CLINICAL STUDY PROTOCOL

NCT Number: NCT04873700

Study Title: Real-world Data of Moderate to Severe Inflammatory Bowel Disease (UC and CD) in Mexico: a Multicenter, Non-interventional Study to Evaluate Disease Control, Treatment Patterns, Burden of Disease and Patient Reported Outcomes

Study Number: IBD-5010

Protocol Version and Date:

Version 2.0: 22-September-2020

Non-Interventional Study Protocol

Short title: Non-interventional Study of Moderate to Severe Inflammatory Bowel Disease (UC and CD) in Mexico (RISE-MX)

Title: Real-world data of Moderate to Severe Inflammatory Bowel Disease (UC and CD) in Mexico: a multicenter, non-interventional study to evaluate disease control, treatment patterns, burden of disease and patient reported outcomes (RISE-MX)

Study ID: IBD-5010

Sponsor: Takeda México S.A. de C.V.
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Study phase: Medical Affairs, Non-registration Company Sponsored (Late Phase Observational)

Date of version of protocol: 21 May 2019

Administrative Amendment: 22 Sep 2020

1 Administrative information

1.1 Contacts

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

Issue	Mexico Contact
Serious Adverse Events, Pregnancy reporting, lack of efficacy	farmacovigilanciamexico@takeda.com

Medical Monitor (medical advice on protocol)	[redacted]
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	[redacted]

1.2 Amendments and updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
2.0	22Sep20	Abbreviations	SAE (Serious Adverse Event)	It is used the abbreviation in the protocol
2.0	22Sep20	1.1	~~informacionmedica@takeda.com (55) 5005 1340 01 8000 825332~~ farmacovigilanciamexico@takeda.com	Actualization of LOC PV information
2.0	22Sep20	1.1	[redacted]	Change in Medical Responsible
2.0	22Sep20	1.3	[redacted]	Change in Medical Responsible
2.0	22Sep20	1.3	~~Clinical Operations and Data Generation~~ [redacted] ~~Takeda Mexico~~ Medical Operations [redacted]	Role Change
2.0	22Sep20	4.2	~~Clinical Study~~ [redacted] Medical Operations	Role Change
2.0	22Sep20	4.2	[redacted] Clinical Operations [redacted]	Change in responsible

2.0	**22Sep20**	**4.2**	[redacted]		**Change in responsible**
2.0	**22Sep20**	**4.2**	[redacted]		**Change in responsible**
2.0	**22Sep20**	**6.1**	Planned Start of Study: Planned Patient In: Planned collection of first data point: Planned End of Study: Planned Final Database Lock: Planned completion of the Study Report:	~~Q1 FY19~~ Q3 FY20 ~~Q4 FY19~~ Q1 FY21 ~~Q4 FY19~~ Q1 FY21 ~~Q2 FY20~~ Q2 FY22 ~~Q3 FY20~~ Q1 FY22 ~~Q1 FY21~~ Q2 FY22	**Timeline Change**
2.0	**22Sep20**	**6.1**	The Start of Study is defined as date of last protocol signature and planned to occur on ~~June 2019~~ October 2020. The collection of first data point (first patient in) will start during ~~4th~~ 1st quarter ~~2019~~ 2021.		**Timeline change**

1.3 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;
- The International Conference on Harmonisation (ICH) 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] *Date*
[redacted]

[redacted] *Date*
Medical Operations [redacted]

[redacted] *Date*
Pharmacovigilance [redacted]
[redacted]

[redacted] *Date*
[redacted], Global Biometrics Biostatistics
Eurotrials Scientific Consultants, now a part of CTI Clinical Trial & Consulting Services

1.4 Summary

Short Title of Study

Non-interventional Study of Moderate to Severe Inflammatory Bowel Disease (UC and CD) in Mexico (RISE-MX).

Study sites

The study will be conducted in approximately 10-12 sites in Mexico.

Objectives

This study aims to understand the journey of UC and CD patients diagnosed with moderate to severe disease in Mexico and to describe their characteristics. In addition, it is essential to understand how patients are managed, the treatment patterns (particularly on the use of available biologic therapies) and obtain the patients' perspective on how the disease impacts on their quality of life (QoL) and work productivity.

Primary Objective:

- To evaluate the disease activity at Day 1 among UC and CD patients diagnosed with moderate to severe disease (i.e., to evaluate the proportion of patients with active Crohn's Disease (CD) defined as Harvey Bradshaw Index (HBI) score ≥ 8 or Crohn's Disease Activity Index (CDAI) ≥ 220, and with active Ulcerative Colitis (UC) defined as 9-point partial Mayo ≥5).

Secondary Objectives:

- To characterize socio-demographic and clinical features of UC and CD patients, overall and by disease activity at Day 1.
- To characterize treatment patterns for UC and CD in the 3 years prior to Day 1, including the use of biologic and conventional therapies and failure to these therapies (if any), overall and by disease activity at Day 1.
- For UC and CD, to compare patients with moderate to severe disease activity with patients with no or mild activity, regarding socio-demographic and clinical variables and treatment patterns at Day 1.
- To evaluate the QoL (36-item Short Form health Survey [SF-36] and Inflammatory Bowel Disease Questionnaire [IBDQ]) in UC and CD patients at Day 1, overall and by disease activity at Day 1.

- To evaluate the work productivity impairment (WPAI) experienced by UC and CD patients at Day 1, overall and by disease activity at Day 1.
- To describe the burden of disease in terms of healthcare resources utilization and costs (direct and indirect) related to the management of UC and CD in the 3 years prior to Day 1.

Methodology

This is a multicenter, non-interventional, cross-sectional study aiming primarily to evaluate the UC and CD activity. At each center, eligible subjects will be identified consecutively as they attend a scheduled clinical appointment with their physician (Day 1). Upon written consent, data regarding disease activity, treatment patterns, burden of disease and QoL will be collected from the patients' medical records and patients will be asked to complete the Patient Report Outcome (PRO) questionnaires. PRO questionnaires include QoL (SF-36 and IBDQ) and WPAI questionnaires. Besides the cross-sectional data collection, the study will have an additional retrospective data collection referring to the three years prior to Day 1, regarding the previous IBD treatments (drug, dose, treatment duration and drug changes), and use of other healthcare resources (surgeries, hospitalizations, medical appointments, imaging and laboratory testing) related with the management of UC and CD. Direct costs calculation will be performed by a micro-cost analysis (i.e. identifying and quantifying each single resource and multiplying it by the corresponding unit cost) and indirect cost by human capital method for absenteeism and presenteeism (i.e. the amount of salary paid to the employee proportional to the hours of absence/productivity impairment at work) based on WPAI data collected.

Number of subjects

It is expected to include 335 patients regardless of IBD (UC or CD) type.

