compare dose frequency escalations (i.e. switching from 8-weeks to 4- or 6- week frequencies) and treatment persistence between cohorts as a proxy-outcome for worsening disease.
- Proportions of dose frequency escalations or treatment persistence (yes/no) will be compared between the TDM and Historical cohort using χ^2 test
- Perform Kaplan Meier survival analysis and Log-Rank test as described above on both cohorts separately to obtain treatment persistence curves and dose escalation curves (one for time from treatment initiation to dose escalation, another for time from dose escalation to treatment discontinuation). For each cohort, subgroup analyses will be performed using clinico-demographic variables such as:
  - Disease subtype (UC vs CD)
  - Line of therapy (Bionaive, 2nd line, 3rd line, 3+ lines)
  - Disease subtype and line of therapy
  - Hazard ratios and 95% CIs will be reported for all analyses and compared between cohorts.

9.1.5 CCI

CCI [redacted]

9.2 Interim Analyses

An interim analysis will be performed to identify missing data and potential general sources of missing data, following the "Methods for handling missing data" section of the SAP. Cohort characterization will be carried out following the "Cohort characterization and comparisons" section of the SAP.

Any deviations from the planned analyses triggered by this interim analysis (e.g. controlling for major demographic imbalances between cohorts), the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised SAP before starting analysis. All later deviations and / or alterations will be summarised in the Clinical Study Report.

9.3 Determination of Sample Size

The retrospective data extraction will include up to 5,500 patients with IBD. This study size is based on all patients within the Takeda Canada PSP Group that received vedolizumab between years 2015 and 2020 and provided consent for secondary data usage.

10 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point.

11 Publication, Disclosure, and Clinical Trial Registration Policy

The Sponsor aims to have the results of this study published.

The Sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

Takeda may post the results of the study on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

12 Archiving of Study Documentation

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

- Written agreement between the Sponsor and the CRO
- The study protocol and any amendments
- Signed and dated protocol agreement and amendment agreements, if any
- Written IEC / IRB approval / vote according to local regulations
- The progress reports

After study completion the CRO must as a minimum store the study data for 25 years, in keeping with Sponsor and CROs SOPs.

No data may be disposed of without the written approval of the Sponsor. Written notification will be provided to the Sponsor prior to transferring any data to another party or moving them to another location.

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