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

NCT Number: NCT02822235

Protocol Approve Date: 19 Apr 2016

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 Brazil

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

Study ID: Vedolizumab_4008

Sponsor: Takeda Pharma Ltda.
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Study phase: Medical Affairs, Non-registration Company Sponsored (Observational)

Date of version of protocol: 19 Apr 2016

Amendment #	Sequence and type of amendment
01	1st Amendment, local, substantial

1 Administrative information

1.1 Contacts

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

Issue	Brazil Contact
Serious adverse event and pregnancy reporting	PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
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	17Oct2016	Cover – Page 1	Corrected the name of the Sponsor.	Information correction.
2	17Oct2016	1.1 Contacts And 4.2 Sponsor Personnel	Updated the name from the Clinical Science / Medical Monitor from Dr PPD Updated the name from the Regulatory Affairs team from PPD	Clarify information to be consistent with the study design.
3	17Oct2016	1.4 Summary - Diagnosis/Disease/ Condition and main criteria for inclusion	Updated information to be consistent with the changes from this amendment in the item 6.3.1 and 6.3.2	Clarify information to be consistent with the changes from this amendment in the item 6.3.1 and 6.3.2
4	17Oct2016	1.4 Summary - Main outcome variables – Secondary Endpoints	Included the data collected from the retrospective phase	Updated information to be consistent with the study design..
5	17Oct2016	6.2 Discussion of Study Design	Updated the Potential confounders according the new amendment terms.	Clarify information to be consistent with the study design.
6	17Oct2016	6.3.1 Inclusion Criteria 6.3.2 Exclusion Criteria	Updated Inclusion Criteria 2 and Exclusion Criteria 5	Clarify the situation when the on label use must be observed for inclusion criteria purpose.
7	17Oct2016	6.3.1 Inclusion Criteria	Updated Inclusion Criteria 3.	Clarify what criteria must be considered to define the moderate to severe disease diagnosis.
8	17Oct2016	6.3.1 Inclusion	Updated Inclusion	To clarify and make

		Criteria	Criteria for Prospective Phase	less restrict the criteria.
9	17Oct2016	6.3.2 Exclusion Criteria	Updated Exclusion Criteria 1.	To clarify the text excluding also “not classified colitis”.
10	17Oct2016	6.3.2 Exclusion Criteria	Updated Inclusion Criteria 2.	To clarify that is related only to interventional trials.
11	17Oct2016	6.3.2 Exclusion Criteria	Exclusion Criteria for Prospective Phase updated to become also exclusion criteria for the Retrospective Phase	To be more consistent with the study design.
12	17Oct2016	6.3.2 Exclusion Criteria	Updated Exclusion Criteria for “Hospitalized Patients”	To clarify that is related for Day 1 only.
13	17Oct2016	7.1 Data Collection Overview	Table updated with information to be collected during the study.	Clarify information to be consistent with the study design.
14	17Oct2016	7.2 Study Variables	Updated information to be consistent with the changes from this amendment in the item 6.3.2.	Clarify information to be consistent with the changes from this amendment in the item 6.3.2.
15	17Oct2016	1.4 Summary - Main outcome variables – Health Economics 7.2 Study Variables 10.1.1 Study Endpoints	Included information about exclusion of the patients who have colostomy or ileostomy from the group to answer IBDQ since this questionnaire is not applicable.	Clarify information to be consistent with the study design.

16	17Oct2016	14. Reference	Added references 31 to 34 to support change in the item 6.3.1.	Added references 31 to 34 to support change in the item 6.3.1.
17	17Oct2016	1.4 Summary – Number of subjects 6.3.4 Enrollment 10.1.2 Statistical Analysis Overview 10.6 Determination of Sample Size	Change the estimated proportion of type of disease from 60%CD/40% UC to 50%CD/50%UC since the original is not supported by the literature in Brasil. The 50% rate for each type of disease will be more reasonable for the study sample size.	Clarify information to be consistent with the study design.
18	17Oct2016	7 Conduct 8 Management and Reporting of Adverse Events	Updated information to be consistent with spontaneous reporting	Updated information to be consistent with spontaneous reporting

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.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good Pharmacoepidemiology practices (GPP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD

1.4 Summary

Short Title of Study

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

Study sites

The study will be conducted in approximately 20 sites in Brazil.