Due to lack of information regarding the rate of UC and CD control in Mexico a rate of inadequate control of disease (i.e. the proportion of patients with moderately to severely active disease) of 50% will be assumed. Hence, a sample of 318 patients, regardless of IBD type (UC or CD), will allow estimates with 95% confidence interval (CI) and a margin of error (ME) less than 5.5%. The following formula was used:

$$n = \frac{1.96^2 \times p \times (1-p)}{ME^2}$$

Rate of uncontrolled disease (p) = 50%

ME = 0.055

To account for a non-evaluable rate of 5%, a total of 335 patients should be included in the study. No stratification sampling methods will be used.

Diagnosis/Disease/Condition and main criteria for inclusion

Subjects must meet all the following inclusion criteria:

- Male or female subjects.
- Subjects aged 18 years or older (at the time of diagnosis of moderate to severe UC or CD).
- Diagnosis of moderate to severe CD or UC established for at least 6 months prior to Day 1 appointment, based on clinical, endoscopic, or imaging criteria.
- The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.

Patients will be excluded if presenting at least one of the following:

- Indeterminate or not classified colitis.
- Current or previous participation in interventional clinical trials (within the previous 3 years).
- Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

Duration of data collection per subject

Cross-sectional at Day 1, with retrospective data collection over the previous 3 years.

Criteria for evaluation

Population descriptors

Date of birth, sex, professional status (employed, unemployed, retired, student, other), educational level, subject income, smoking habits, anthropometric information, date of diagnosis of CD or UC, date of diagnosis of moderate to severe CD or UC (if not the same as previous), steroid dependence or

refractoriness, family history of IBD, comorbidity(ies), disease presentation (location, behavior, extraintestinal manifestations).

Main outcome variables

Primary Endpoints:

- For CD: Proportion of patients with active disease (HBI ≥ 8 or CDAI ≥ 220 points) at Day 1.
- For UC: Proportion of patients with active disease (9-point partial Mayo ≥5) at Day 1.

Secondary Endpoints:

- Distribution of age, sex, professional status, educational level, subject income.
- Distribution of clinical variables (smoking habits, anthropometric information, duration and age at diagnosis, steroid dependence or refractoriness, family history, medical history and comorbidities, criteria used for diagnosis, calprotectin, extraintestinal manifestations and clinical presentation of IBD [CD - location, behavior, perianal disease, achievement of ileal disease; UC - extent of inflammation and severity]).
- Therapies for IBD (UC or CD) (aminosalicylates, steroids, immunomodulators, immunosupressors, biologics, antibiotics, probiotics and surgeries) and the length of these therapies during the previous 3 years.
- Proportion of biologic-experienced patients at Day 1.
- Proportion of patients who have not responded to previous lines of biologic therapies and reason.
- UC and CD treatment introduced at Day1 (if applicable).
- Socio-demographic, clinical and treatment-related variables in patients with moderate to severe activity of CD (HBI ≥ 8 or CDAI ≥ 220 points) versus patients with mild or no activity (HBI < 8 or CDAI < 220 points) at Day 1.
- Socio-demographic, clinical and treatment-related variables in patients with moderate to severe activity of UC (partial Mayo [pMayo] score ≥5) versus patients with mild or no activity (partial Mayo <5).
- Mean score of different components of SF-36.
- Mean total score of IBDQ and by domain (bowel symptoms, systemic symptoms, emotional function and social function).
- Mean total percentage of work impairment (WPAI) in hours, for patients with moderate to severe activity compared with patients with no or mild activity.

- Mean work time missed (WPAI), in hours, for patients with moderate to severe activity compared with patients with no or mild activity.
- Mean productivity impairment while working (WPAI), in hours, for patients with moderate to severe activity compared with patients with no or mild activity.
- Mean total activity impairment (WPAI).
- Proportion of patients who quit their job due to IBD (UC or CD) and have not been able to return to work.
- Distribution of surgeries, hospitalizations, medical appointments, imaging and laboratory testing in the 3 years prior to Day 1.
- Direct medical costs: distribution of healthcare resources consumption and unitary cost per resource.
- Indirect costs (only for active workers): mean number of workhours missed or with productivity reduced due disease and average salary/hour/person.

Statistical methods

All data will be summarized for total UC and CD patients and by IBD type (CD or UC). Descriptive statistics will be used for all variables including mean, median, standard deviation and range for numerical variables and absolute and relative frequencies for categorical variables. 95% CI will be computed whenever relevant.

For each UC or CD type, patients with disease activity will be compared with patients with mild or no activity regarding socio-demographic and clinical variables of interest. Chi-square/Fisher tests will be used to compare activity *vs* non-activity regarding qualitative variables and t-test/Mann-Whitney will be used for comparison of quantitative variables. All tests will be two-sided with a significance level of 5%.

Table of Contents

List of Abbreviations and Definition of Terms

5-ASA	5-aminosalicilic acid
ADR	Adverse Drug Reaction
AE	Adverse Event
BMI	Body Mass Index
CA	Competent Authority
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
CPI	Consumer price index
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EIM	Extraintestinal Manifestations
GPP	Good Pharmacoepidemiology Practices
HBI	Harvey Bradshaw Index
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ME	Margin of error
MedDRA	Medical Dictionary for Regulatory Activities

pMayo	partial Mayo score
PRO	Patient Reported Outcomes
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SF-36	36-item Short Form health Survey
SSR	Special Situation Report
TNF	Tumor Necrosis Factor
TWPI	Total Work Productivity Impairment
UC	Ulcerative Colitis
VAS	Visual Analog Scale
WPAI	Work Productivity and Activity Impairment questionnaire

2 Introduction

Inflammatory bowel diseases (IBD) comprise mainly Crohn's disease (CD) and ulcerative colitis (UC) (1). Signs and symptoms of active UC and CD may include abdominal pain, rectal bleeding, and fatigue. Treatment is not curative although it is generally effective in relieving symptoms (2). In some cases, surgery may be a solution but postoperative complications may occur, alongside with continued abnormal bowel function, and poor improvement in patient quality of life (QoL) (3).

IBD are multifactorial diseases associated with genetic, immunological and environmental factors, and with episodes of relapse and remission (4). UC and CD impact on patient QoL is particularly relevant as it affects mainly young individuals, with unpredictable disease flares and, sometimes, severe symptoms (5). Alongside with loss of patient QoL, symptoms may also impact work productivity thus increasing the economic burden of these diseases (4,6,7).

Globally, the prevalence of CD is reported to be from 0.9 - 322.0 per/10^5 inhabitants, while UC prevalence range is 2.42 - 505.0 per 10^5 inhabitants. On the other hand, the incidence reaches up to 29.3/10^5 inhabitants and 0.15 – 57.9/10^5 inhabitants for CD and UC, respectively (8). Furthermore, the incidence of CD and UC have been increasing in several world regions, namely in developing countries (9,10). In South American countries, incidence of CD and UC seem to be lower than in Europe and North American countries but some studies have reported an increase in recent years (4,11).

