Title: BD-5004 - Real-world data of Moderate to Severe Inflammatory Bowel Disease in Argentina: a non-interventional, multicenter study to evaluate disease control, treatment patterns, burden of disease and quality of life (RISE AR)

NCT Number: NCT03488030

Protocol Approve Date: 24Jan2018

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

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

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

Non-Interventional Study Protocol

Short title: Non-interventional Study of Moderate to Severe Inflammatory Bowel Disease in Argentina

Title: Real-world data of Moderate to Severe Inflammatory Bowel Disease in Argentina: a non-interventional, multicenter study to evaluate disease control, treatment patterns, burden of disease and quality of life (RISE AR)

Study ID: IBD-5004

Sponsor: Takeda Pharma S.A.
Tronador 4890 C1430DNN - Buenos Aires - Argentina
Phone: +54 (011) 4546-4700
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Study phase: Medical Affairs, Non-registration Company Sponsored (Observational)

Date of version of protocol: Version 1.0 – 24Jan2018

1 Administrative information

1.1 Contacts

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

Issue	Argentina Contact
Serious adverse event and pregnancy reporting	PPD
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Amendments and updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason

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

PPD

1.4 Summary

Short Title of Study

Non-interventional Study of Moderate to Severe Inflammatory Bowel Disease in Argentina.

Study sites

The study will be conducted in approximately 7 sites in Argentina.

Objectives

Knowledge regarding the control of disease activity in Inflammatory Bowel Disease (IBD) is limited in Argentina. Therefore, it is pertinent to describe the journey of moderate to severe IBD patients in Argentina, their characteristics and how they are managed, and to understand treatment patterns, particularly on the use of available biologic therapies.

Primary Objective:

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

Secondary Objectives:

- To characterize socio-demographic and clinical aspects of moderate to severe IBD.
- To characterize treatment patterns for IBD during the 3 years previous to Day 1, including the use of biologic therapies and failure to these therapies (if any).
- For each IBD type, to compare patients with moderate to severe disease activity with patients with no or mild activity regarding socio-demographic and clinical variables of interest and treatment patterns.
- To evaluate the quality of life (SF-36, EQ-5D and IBDQ) in moderate to severe IBD patients.
- To evaluate the work productivity impairment (WPAI) experienced by moderate to severe IBD patients.
- To describe the use of healthcare resources related with the management of IBD during the 3 years previous to Day 1.

- To estimate UC or CD-related healthcare costs during the 3 years previous to Day 1.

Methodology

This is a multicenter, non-interventional, cross-sectional study aiming primarily to determine the rate of control of IBD activity (Crohn's Disease [CD] or Ulcerative Colitis [UC]). 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 quality of life will be collected from the patients' medical records and administered Patient Report Outcome (PRO) questionnaires, including quality of life (SF-36, EQ-5D and IBDQ) and work productivity (WPAI) questionnaires. Besides the cross-sectional data collection, the study will have an additional retrospective data collection referring to the three years previous to Day 1, regarding the previous IBD treatments (drug, dose, treatment duration and drug changes), and use of other healthcare resources related with the management of IBD.

Number of subjects

It is expected to include 246 patients regardless of IBD type.

This sample size will allow estimates with 95% confidence interval and a margin of error less than 5%, and assuming a rate of inadequate control of disease of 20% (conservative approach), regardless of IBD type. The following formula was used:

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

Rate of uncontrolled disease (p) = 20%

Margin of error (ME) = 0.05

Expected recruitment period: 6 months

Diagnosis/Disease/Condition and main criteria for inclusion

Subjects must meet all of the following inclusion criteria: 1) male or female subjects, 2) subjects aged 18 years or older, 3) with diagnosis of moderate to severe CD or UC for at least 6 months prior to Day

1 appointment based on clinical, endoscopic, or imaging criteria, 4) who provided the written informed consent.

Patients will be excluded if 1) presenting indeterminate or not classified colitis, 2) having current or previous participation in interventional clinical trials (within the last 3 years), 3) presenting 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, gender, smoking habits, professional status (employed, unemployed, retired, student, other), date of diagnosis of CD or UC, date of diagnosis of moderate to severe CD or UC (if not the same as previous), family history of IBD, disease presentation (location, behavior, extraintestinal manifestations), steroid behavior, comorbidities.

Main outcome variables

Primary Endpoints:

- For Crohn's Disease: Proportion of patients with active disease (HBI ≥ 8 or CDAI ≥ 220 points - based on criteria used by the site) at Day 1.
- For Ulcerative Colitis: Proportion of patients with active disease (9-point partial Mayo ≥5) at Day 1.