Objectives

Knowledge regarding the control of disease activity in Inflammatory Bowel Disease (IBD) is limited in Brazil. Therefore, it is pertinent to gather information regarding the population with moderate to severe IBD, the burden of the disease, and understand their treatment patterns, particularly on the use of available biologic therapies.

Primary Objective:

- To evaluate the disease activity in moderate to severe IBD patients [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 in the previous 3 years, 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.
- For patients with active IBD at study appointment (Day 1):
    a) To assess clinical activity after 12 months of follow up.
    b) To describe physician's drivers for therapeutic decision during the 12-month follow up period.
- 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 health resources related with the management of IBD in the previous 3 years.
- To estimate UC or CD-related health care costs in data from the previous 3 years.

Methodology

This is a multicentre, non-interventional study to determine the rate of control of disease activity. At each site, eligible subjects will be identified consecutively as they attend scheduled clinical appointment (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 Patient Report Outcome 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), and use of other health resources related with the management of IBD.

For patients with active disease at Day 1, a prospective period of 12 months will be conducted to follow up the course of the disease. Ulcerative colitis (UC) patients with no or mild disease activity at Day 1 will not continue to 12-month follow up. Crohn's Disease (CD) patients with no or mild disease activity at Day 1 but with colonoscopy or calprotectin levels (i.e, calprotectin >200ug/g) in the previous year suggestive of inadequate control of activity will progress to 12-month follow up.

Number of subjects

It is expected to include approximately 400 patients regardless of IBD type. This sample size will allow estimates with 95% confidence interval and a margin of error less than 5%.

Based on the above and considering an expected ratio of CD/UC of approximately 50%/50%, and that the rate of inadequate control of disease activity varies from 20-30% (regardless of the IBD type), it is expected to analyse 40-60 patients with CD and 30-50 patients with UC during the 12-month follow up.

Diagnosis/Disease/Condition and main criteria for inclusion

Subjects must meet all of the following inclusion criteria: 1) male or female subjects, 2) aged 18 years or older (at the time of diagnosis of moderate to severe UC or CD), 3) with diagnosis of moderate to severe CD or UC for at least 6 months prior to Day 1 appointment according the clinical or endoscopic criteria [23, 24, 25, 26, 27], 4) who provided the written

informed consent.Patients will be excluded if (1)presenting indeterminate or not classified colitis, or (2) having current or previous participation in interventional clinical trials (within the last 3 years), or (3) presenting mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation, or (4) hospitalized patients at Day 1, or (5) in current off label treatment with Vedolizumab.

Duration of data collection per subject

Cross-sectional at Day 1, with retrospective data collection over the previous 3 years. For patients enrolled in the prospective phase, information will be collected at all clinical appointments occurring within 12 months.

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 (e.g.: type of IBD, steroid behavior, anthropometric information, medical history and comorbidities, clinical characterization of disease) by IBD type.
- Therapies for IBD (aminosalicylates, steroids, immunomodulators, immunosupressors biologics, antibiotics, probiotics, surgeries) within 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.
- 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).
- Among patients who had moderately to severely active CD at Day 1: HBI or CDAI score after 12 months.
- Among patients who had moderately to severely active UC at Day 1: Partial Mayo score after 12 months.
- Among patients who had moderately to severely active CD or UC at Day 1: Treatment after 12 months; In case of change of current treatment: reason for change.

Health economics:

- 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 of subjects total percentage of work impairment (WPAI).
- Mean work time missed (WPAI).
- Mean impairment while working (WPAI).
- Mean total activity impairment (WPAI).
- Health resources (previous 3 years): drug therapies, imaging and laboratory testing, surgeries, hospitalizations, and consultations.

Statistical methods

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.

Data will be summarized by IBD type (Crohn's Disease and Ulcerative Colitis).