A Mexican consensus on the diagnosis and treatment of UC estimated a three-fold increase in the adjusted incidence rates in the last twenty years (12). A single center study in a referral hospital from Mexico City showed an increase of the UC incidence between 1987 and 2006, with a 2.6-fold increase when comparing the periods 1987-1996 and 1997-2006 (mean number of new cases per year: 28.8 vs. 76.1, respectively) (13). Another single center study in the Northwest Mexico also reported an increase of the rate of new UC patients, from 2.3/1000 admissions in 2004 to 4.1/1000 admissions in 2008 (14). Of notice, there is no available estimates of the incidence and prevalence of CD in Mexico, even though some experts estimate that CD incidence would be approximately 2% (15).

There are several strategies available for the treatment of UC and CD, which remains challenging (1,16). Corticosteroids are indicated to induce clinical remission in active UC of moderate to severe intensity and active CD of mild to severe intensity (4,17). However, resistance and dependence may occur, ranging from 8%-20% and from 15%-36%, respectively, among CD cases. In UC, corticosteroid-resistance and dependence can reach more than 20% for both outcomes (17,18). Furthermore, prolonged exposure with steroids is not recommended, given the lack of efficacy in the

maintenance of remission and risk of adverse events (4).

Sulfasalazine and 5-ASA are indicated to induce and maintain clinical remission of mild to moderate UC but are not recommended in CD treatment neither moderate to severe UC cases (4,19,20). Immunosuppressors are effective in maintaining remission in CD and UC and while promoting corticosteroid withdrawal in corticosteroid-dependent patients. However, methotrexate is nowadays a second-line immunosuppressor for CD patients resistant or intolerant to azathioprine or 6-mercaptourine, and is not recommended in the maintenance treatment of UC (4). Cyclosporine seems to have no therapeutic value in treatment of CD (4).

The use of biological therapy has been increasing, namely for moderate to severe IBD or when there is no response to conventional treatments (4). In fact, infliximab, adalimumab and vedolizumab have shown to be effective in induction and maintenance of clinical remission of UC and CD (4,19,20). Side effects usually occur in less than 10% of cases, and it has been described that biological therapy can promote endoscopic and histologic improvement. Biologics have also the potential to improve QoL in IBD patients (21).

The therapy with vedolizumab is an alternative for patients with refractory CD or those who cannot tolerate treatment with corticosteroids, thiopurines (azathioprine or mercaptopurine) and who have failed with anti-TNF therapy. Treatment with vedolizumab is effective for the induction and maintenance of remission in CD patients who have never received anti-TNF therapy (4).

In face of IBD complexity and heterogeneity, treatment decision should consider the activity and severity level, the extension of inflammatory process and corticoid dependency (4). If the first-line immunosuppressive maintenance therapy fails, several other factors should be taken into account when deciding the following treatment, including patient's preferences, fecundity and patient age (16).

2.1 Study Rationale

No studies have been conducted in Mexico with large territorial coverage, to evaluate demographic and clinical aspects of IBD, namely the level of disease activity and the burden of both CD and UC. Therefore, it is pertinent to gather information regarding the characteristics of the population with moderate to severe IBD (UC and CD), the IBD (UC and CD) burden in terms of patient QoL and work productivity, consumption of healthcare resources, and to understand UC and CD treatment patterns, particularly on the use of available biologic therapies.

3 Study Objectives

Primary Objective:

- To evaluate the disease activity at Day 1 among UC and CD patients diagnosed with moderate to severe disease.
  - Active CD defined as Harvey Bradshaw Index [HBI] ≥ 8 or Crohn's Disease Activity Index [CDAI] ≥ 220 points.
  - Active UC defined as 9-point partial Mayo (pMayo) score ≥5.

Secondary Objectives:

- To characterize socio-demographic and clinical features of UC and CD patients, overall and by disease activity at Day 1.
- To characterize treatment patterns for UC and CD in the 3 years prior to Day 1, including the use of biologic therapies and failure to these therapies (if any), overall and by disease activity at Day 1.
- For UC and CD, to compare patients with moderate to severe disease activity with patients with no or mild activity, regarding socio-demographic and clinical variables and treatment patterns at Day 1.
- To evaluate the QoL (36-item Short Form health Survey [SF-36] and Inflammatory Bowel Disease Questionnaire [IBDQ]) in UC and CD patients at Day 1, overall and by disease activity at Day 1.
- To evaluate the work productivity impairment (WPAI) experienced by UC and CD patients at Day 1, overall and by disease activity at Day 1.
- To describe the burden of disease in terms of healthcare resources utilization and costs (direct and indirect) related to the management of UC and CD in the 3 years prior to Day 1.

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in approximately 10-12 sites in Mexico. The selected sites are public/private reference hospitals from regions of Mexico, institutions recognized by their large experience in the IBD management, and that follow UC and CD patients in ambulatory care.

4.2 Sponsor Personnel

Takeda LOC will keep a record of all relevant sponsor personnel.

Name	Study Team Role
[redacted]	Medical Operations [redacted]
[redacted]	Clinical Operations [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	Regulatory Affairs [redacted]
[redacted]	Pharmacovigilance [redacted]

4.3 Contract Research Organisation (CRO)

A CRO will be responsible for the development of electronic Case Report Form (eCRF), study implementation and monitoring, data management, data analysis and development of the final clinical study report (CSR). The CRO will keep a record of all involved CRO personnel.

4.4 Essential Documents

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

- Written agreement between Takeda or appointed CRO and the selected Sites.
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible.
- Informed Consent Form (ICF) in local language, approved by Independent Ethics Committees (IEC) as locally required.
- Written IEC approval according to local regulations.
- Authority approval according to local regulations.

5 Ethics

This study is an 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 and use of Patient Report Outcomes (PRO) tools, to collect information about health related QoL and WPAI due to UC or CD (22). These procedures will not impact the usual care provided to the subjects. PRO tools will be submitted to IEC for ethical approval.

5.1 Ethical conduct of the Study

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have origin in the the Declaration of Helsinki (23), Guidelines for Good Pharmacoepidemiology Practices (GPP) (24). Each Investigator will conduct the study according to applicable Mexico regulatory requirements. A special attention will be paid to subject's data protection and confidentiality.

Takeda/the appointed CRO will ensure that the protocol, any amendments and the ICF are submitted to the relevant IECs according to local requirements.

Takeda, as the sponsor, is responsible for meeting the ICH requirement for yearly updates to the IECs, if applicable.

5.2 Independent Ethics Committee

IEC

IECs must be constituted according to the applicable Mexican regulations (Guidance from Comisión Nacional de Bioética). The sponsor or designee will require documentation noting all names and titles of members who make up the respective IEC. If any member of the IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. The sponsor or designee will supply relevant documents for submission to the respective IEC for the protocol's review and approval. This protocol, a copy of the ICF and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to the local IEC for approval. The IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before study specific screening activity). The IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date.