Secondary Endpoints:

- Distribution of age, gender, smoking habits, professional status, family history, educational level, subject income by IBD type.
- Distribution of clinical variables (steroid behaviour, anthropometric information, medical history and comorbidities, clinical characterization of disease) by IBD type.
- Therapies for IBD (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.
- Proportion of patients who have not responded previously to biologic therapies and reason.
- IBD treatment introduced at Day 1 (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).
- Socio-demographic, clinical and treatment-related variables in patients with moderate to severe activity of UC (partial Mayo score ≥5) versus patients with mild or no activity (partial Mayo <5).
- Mean score of EQ-5D by IBD type.
- Mean score of different components of SF-36 by IBD type.
- Mean total score of IBDQ and by domain (bowel symptoms, systemic symptoms, emotional function and social function). 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).
- Mean work time missed (WPAI).
- Mean impairment while working (WPAI).
- Mean total activity impairment (WPAI).
- Proportion of patients who quit their job due to IBD and have not been able to return to work.
- Healthcare resources (previous 3 years): drug therapies, imaging and laboratory testing, surgeries, hospitalizations and consultations.

Statistical methods

Data will be summarized for total IBD patients and by IBD type (Crohn's Disease and Ulcerative Colitis). 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 will be computed whenever relevant.

For each IBD 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

AE	Adverse Event
ADR	Adverse Drug Reaction
CA	Competent Authority
CCSI	Company Core Safety Information
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
CV	Curriculum Vitae
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EIM	Extraintestinal Manifestations
EQ-5D	5-dimensional EuroQoL measure
GPP	Good Pharmacoepidemiology Practices
HBI	Harvey Bradshaw Index
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MCS	Mental Component Summary
PCS	Physical Component Summary

pMayo	partial Mayo score
PRO	Patient Reported Outcomes
QoL	Quality of Life
SAE	Serious Adverse Event
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SF-36	36-item Short Form health Survey
SSR	Special Situation Report
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 IBD 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). IBD 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 incidence of UC varies between 0.5-24.5/10^5 inhabitants, while CD incidence varies between 0.1-16/10^5 inhabitants worldwide; overall, IBD prevalence is estimated to reach up to 396 per 10^5 people (8). Furthermore, the incidence of IBD has been increasing in several world regions, namely in developing countries (9,10). In South American countries, incidence of IBD seems to be lower than in Europe and North American countries but some studies have reported an increase in recent years (4,11). There are no available data to estimate the incidence and prevalence in Argentina, nationwide. Linares et al have estimated incidences of UC and CD were 2.2 and 0 per 10^5 people, respectively, during 1987-1993 in the district of *Partido General Pueyrredón* (12). More recently, a local study in Córdoba city have described a prevalence ratio of UC (86.8%) and CD (12.3%) of 7.04:1, during 2014-2016 (13). Besides the scarce information about IBD epidemiology, there is no published study about the disease pattern and treatment in Argentina.

There are several strategies available for the treatment of IBD, which remains challenging (1,14). Corticosteroids are indicated to induce clinical remission in active UC of moderate to severe intensity and active CD of mild to severe intensity (4). However, resistance and dependence may occur, ranging from 8%-20% and from 15%-36%, respectively, among CD cases. In UC, corticosteroid-resistance and dependence were 29% and <10%, respectively (15). 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 (4,16,17).

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 (4,16,17). 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 (18).

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 patients with CD who have never received biological therapy with anti-TNF (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). Furthermore, if the first-line immunosuppressive maintenance therapy fails, several other factors should be taken into account when deciding the following treatment, including patient's wishes, fecundity and patient age (14).

2.1 Study Rationale

No studies have been conducted in Argentina with large territorial coverage, to evaluate demographic and clinical aspects of IBD, namely the level of disease activity and the burden of disease. Therefore, it is pertinent to gather information regarding the population with a moderate to severe IBD and the burden of the disease, and to understand their treatment patterns, particularly on the use of available biologic therapies.

3 Study Objectives

Primary Objective:

- To evaluate the proportion of moderate to severe IBD patients with active disease at Day 1 (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 score ≥5).