Sites must adhere to all requirements stipulated by their respective IEC. This may include notification to the IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IEC, and submission of the investigator's final status report to IEC. All IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Sponsor will keep an updated list of all submission and approval dates of all documents submitted to the IEC and will provide the Study Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

Authorities

Sponsor or the appointed CRO will send required documents to the regulatory authority Federal Commission for the Protection against Sanitary Risks (COFEPRIS). Sponsor will keep an updated list of submission and approval dates and a copy of all documents submitted.

5.3 Subject Information and Written Informed Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information (hereinafter referred to as personal data) for purposes of conducting the study. The ICF further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF details the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IEC approval of the ICF. The ICF, must be approved by both the IEC and the sponsor prior to use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study.

If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

6 Study Design and Plan

This study is a 'non-interventional study' as defined in: PROC-0002555, PROC-0003026, Clinical trials - Regulation EU No 536/2014 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.

This is a multicenter, non-interventional study to evaluate the control of disease activity (Figure 1), with a cross-sectional evaluation at Day 1, complemented with retrospective chart review.

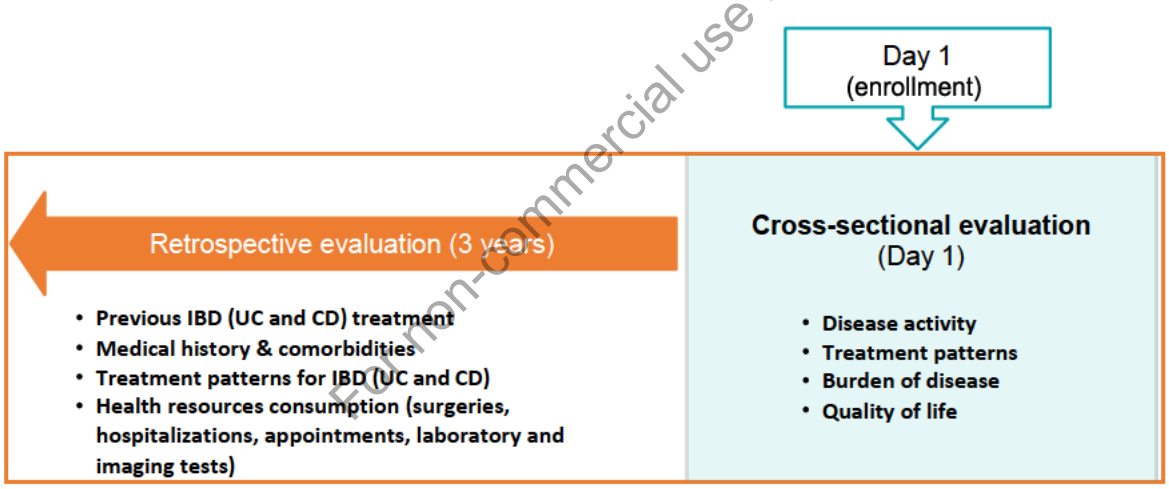

Figure 1. Study design scheme

At each site, eligible subjects will be identified consecutively as they attend scheduled clinical appointment with their physician (Day 1). Upon written consent, data regarding disease activity, treatment patterns, burden of disease and QoL will be collected from medical records and PRO tools. These tools include QoL (SF-36 and IBDQ) and work productivity (WPAI) questionnaires. Retrospective data will refer to the previous three years and will include the previous UC and CD treatments (drug, dose, treatment duration, drug changes), and use of other healthcare resources related with the management of UC and CD (surgeries, hospitalizations, medical appointments, imaging and

laboratory testing). Direct costs calculation will be performed by a micro-cost analysis (i.e. identifying and quantifying each single resource and multiplying it by the corresponding unit cost) and indirect cost by human capital method for absenteeism and presenteeism (i.e. the amount of salary paid to the employee proportional to the hours of absence/productivity impairment at work) based on WPAI data collected.

6.1 Study Schedule

Planned Start of Study:	Q3 FY20
Planned Patient In:	Q1 FY21
Planned collection of first data point:	Q1 FY21
Planned End of Study:	Q2 FY22
Planned Final Database Lock:	Q1 FY22
Planned completion of the Study Report:	Q2 FY22

The Start of Study is defined as date of last protocol signature and planned to occur on October 2020. The collection of first data point (*first patient in*) will start during 1st quarter 2021. The recruitment period is expected to last up to 6 months. The End of Study is defined as the date of collection of the last data point for the last patient recruited.

CRO (on behalf of the Sponsor) will ensure that End of Study notification is submitted to the concerned authorities and IEC for each site, for the country and for the complete study, as locally required.

Based on upcoming knowledge, Sponsor might choose to terminate the study prematurely. In such case, the, study sites, IECs and COFEPRIS will be informed promptly.

6.2 Discussion of Study Design

This is a non-interventional study, with a cross-sectional evaluation and retrospective chart review, designed to evaluate disease control, treatment patterns, burden of disease and health related QoL

among patients with UC and CD. The cross-sectional design with no control group is suitable and feasible to address the study objectives, which are mainly descriptive.

In terms of external validity, two major points should be considered. First, the 10-12 study sites will be selected among reference public/private institutions for IBD management in different districts in Mexico. It is expected that their patients will be representative in Mexico. In addition, the inclusion and exclusion criteria are not restrictive and will enable the assessment of real-world data about UC and CD control in Mexico. Internal validity will be reinforced by training of Investigators and the use of same study procedures and forms. Hence, observation bias is not expected to occur during the cross-sectional evaluation. Although retrospective data collection is challenged by the quality of medical records, treatment patterns and hospitalizations are frequently recorded, and no significant missing data is expected, which could lead to underestimation of health care utilization data. In addition, it is expected that completeness of medical records will be high in the previous 3 years (retrospective period), namely regarding the use of biological treatments (if prescribed).

Because this is an observational study, some limitations should be minimized. All eligible patients will be consecutively invited to the study and the enrolment period will be of at least 6 months. Disease control may be underestimated due to selection bias, since patients with active UC or CD are expected to have more medical appointments and thus, may be have more frequent visits to the center. Nevertheless, the 6-month period will also enable the inclusion of patients with mild or no active disease (although, for the same reason, these patients may be underestimated).

Potential confounders will be addressed at:

- Enrolment – with the exclusion of patients with indeterminate or not classified colitis and that have participated in interventional clinical trials during the last 3 years. In fact, during a trial the subject has access to special and specific treatment and diagnosis procedures. The participation in an interventional trial during the previous 3 years may cause misunderstanding about treatment patterns and resources utilization, because in this project the retrospective data will be collected exactly about this period.
- Statistical analysis – with the inclusion in the logistic regression models of variables associated with both disease control and other variables of interest.

6.3 Selection of Study Population

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.

6.3.1 Inclusion Criteria

Subjects must meet all the following inclusion criteria:

- Male or female subjects.
- Subjects aged 18 years or older (at the time of diagnosis of moderate to severe UC or CD).
- Diagnosis of moderate to severe CD or UC established for at least 6 months prior to Day 1 appointment, based on clinical, endoscopic or image criteria (19,20). The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.

6.3.2 Exclusion Criteria

Subjects will be excluded if presenting at least one of the following:

- Indeterminate or not classified colitis.
- Current or previous participation in interventional clinical trials (within the last 3 years).
- Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

6.3.3 Enrolment

Each Study Site Responsible (Investigator) should include consecutive subjects who meet eligibility criteria, from patients attending pre-scheduled routine medical appointments.

The recruitment of study subjects is expected to occur during a 6-month period. A patient tracking log form will be used by each site.

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

This is a non-interventional study and, thus, no treatments/pharmacotherapy are predefined in the protocol.

All clinical decisions will be full responsibility of the investigator.

7 Conduct

7.1 Data collection overview

Table 1. Study Flow Chart

Study variables	Day 1	Retrospective data, concerning the 3 years before
Timing of data collection	Day 1 visit	During visit
Informed consent	X	
Inclusion criteria	X	
Exclusion criteria	X	
Socio-demographic variables	X	
Smoking habits	X	
Anthropometric Information (Weight, Height, BMI)	X	
IBD type (CD or UC)	X	
Date of diagnosis of CD or UC (based on medical records)	X	
Date and criteria of diagnosis of moderate to severe CD or UC (based on medical records)	X	
Steroid dependence or refractoriness	X	
Family history of IBD	X	
Medical history / Comorbidities	X	

Study variables	Day 1	Retrospective data, concerning the 3 years before
Disease activity: CD (HBI score or CDAI); UC (partial/total Mayo score)	X	
Clinical Characterization of Disease: location, behavior, EIM	X	
SF-36	X	
IBDQ [1]	X	
WPAI	X	
Previous treatments or regimens [2]		X
Treatment started at Day 1 (if applicable)	X	
Previous surgeries for IBD (UC and CD)		X
IBD (UC and CD)-related hospitalizations		X
Previous medical appointments related with IBD (UC and CD) management		X
Previous CDAI, HBI, Mayo score (when available)		X
Previous calprotectin levels and colonoscopy (when available)		X
Other previous imaging, laboratory (including PCR) and histology testing (when available)		X

[1] Not applicable for patients who have a colostomy or ileostomy.
[2] Excludes new treatments prescribed at Day 1 visit.

7.2 Study Variables

Data will be collected from medical charts and during the routine clinical appointment, for the following variables:

Socio-Demographic variables

- Date of birth;
- Sex;
- Professional status (employed, unemployed, retired, student, other);
- Educational level;
- Subject income.

Clinical variables

- IBD type: CD or UC;
- Smoking habits;
- Anthropometric information (weigh, height, body mass index [BMI]);
- Date of diagnosis of CD or UC (and disease duration at Day 1);
- Date of diagnosis of moderate to severe CD or UC (if not the same as previous);
- Steroid dependence or refractoriness or not applicable);
- Family history of IBD;
- Medical History / Comorbidities (including prior tuberculosis and hepatitis infection);
- Disease presentation [location, behavior, extraintestinal manifestations (EIM)];
- Colonoscopy in the previous 12 months suggestive of inadequate control of activity (yes/no) (qualitative data/Mayo subscore);
- Calprotectin levels in the previous 12 months suggestive of inadequate control of activity, if it is available (i.e., calprotectin >200ug/g) (yes/no) (qualitative data).

Disease activity (at Day 1)

- For CD patients: HBI score or CDAI;
- For UC patients: 9-item pMayo score (always collected) and the total Mayo score (when available).

Both HBI and CDAI are commonly used to assess CD activity.

The HBI score considers five easily assessed dimensions (general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and complications). These dimensions are scored from the previous day (no diary cards are required). Patients with HBI ≥ 8 are classified as presenting moderately to severely active CD (25).

The CDAI evaluates the severity of signs and symptoms of CD. Collected data include information on the number of liquid stools, intensity of abdominal pain, general well-being, presence of comorbid conditions, use of medications for diarrhea, physical examination, and laboratory findings (abdominal mass, hematocrit, body weight), yielding 8 items that are combined with data from a 7-day diary to obtain the total CDAI score. Higher scores indicate a greater disease activity. Moderately to severely active CD is defined as CDAI ≥ 220 (26).

The Mayo score is composed of four categories (bleeding, stool frequency, physician assessment, and endoscopic appearance) rated from 0–3 that are summed into a total score ranging from 0–12. The pMayo score was previously compared with the full Mayo score and categorizes UC patients as being in remission (score of 0–2), having mild activity (pMayo of 3 or 4) or moderate to severe activity (pMayo of ≥5) (27).

Health-Related Quality of Life and Work Productivity (at Day 1)

- 36-item Short Form Health Survey (SF-36)
- Inflammatory Bowel Disease Questionnaire (IBDQ) - 32 items
- Work Productivity and Activity Impairment Questionnaire (WPAI) – 6 items

SF-36 is a general QoL-questionnaire, which evaluates 8 health dimensions: physical functioning, bodily pain, role physical (limitations due to physical problems), role emotional (limitations due to personal or emotional problems), mental health, social functioning, vitality, and general health perceptions. Based on these 8 dimensions, two weighted scores are generated: the physical component summary score and the mental component summary score. Scores range between 0 and 100, with higher scores indicating a better quality of life (28). For additional information, please consult

http://www.rand.org/health/surveys_tools/mos/mos_core_36item_survey_print.html.

IBDQ is a disease-specific questionnaire with 32 items that measures four dimensions: bowel function, emotional status, systemic symptoms, and social function. Within dimensions, each question presents seven possible answers/points. The score for each dimension results from the sum of points. Hence, the total score ranges from 32 to 224, with higher scores representing better QoL (29). The IBDQ is not validated for patients with ostomies and therefore should not be applied for these patients. For more information, please consult http://www.flintbox.com/public/project/641.

Work Productivity will be measured by the WPAI, a patient-reported quantitative assessment of the amount of absenteeism, presenteeism and daily activity impairment attributable to general health (WPAI:GH) or a specific health problem (WPAI:SHP). It presents six questions that cover the impact of IBD on work productivity and daily activities during the previous 7 days. In brief, the WPAI questions are: 1) if currently employed, 2) hours missed due to disease, 3) hours missed other reasons, 4) hours actually worked, 5) degree disease affected productivity while working, 6) degree disease affected regular activities (7). WPAI generates four component scores: percentage of work time missed (absenteeism); percentage of impairment while working (presenteeism); percentage of overall work

impairment (absenteeism and presenteeism combined); and percentage of regular activity impairment. Unemployed patients only answer to questions related to employment status and regular activities impairment. Scores for WPAI range from 0% ('no impairment') to 100% ('total loss of work productivity/activity'). For more information, please consult http://www.reillyassociates.net/WPAI_General.html.