Secondary Objectives:

- To characterize socio-demographic and clinical aspects of moderate to severe IBD.
- To characterize treatment patterns for IBD during the 3 years previous to Day 1, including the use of biologic therapies and failure to these therapies (if any).
- For each IBD type, to compare patients with moderate to severe disease activity with patients with no or mild activity, regarding socio-demographic and clinical variables of interest and treatment patterns.
- To evaluate the quality of life (SF-36, EQ-5D and IBDQ) in moderate to severe IBD patients.
- To evaluate the work productivity impairment (WPAI) experienced by moderate to severe IBD patients.
- To describe the use of healthcare resources related with the management of IBD during the 3 years previous to Day 1.
- To estimate UC or CD-related healthcare costs during the 3 years previous to Day 1.

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in approximately 7 sites in Argentina. The selected sites are public and private institutions in Argentina recognized by their large experience in the IBD management, and that follow IBD patients in ambulatory care.

4.2 Sponsor Personnel

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

Name	Study Team Role
PPD	Clinical Study Manager Lead
	Clinical Research Coordinator
	Head Medical South America Cluster
	Clinical Science Lead
	Clinical Science
	Regulatory Affairs Manager
	Pharmacovigilance

4.3 Contract Research Organisation (CRO)

The CRO (CCI) will be responsible for the development of electronic CRF (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.

- Subject Information Sheet and Informed Consent Form 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 (i.e., Notification of Clinical Trial).

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 Outcome (PRO) tools, to collect information about health related quality of life and work productivity impairment due to IBD (19). 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 in accordance with the protocol, the current version of the Declaration of Helsinki (20), Good Pharmacoepidemiology Practices (GPP) (21), and Argentine regulations. 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 Subject Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (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

According to applicable regulations, the appointed CRO or the Study Site Responsible will notify or obtain approval from the relevant IEC of the protocol, any amendments and the Subject Information Sheet / Informed Consent Form and other study-related documents, e.g., PRO tools.

The appointed CRO or the Study Site Responsible will submit required documents to the IEC, such as:

- periodic updates on the progress of the study;
- notification of the end-of-study;
- a summary of the study results.

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 competent authority (CA) and/or other national or regional authorities. 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

The Study Site 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 can understand, and obtain the subject's written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject 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 see and is not consent to any interventional procedure or treatment.

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

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to

third parties, e.g., other companies or authorities, that may be located in other countries with potentially different regulations for data.

The subject has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form (ICF) it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed ICF must be kept on the Site.

For details, see the Subject Information Sheet and ICF.

6 Study Design and Plan

This study is a 'non-interventional study' as defined in**:** G-STND-PV-006, G-SOP-MA-005, Directive 2001/20/EC and will follow the guidelines for GPP.

This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the subjects.
- Epidemiological methods shall be used for the analysis of collected data.

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.

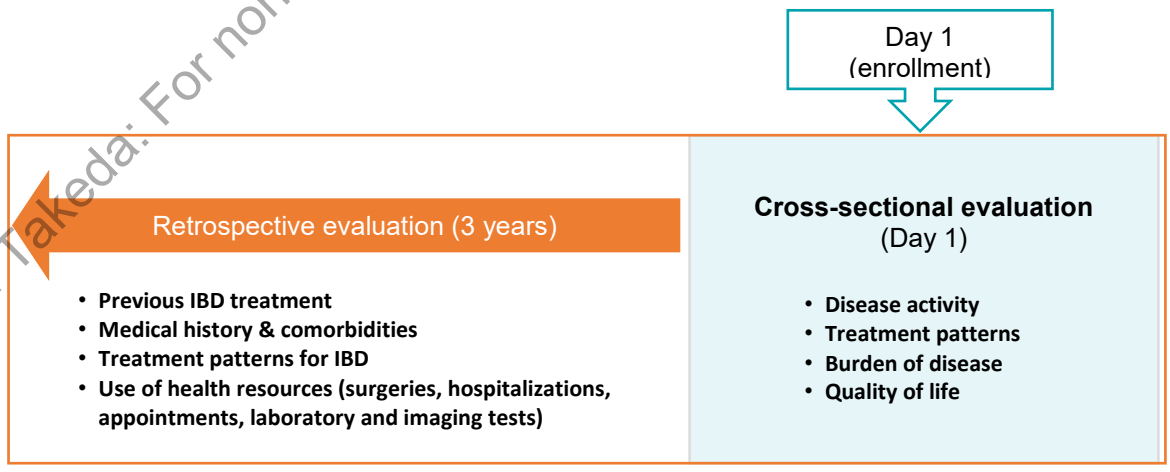

Figure 1. Study design scheme

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 quality of life will be collected from medical records and PRO tools, including quality of life (SF-36, EQ-5D and IBDQ) and work productivity (WPAI) questionnaires. Retrospective data will refer to the previous three years and will include the previous IBD treatments (drug, dose, treatment duration, drug changes, surgeries), and use of other healthcare resources related with the management of IBD.

6.1 Study Schedule

Planned Start of Study:	1st quarter 2018
Planned collection of first data point:	1st quarter 2018
Planned End of Study:	1st quarter 2019
Planned completion of the Study Report:	3rd quarter 2019

The Start of Study is defined as date of last protocol signature and planned to occur on the 1st quarter 2018. The collection of first data point (*first patient in*) will start during 1st quarter 2018. 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, Takeda might choose to terminate the study prematurely. In such case, the Committee(s), study sites, IECs and authorities 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 quality

of life among patients with IBD. 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 7 study sites will be selected among reference public and private institutions for IBD management in different districts in Argentina. It is expected that their patients will be representative of patients with moderate to severe IBD in Argentina. In addition, the inclusion and exclusion criteria are not restrictive and will enable the assessment of real-world data about IBD control in Argentina. 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 last 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 IBD 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 of the following inclusion criteria:

1) Male or female subjects.
2) Subjects aged 18 years or older.
3) Diagnosis of moderate to severe CD or UC for at least 6 months prior to Day 1 appointment based on clinical or endoscopic or image criteria (16,17).
4) Subjects who provided the written informed consent.

6.3.2 Exclusion Criteria

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

1) Indeterminate or not classified colitis.
2) Current or previous participation in interventional clinical trials (within the last 3 years).
3) Presenting 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 expected recruitment of study subjects will 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

Non-interventional study – 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** ***Collection data points approximately 3 years***
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	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 behavior	X	
Family history of IBD	X	
Medical history / Comorbidities	X	X
Disease activity: CD (HBI score or CDAI); UC (partial/total Mayo Score)	X	X
Clinical Characterization of Disease: location, behavior, EIM	X	
SF-36	X	

Study variables	Day 1	Retrospective data *Collection data points approximately 3 years*
EQ-5D	X	
IBDQ**	X	
WPAI	X	
Previous treatments or regimens [1]	X	X
Treatment started at Day 1 (if applicable)	X	
Previous surgeries for IBD		X
IBD-related hospitalizations		X
Previous medical appointments related with IBD 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] Excludes new treatments prescribed at Day 1 visit.
** Not applicable for patients who have a colostomy or ileostomy.

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;
- Gender;
- Professional status (employed, unemployed, retired, student, other).

Clinical variables

- IBD type: CD or UC;
- 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);

- Family history of IBD;
- Smoking habits;
- Medical History / Comorbidities (including prior TB and Hepatitis infection);
- Disease presentation [location, behavior, extraintestinal manifestations (EIM)];
- Steroid behavior (dependent, refractory, not applicable);
- 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 (i.e., calprotectin >200ug/g) (yes/no) (qualitative data);

Disease activity (at Day 1)

- For CD patients: Harvey Bradshaw Index (HBI) score or Crohn's Disease Activity Index (CDAI);
- For UC patients: 9-item partial Mayo Score (always collected) and the total Mayo score (when available).

The Harvey Bradshaw Index (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 moderate to severe active disease (22).

The Crohn's Disease Activity Index (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 severity. Moderate to severe active CD is defined as CDAI ≥ 220 (23).

The Mayo score is composed of four categories (bleeding, stool frequency, physician assessment, and endoscopic appearance) rated from 0–3 that are summed to give a total score that ranges from 0–12. The partial Mayo Score (pMayo) was previously compared with the full Mayo score and categorizes patients as being in remission (score of 0–2), having mild disease (pMayo of 3 or 4) or moderate to severe disease (pMayo of ≥5) (24).

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

- 36-item Short Form Health Survey (SF-36)
- 5-dimensional EuroQoL measure (EQ-5D)
- Inflammatory Bowel Disease Questionnaire (IBDQ) - 32 items
- Work Productivity and Activity Impairment Questionnaire (WPAI) – 6 items

The Short Form-36 (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, with higher scores indicating a better quality of life (25). For additional information, please consult

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

EuroQoL questionnaire (EQ-5D-5L) considers five attributes of quality of life evaluation, i.e. mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has five possible levels, 1-no problems, 2 slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems, thus defining a total of 3125 possible health states, each one referred to in terms of a 5 digit code. EQ-5D also include an additional visual analogic scale (EQ-VAS), which ranges from 0, worst imaginable health state, to 100, best imaginable health state (26). For more information, please consult http://www.euroqol.org/.