Treatment

- Previous treatments or regimens (aminosalicylates, steroids, immunomodulators, immunossupressors, biologics, probiotics, antibiotics); start date; end date, dose, reason for discontinuation;
- First treatment after diagnosis of moderate to severe UC or CD (name, dose);
- Treatment started at Day 1 (name, dose);

Other healthcare resources related with UC and CD management

- Surgeries;
- Hospitalizations;
- Medical appointments;
- Imaging and laboratory testing.

8 Management and Reporting of Adverse Events

8.1 Definitions

Adverse Events

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

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

- A laboratory test result that meets the criteria for 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

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

A SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

Adverse Reactions

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes the following, regardless of whether adverse reactions arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse, medication errors, use of falsified medicinal product, suspected transmission of an infectious agent, breast feeding: infant exposure from breast milk, lack of efficacy of a Takeda product and occupational exposure*.

* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

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.
- Accidental exposure.
- Use outside the terms of the marketing authorisation, also known as "off-label".
- Use of falsified medicinal product.
- Unintended benefit
- Drug-drug or drug-food interactions

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

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

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 hospitalization or prolongation of existing hospitalization, 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.

Severity

Severity is a clinical observation and describes the intensity of the event.

- Mild: Transient symptoms, no interference with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities.

Causality

The following definitions of Related should be used to characterize the suspected causality of an AE. This assessment should be based on the Investigator's consideration of all available information about the event, including temporal relationship to drug administration, recognized association with drug product/class, pharmacological plausibility, and alternative etiology (e.g., underlying illness, concurrent conditions, concomitant treatments):

- 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 of Adverse Events, Special Situation Reports and Product Quality Issues

If during the conduct of the study a member of the research team is spontaneously informed of an AE, SAE, SADR, SSR or product quality issue and that event pertains to a Takeda product, they, must be reported relevant Takeda Mexico Pharmacovigilance Department within 1 calendar day for deaths, within 4 calendar days for other SAES and within 7 calendar days for all other events in order to comply with local regulations. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

No data on AEs or ADRs will be pro-actively collected as part of the study database.

All safety-related data on study subjects collected in the study database or reported to Takeda according to the normal procedure for marketed drugs, e.g. serious and non-serious ADRs, must be summarized in the Non-Interventional Study Report.

9 Data Quality Control and Assurance

9.1 Quality Control

The study will use electronic data collection, for which a set of automatic data checks with data queries will be programmed for data cleaning. Manual data monitoring will include on and off-site visits and on-site Source Data Verification will include the check of the signed ICF for all subjects. Source documents (e.g., medical records, original laboratory records) and signed ICF should be available to study monitors whenever possible, and consent to such access will be explicitly included in the ICF.

Additional details will be specified in the Monitoring Plan.

9.2 Audit from Quality Assurance Unit

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

9.3 Inspection by IEC or Competent Authority (CA)

Representatives from IEC or CA may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately escalate (according to the escalation line information) and must make the records available as requested.

9.4 Data Management

Data management must be written and approved before the design of the study database is finalized. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a subject is known not to be available despite 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.

The current Standard Coding Instructions for coding of medical history, concomitant illness (Medical Dictionary for Regulatory Activities - MedDRA) and concomitant medication (WHO-Drug) must be followed.

The subjects will be identified in the database only by Study ID, Site ID, and subject number. No personal identifiable data will be collected.

9.4.1 Data Collection Tools and Flow

The Study Site will receive data collection tools (access to eCRFs and PRO tools) from Takeda or Designee. 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.

All data collected for the purpose of this study will be entered, stored and retrieved with the use of an eCRF specifically designed for the study. The system will comprise a web-based interface for use by investigators, and a central database for storage and retrieval. The database will be physically stored at a data center designated by Takeda or the appointed CRO, with appropriate measures for back-up of data and stability of the system. The system will ensure patient confidentiality, as well as security and confidentiality of the data for the duration of the study. Each Site Responsible or designee will receive from Takeda or the appointed vendor a login name and a password and will hold the responsibility for data entry into the system. Investigators will be able to access the database for the whole duration of the study. The database will contain single-choice, multiple-choice and open-field options for the entry of patient demographic and clinical data. Moreover, the system will allow for automatic data checks and the negation of queries based on programming logic. A detailed Data Validation Plan that will identify missing data, out-of-range data, and other data inconsistencies will be implemented prior to study start. To resolve any questions arising from the data review process, data queries and/or site notifications will be created in the Electronic Data Capture (EDC) system for site resolution and closed by the sponsor reviewer.

At any time during the study, the investigator (or site staff) may contact the study monitor in order to clarify any study procedures. All source documentation supporting entries into the eCRF must be maintained and readily available. Given that source documents (institutional charts and reports of results from laboratory and imaging studies) will not necessarily be available for auditing in the future, the Site

Responsible will ensure that data collection for the study be done in a proper way and by individuals who are under their direct supervision. Moreover, the Site Responsible will ensure data are attributable, accurate, complete, contemporaneous, and consistent. The Site Responsible must sign off the complete data set for each subject, confirming the collected data.

10 Statistical Methods and Determination of Sample Size

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 Statistical Analysis Plan (SAP) before completion of data collection. All later deviations and / or alterations will be summarised in the CSR.

10.1 Statistical Analysis Plan

This study is observational and epidemiological methods will be employed for data analyses. Data analysis will be performed using SAS ® (version 9.4; SAS Institute Inc, Cary, USA).

Descriptive analysis will be performed of all collected data (listed in section 7.2) except data collected only for the purpose of data cleaning.

10.1.1 Study Endpoints

The main study endpoints are:

Primary Endpoints:

- Percentage of Participants with Active Crohn's Disease (CD) at Day 1 [Time Frame: Day 1] Percentage of participants with active CD observed, where active CD is defined as Harvey Bradshaw index (HBI) greater than or equal to (≥) 8 or Crohn's disease active index (CDAI) ≥ 220 to total CD participants multiplied by 100. CDAI assesses CD based on clinical signs and symptoms such as number of liquid stools, intensity of abdominal pain, general wellbeing, presence of comorbid conditions, use of antidiarrheal, physical examination and laboratory findings. Total score ranges from 0 to 600 points. Higher score indicates more severe disease.

HBI consists of 5 clinical parameters: general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and complications. Total score is sum of individual parameters. Score ranges from a minimum score of 0 to no pre-specified maximum score as it depends on number of liquid stools, where higher scores indicates more severe disease.

- Percentage of Participants with Active Ulcerative Colitis (UC) at Day 1 [Time Frame: Day 1] Percentage of participants with active UC will be calculated as the ratio of UC participants with Mayo score ≥5 to the total UC participants multiplied by 100. Mayo score is an instrument used to measure disease activity. It consists of 3 sub scores: stool frequency, rectal bleeding, and physician global assessment of disease severity, each graded from 0 to 3 with higher scores indicating more severe disease. These scores are summed to give a total score range of 0 to 9; where higher scores indicating more severe disease.