The Inflammatory Bowel Disease Questionnaire (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. 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 (27). 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.

The Work Productivity and Activity Impairment questionnaire (WPAI) assesses 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 activity impairment. Unemployed patients only answer to questions related to employment status and activity 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 IBD (name, dose);
- Treatment started at Day 1 (name, dose);
- Previous surgeries for IBD.

Other healthcare resources related with IBD management

- Imaging and laboratory testing;
- Surgeries;
- Hospitalizations;
- Consultations.

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.

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 of Takeda Product.
- Occupational exposure.
- Use outside the terms of the marketing authorisation, also known as "off-label".
- Use of falsified medicinal product.

A Product Quality Issue refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, 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, ADR, SSR or product quality issue, where the event/issue pertains to a Takeda product (or unbranded

generic), such information should be reported to the Sponsor. 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 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

Representatives from 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.

9.4 Data Management

Data management will be performed by the appointed CRO which 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 in spite of it being required, data for this subject is not entered into or is deleted from the database.

If a subject is erroneously included in the study more than once only the data relating to the first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e., if collected within the time frame of the first follow-up period.

The current Standard Coding Instructions for coding of medical history, concomitant illness (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.

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.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data. ADR data reported according to section 8 and data on serious AE/ADR reactions collected according to section 8 should be signed off separately by a physician who may or may not be involved in the study.

All data collected for the purpose of this study will be entered, stored and retrieved with the use of an electronic 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 course of 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. Serious and non-serious AE collected according section 8 should be signed off separately, in a specific form, by a study team member previously trained.

10 Statistical Methods and Determination of Sample Size

Statistical analyses will be performed by the designated CRO. 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 Clinical Study Report.

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 - running under Windows 8).

Descriptive analysis will be performed of all collected data except data collected only for the purpose of data cleaning, i.e., all data listed in section 7.

10.1.1 Study Endpoints

The main study endpoints are:

Primary Endpoints:

- For Crohn's Disease: Proportion of patients with active disease (HBI ≥8 or CDAI ≥220 points - based on criteria used by the site) at Day 1.
- For Ulcerative Colitis: Proportion of patients with active disease (9-point partial Mayo score ≥5) at Day 1.

Secondary Endpoints:

- Distribution of age, gender, smoking habits, professional status, family history, educational level, subject income, by IBD type.
- Distribution of clinical variables (steroid behaviour, anthropometric information, medical history and comorbidities, clinical presentation of disease) by IBD type.
- Therapies for IBD (aminosalicylates, steroids, immunomodulators, immunossupressors, biologics, antibiotics, probiotics, surgeries) and the length of these therapies during the previous 3 years.
- Proportion of biologic-experienced patients.
- Proportion of patients who have not responded previously to biologic therapies and reason.
- IBD treatment introduced at Day 1 (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).
- Socio-demographic, clinical and treatment-related variables in patients with moderate to severe activity of UC (partial Mayo score ≥5) versus patients with mild or no activity (partial Mayo <5).
- Mean score of EQ-5D by IBD type.
- Mean score of different components of SF-36 by IBD type.
- Mean total score of IBDQ and by domain (bowel symptoms, systemic symptoms, emotional function and social function).
- Mean total percentage of work impairment (WPAI).
- Mean work time missed (WPAI).
- Mean impairment while working (WPAI).
- Mean total activity impairment (WPAI).
- Proportion of patient who quit their job due to IBD and have not been able to return to work.
- Healthcare resources (previous 3 years) imaging and laboratory testing, surgeries, hospitalizations and consultations.

10.1.2 Statistical analyses overview

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

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, the patients with 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 activity vs non-activity regarding qualitative variables and t-student / Mann-Whitney tests will be used for comparison of quantitative variables. If applicable, logistic regression will be used for evaluating associated variables. All tests will be two-sided 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 Crohn's Disease (CD), the proportion of patients with active disease at Day 1 will be presented as percentage and calculated as:

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

For Ulcerative Colitis (UC), the proportion of patients with active disease at Day 1 will be presented as percentage and calculated as:

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

The 95% confidence intervals will be computed for each estimate.

10.3 Secondary Analyses

The following objectives will be addressed for all IBD patients:

- In order to characterize socio-demographic and clinical aspects of moderate to severe IBD, 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 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, 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 gender, smoking habits, professional status, family history of IBD, steroid behavior (dependent/refractory), previous treatment with biologic therapies, and previous surgery for IBD, 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.

- 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.
- For each IBD disease, descriptive statistics – mean, standard-deviation (SD), median, minimun, maximun – will be used to summarize patients' QoL, overall and according to disease activity
  - The score of EQ-5D analog scale and responses to each item.
    - Utilities will be configured such that 0.0 is associated with being dead and 1.0 is associated with perfect health; thus, a higher utility value is considered better. Mean (SD) utility index will be estimated for CD and UC patients, overall and according to disease activity.
  - The SF-36 uses 36 items to evaluate eight health dimensions:
    - Physical functioning (PF) – Average of Q3a, Q3b, Q3c, Q3d, Q3e, Q3f, Q3g, Q3h, Q3i and Q3j scores;
    - Role Physical (RP) – Average of Q4a, Q4b, Q4c and Q4d scores;
    - Body pain (BP) – Average of Q7 and Q8 scores;
    - General health (GH) – Average of Q1, Q11a, Q11b, Q11c and Q11d scores;
    - Vitality (VT) – Average of Q9a, Q9e, Q9g and Q9i scores;
    - Social Functioning (SF) – Average of Q6 and Q10 scores;
    - Role-Emotional (RE) – Average of Q5a, Q5b and Q5c scores;
    - Mental Health (MH) – Average of Q9b, Q9c, Q9d, Q9f and Q9h scores;
    - Based on SF-36 standardized scores, two summary scores are estimated, the Physical Component Score (PCS) and the Mental Component Score (MCS).
  - The IBDQ score and each of the four IBDQ domains:
    - Bowel systems – Add up scores of questions 01, 05, 09, 13, 17, 20, 22, 24, 26 and 29 and divide by 10;

- Emotional health – Add up scores of questions 03, 07, 11, 15, 19, 21, 23, 25, 27, 30, 31 and 32 and divide by 12;
- Systematic systems – Add up scores of questions 02, 06, 10, 14 and 18 and divide by 5;
- Social function – Add up scores of questions 04, 08, 12, 16 and 28 and divide by 5;

  - The comparison of SF-36 scale scores or component summary scores, EQ-5D 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. The association between each EQ-5D dimension and disease activity will be determined for each IBD type using Chi-Square Test.

- To evaluate the work productivity impairment (WPAI) experienced by moderate to severe IBD patients, the following variables will be estimated and summarized, by CD or UC, overall 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.
  - Mean (SD) total work productivity impairment (TWPI), defined as the mean of subjects total percentage of work impairment associated with IBD that results from both absenteeism and presenteeism, and assessed with specific WPAI for each IBD type. The TWPI due to IBD will be calculated as Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]*100
  - Mean (SD) work time missed due to IBD. The percentage of work time missed due to IBD will be calculated for each subject as Q2/(Q2+Q4)*100
  - Mean (SD) impairment while working due to IBD. The percentage of impairment while working due to IBD will be calculated for each subject as Q5/10*100
  - Mean (SD) total activity impairment due to IBD. The percentage of total activity impairment due to IBD will be calculated for each subject as Q6/10 *100
  - Additionaly, the proportions of patients reporting some absenteeism, some work impairment, and some activity impairment due to IBD will be presented.

- Patients with moderate to severe disease will be compared with patients with no or mild disease regarding WPAI data (percent total work productivity impairment due to IBD, percent work time missed due to IBD, percent impairment while working due to IBD and percent total activity impairment due to IBD) 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 and by disease activity, for the following events: drug therapies, number and type of imaging and laboratory testing, surgeries, number, reason and duration of hospitalizations, number and type of consultations with gastroenterologists or other medical specialists and adverse events.
- Healthcare resource costs: costs will be reported in total and on a *per patient per month* basis. Costs will be obtained by multiplying resource use with relevant unit costs. Unit costs for resource items will be collected in Argentine reliable administrative databases or other sources.
    - UC or CD-related health care costs. Consumer price index (CPI)-adjusted IBD-related health care costs will be computed as total costs, medical costs, drug costs, and other 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.

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 246 patients regardless of IBD type. This sample size will allow estimates with 95% confidence interval and a margin of error less than 5% and assuming a rate of inadequate control of disease of 20% (conservative approach), regardless of IBD type.

The following formula was used:

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

Rate of uncontrolled disease (p) = 20%

Margin of error (ME) = 0.05

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 within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalized.

12 Publications

Takeda aims to have the results of this study published.

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

13 Archiving of Study Documentation

During the course of the study the 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 of time as required by any local regulations and/or hospital requirement.

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