Secondary Endpoints:

- Number of UC or CD participants based on socio-demographic variables [Time Frame: Day 1] (Socio-demographic variables age, sex, professional status, educational level, subject income).
- Number of UC or CD participants based on smoking habits, anthropometric information and clinical variables. [Time Frame: from initial diagnosis until Day 1]- (Clinical variables include duration and age at diagnosis, steroid dependence or refractoriness, family history, medical history and comorbidities, criteria used for diagnosis, calprotectin, EIM).
- Number of participants based on clinical presentation [CD - location, behavior, perianal disease, achievement of ileal disease; UC - extent of inflammation and severity]) [Time Frame: Day 1].
- Number of UC or CD participants based on IBD therapies and the duration of these therapies. [Time Frame: From 3 years prior to Day 1 until Day 1]. (IBD therapies include aminosalicylates, steroids, immunomodulators, immunossupressors, biologics, antibiotics, probiotics and surgeries)
- Percentage of UC or CD participants with biologic-experience [Time Frame: From 3 years prior to Day 1 until Day 1]
- Percentage of UC or CD participants who have not responded previously to biologic therapies and reason [Time Frame: From 3 years prior to Day 1 until Day 1].
- Number of UC or CD participants with IBD treatment introduced at Day 1 (if applicable) [Time Frame: Day 1].

- Number of participants with HBI ≥ 8 or CDAI ≥ 220 points versus HBI < 8 or CDAI < 220 points based on socio-demographic, clinical and treatment-related variables in CD participants [Time Frame: Day 1].
- Number of participants with pMayo score ≥5 versus pMayo <5 based on socio-demographic, clinical and treatment-related variables in UC patients [Time Frame: Day 1].
- Mean score of different components of SF-36 by IBD type [Time Frame: Day 1] The SF-36 evaluates 8 health dimensions: physical functioning, bodily pain, role physical (limitations due to physical problems), role emotional (limitations due to personal or emotional problems), mental health, social functioning, vitality, and general health perceptions. Based on these 8 scales, two weighted scores are generated: the physical component summary (PCS) and the mental component summary (MCS) score. Scores range between 0 and 100, where higher scores indicate a better quality of life.
- Mean total score of IBDQ [Time Frame: Day 1]
  The IBDQ is a 32-item questionnaire that measures 4 dimensions: bowel function, emotional status, systemic symptoms, and social function. Within dimensions, each question presents seven possible answers/points. Each domain score is the sum of 8 responses each ranging from 1 to 7, where 1 indicates worst function and 7 the best. The sub-score ranges from 8 to 56 and thus the total score ranges from 32 to 224, where higher score indicates better quality of life. Patients with ostomy will not be evaluated since this questionnaire is not validated to be used in this population.
- Mean total percentage of work impairment (WPAI) in hours [Time Frame: Day 1].
  The WPAI assess the impact of IBD on work productivity and daily activities during the previous 7 days. The WPAI includes 6 questions: 1 (if currently employed); 2 (hours missed due to disease); 3 (hours missed other reasons); 4 (hours actually worked); 5 (degree disease affected productivity while working); 6 (degree disease affected regular activities). WPAI generates four component scores: percentage of work time missed (absenteeism); percentage of impairment while working (presentisms); percentage of overall work impairment (absenteeism and presentisms combined); and percentage of activity impairment. Unemployed participants only answer questions related to employment status and activity impairment. Scores for WPAI range from 0% to 100%, where 0 % indicates no impairment and 100% is total loss of work productivity/activity.
- Mean work time missed (WPAI) [Time Frame: Day 1]
- Mean impairment while working (WPAI) [Time Frame: Day 1].

- Mean total activity impairment (WPAI) [Time Frame: Day 1]
- Percentage of UC or CD participants who quit their job due to IBD and have not been able to return to work [Time Frame: Day 1].
- Percentage of UC or CD participants based on the use of surgeries, hospitalizations, medical appointments, imaging and laboratory [Time Frame: From 3 years prior to Day 1 until Day 1]
- Number of healthcare resources used and unitary cost per resource (direct medical cost) [Time Frame: From 3 years prior to Day 1 until Day 1].
- Number of workhours missed or with productivity reduced due disease and average salary/hour/person (indirect costs applicable to active workers) [Time Frame: From 3 years prior to Day 1 until Day 1]

10.1.2 Statistical analyses overview

For each study endpoint, all data will be summarized for total UC and CD patients and by IBD type (UC or CD).

Statistical analysis will allow a characterization of the study population, the estimation of primary endpoints and to compare the subgroup of patients with mild or no activity of disease and those with moderate to severe activity. Hence, for each IBD type (UC and CD), the patients with disease activity will be compared with patients with mild or no activity regarding socio-demographic, clinical and treatment variables of interest.

Descriptive statistics will be used for all variables including mean, median, standard deviation and range for numerical variables and absolute and relative frequencies for categorical variables. 95% confidence intervals (CI) will be computed whenever relevant. Chi-square or Fisher exact tests will be used to compare activity vs non-activity regarding qualitative variables and t-student or Mann-Whitney tests will be used for comparison of quantitative variables. If applicable, multivariable logistic regression model will be performed to evaluate association of independent variables with disease activity at Day 1 with odds ratios (ORs) estimates and the respective 95% CI. All tests will be two-sided and considering a significance level of 5%.

For further details of the statistical analyses to be performed, please refer to the SAP.

10.2 Primary Analyses

For CD, the percentage of patients with active disease at Day 1 will be calculated as:

$$\frac{CD\ patients\ with\ HBI \geq 8\ or\ CDAI \geq 220}{Total\ CD\ patients}\ x\ 100$$

For UC, the percentage of patients with active disease at Day 1 will be calculated as:

$$\frac{UC\ patients\ with\ partial\ Mayo\ score \geq 5}{Total\ UC\ patients}\ x\ 100$$

The 95% CIs will be computed for each estimate.

10.3 Secondary Analyses

In order to characterize socio-demographic and clinical aspects of UC and CD, a summary table with the descriptive statistics of the selected variables, by CD and UC patients.

Descriptive statistics will also be used to summarize treatment patterns for CD and UC in the previous 3 years, including the use of conventional and biologic therapies and failure to these therapies (if any), time between IBD diagnosis and initial treatment, first treatment after diagnosis of moderate to severe IBD, time for of biologic from date of diagnosis of UC or CD, among other variables of interest.

Within CD and UC groups, the patients with moderate to severe disease activity will be compared with patients with mild or no activity, regarding socio-demographic, clinical and treatment variables of interest:

- Chi-square or Fisher exact tests will be used to compare qualitative variables, such as sex, smoking habits, professional status, family history of IBD, steroid dependence or refractoriness, previous treatment with biologic therapies, and previous surgery for IBD (UC and CD), among others.
- The t-student or Mann-Whitney tests will be used for comparison of quantitative variables, such as age, time since diagnosis, and duration of treatment, among others.
- If applicable, logistic regression models (for CD and UC patients) will be used to identify independent variables associated with disease control at Day 1, and odds ratios (OR) with 95% CI will be presented.

Descriptive statistics will also be summarized regarding patients' QoL, overall and according to disease activity. For each score estimate, the 95% CI will be computed.

- The SF-36 uses 36 items to evaluate the eight health dimensions. After the standard scoring (section 7.2) the dimension score will be calculated by averaging the score items of the same scale.
  - Physical functioning – Average of Q3a, Q3b, Q3c, Q3d, Q3e, Q3f, Q3g, Q3h, Q3i and Q3j scores.
  - Role Physical – Average of Q4a, Q4b, Q4c and Q4d scores.
  - Body pain – Average of Q7 and Q8 scores.
  - General health – Average of Q1, Q11a, Q11b, Q11c and Q11d scores.
  - Vitality – Average of Q9a, Q9e, Q9g and Q9i scores.
  - Social Functioning – Average of Q6 and Q10 scores.
  - Role-Emotional – Average of Q5a, Q5b and Q5c scores.
  - Mental Health – Average of Q9b, Q9c, Q9d, Q9f and Q9h scores.

  A summary score for each component will be obtained through a standardization of each scale score followed by the computation of aggregate scores for the physical and mental summaries using weights. The component summary will be scored from 0 to 100, with a high score denoting a more favorable health state:

  - Physical Component Score
  - Mental Component Score
- The IBDQ questions have seven optional choices. In order to obtain a score, each question corresponds to the given number, with question 1 representing a worse status of quality of life and 7 a better, adding up the total of points in each dimension. The dimension score will be calculated by the average of the questions scores associates to each dimension. A higher score shows better function in that area.
  - Bowel function – sum of questions 01, 05, 09, 13, 17, 20, 22, 24, 26, 29.
  - Emotional status – sum of questions 03, 07, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32.
  - Systemic symptoms – sum of questions 02, 06, 10, 14, 18.
  - Social function – sum of questions 04, 08, 12, 16, 28.

The comparison of SF-36 scale scores or component summary scores, EQ-VAS scale and IBDQ domain scores or total score according to disease activity will be performed through the t-test for independent samples or Mann-Whitney test in case of non-normality of the quantitative variable distribution.

Descriptive statistics will be summarized regarding work productivity impairment (WPAI), experienced by IBD patients (overall, by IBD type (UC and CD) and according to disease activity):

- In brief, the WPAI questions are: 1) if currently employed, 2) hours missed due to disease, 3) hours missed other reasons, 4) hours actually worked, 5) degree disease affected productivity while working, 6) degree disease affected regular activities.
- Percent total work productivity impairment (TWPI) due to UC or CD defined as the mean of subjects' total percentage of work impairment associated with UC or CD that results from both absenteeism and presenteeism. The TWPI, assessed by each IBD (UC or CD), will be calculated as following:

$$\frac{Q2}{Q2+Q4} + [(1 - \left(\frac{Q2}{Q2+Q4}\right)) * \frac{Q5}{10}] * 100$$

- Percent work time missed due to UC or CD will be calculated for each subject as following:

$$\frac{Q2}{Q2+Q4} * 100$$

- Percent impairment while working due to UC or CD will be calculated for each subject as following:

$$\frac{Q5}{10} * 100$$

- Percent total activity impairment due to UC or CD will be calculated for each subject as following:

$$\frac{Q6}{10} * 100$$

- Additionally, the proportions of patients reporting some absenteeism, some work impairment, and some activity impairment due to UC or CD will be presented.

Patients with moderate to severe activity will be compared with patients with no or mild activity regarding WPAI data (percent TWPI due to UC or CD, percent work time missed due to UC or CD, percent impairment while working due to UC or CD and percent total activity impairment due to UC or CD) through the t-test for independent samples or Mann-Whitney test in case of non-normality of the quantitative variable distribution.

Healthcare resources (previous 3 years) will be described by IBD group (UC or CD) and by disease activity at Day 1, for the following events: drug therapies; surgeries; number, reason and duration of hospitalizations; number and type of medical appointments with gastroenterologists or other medical specialists; and number and type of imaging and laboratory testing.

Healthcare resource costs will be reported in total and on a *per patient per month* basis. Direct costs will be obtained by multiplying resource use with relevant unit costs. Unit costs for each resource items will be collected in Mexican reliable administrative databases or other sources.

- UC or CD-related health care costs: Consumer price index (CPI)-adjusted IBD (UC or CD)-related health care costs will be computed as total costs, medical costs, UC and CD drug costs, and other costs (sum of surgeries, hospitalization, medical appointments; imaging and laboratory testing costs).
- Treatment pattern costs. Treatment pattern costs will be calculated as total UC or CD-related health care costs, stratified by the defined treatment patterns. In addition to the descriptive cost data, multivariate cost models may be developed where the observation time is divided into intervals of equal length.

The indirect costs will be reported as the cost of productivity loss by absenteeism and presenteeism per patient. In the present study it was considered relevant to consider the human capital method since it was understood that the disease is not incapacitating, and the period of absence would not be long enough to justify the replacement of the employee.

- In the human capital method, the calculation considers exactly the cost of the salary paid to the employee proportionally to the hours of absence/ work impairment based on the average mexican incomes and the absence/impaired work hours reported during the study.

10.4 Interim Analyses

No interim analyses are planned for this study.

10.5 Handling of missing data

Given that all analyses are descriptive in nature, no imputation of missing data will be performed, except when detailed in the SAP regarding the PRO tools.

10.6 Determination of Sample Size

It is expected to include 335 patients regardless of IBD type (UC or CD).

Due to lack of information regarding the rate of UC or CD control in Mexico, a rate of inadequate control of disease (i.e. the percentage of patients with moderately to severely active disease) of 50% will be assumed. Hence, a sample of 318 patients, regardless of IBD type (CD or UC), will allow estimates with 95% CI and a margin of error (ME) less than 5.5%. The following formula was used:

$$n = \frac{1.96^2 \times p \times (1-p)}{ME^2}$$

Rate of uncontrolled disease (p) = 50% ME = 0.055

ME = 0.055

To account for a non-evaluable rate of 5%, a total of 335 patients should be included in the study. No stratification sampling methods will be used.

11 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted for distribution. This Study Report should be available in compliance to Sponsor policies, and the participating sites should be informed about the results when the report is finalized.

12 Publications

The investigator is obliged to provide the sponsor all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Takeda aims to have the results of this study published.

13 Archiving of Study Documentation

During the course of the study the Study Site Responsible must as a minimum file the essential documents (Section 4.4), 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 Study Site Responsible must keep a minimum store the list of participating subjects and the signed ICFs on site for 5 years. The Study Site Responsible should store additional study documentation for a longer period if required by any local regulations and/or hospital requirement.

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