Cross-sectional analysis - For each IBD type, the patients with disease activity will be compared with patients with no or mild activity regarding socio-demographic and clinical variables of interest. Chi-square/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 quantitative variables comparisons. The cross-sectional analysis will be conducted once all patients have completed the Day 1 assessment (expected to occur 6 months after start of enrolment).

Longitudinal analysis - The proportion of controlled patients will be presented as well as the 95%CI at the 12-month follow up assessment. If applicable, logistic regression will be used for calculating odd ratios and 95% confidence intervals for the patient control at month 12 determined by independent numerical/categorical variables. All tests will be two-sided considering a significance level of 5%. Utility scores will be calculated from EQ-5D and SF-36. The longitudinal analysis will be performed once all the concerned patients complete the 12-month follow up.

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 Organisation
CV:	Curriculum Vitae
DSO:	Drug Safety Officer
eCRF:	electronic Case Report Form
EDC:	Eletronic Data Capture
EIM:	Extraintestinal Manifestations
EQ-5D:	5-dimensional EuroQoL measure
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
HBI:	Harvey Bradshaw Index
IBD:	Inflammatory Bowel Disease
IBDQ:	Inflammatory Bowel Disease Questionnaire
ICH:	International Conference on Harmonisation
IDS:	International Drug Safety
IEC:	Independent Ethics Committee
MCS:	Mental Component Summary
PCS:	Physical Component Summary
pMayo:	partial Mayo score
PRO:	Patient Reported Outcomes
PSUR:	Periodic Safety Update Report
QA:	Quality Assurance
QoL:	Quality of Life

SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
SDV:	Source Data Verification
SF-36:	36-item Short Form health Survey
SPC:	Summary of Product Characteristics
UC:	Ulcerative Colitis
VAS:	Visual Analog Scale
WPAI:	Work Productivity and Activity Imparment 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).

With episodes of relapse and remission, IBD presents relevant health and economic burden (4,5). In fact, IBD impact on patient quality of life is particularly relevant since it affects mainly young individuals, may present severe symptoms and disease flares are unpredictable (6). Alongside with loss of patient's QoL, symptoms may also impact work productivity and increase the economic burden of these diseases (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; IBD prevalence is estimated to reach up to 396 per 10^5 people (8). The incidence of inflammatory bowel disease (IBD) has been increasing in several world regions, namely in developing countries (9,10).

In Brazil, epidemiologic and cost of illness information about IBD is scarce. Increased frequencies of outpatient visits and hospitalizations in the major urban centers of Brazil have been observed (11, 12,13). A retrospective hospital study in Piauí (North-eastern Brazil) with 252 IBD patients, observed that 152 (60.3%) were UC patients and 100 (39.7%) CD patients (14). More recently, a cross-sectional study in two IBD treatment referral centers in Bahia (North-eastern Brazil) has described demographic and clinical characteristics of 267 patients with UC, being observed that extensive colitis was positively associated with male gender, diarrhea, weight loss, and a younger age at diagnosis (15). And there are no studies describing the health care resources and costs of IBD in Brazil.

Treatment of IBD remains challenging, with several strategies available (1,11). In Brazil, treatment options include salicylic derivatives [namely, sulfasalazine and mesalazine (5-ASA)], corticosteroids, immunosuppressors (azathioprine, 6-mercaptourine, methotrexate, cyclosporine), and biological therapy (infliximab, adalimumab and, more recently, vedolizumab) (12,13,14).

Corticosteroids (oral prednisolone 0.75-1mg/kg/day) are indicated to induce clinical remission in patients with active UC or CD of mild and moderate intensity. Clinical remission is achieved in 70%-90% of cases after 4-6 weeks of treatment but endoscopic and histologic remission are only achieved in approximately 30% of cases. In addition, corticosteroid-resistant and corticosteroid-dependent CD cases ranges from 8%-20% and from 15%-36%, respectively. In UC, reported frequencies of corticosteroid-resistance and dependence were 29% and <10%, respectively (12).

Regarding maintenance treatment, corticosteroids are not indicated due to side effects. Sulphasalazine and 5-ASA are recommended in the maintenance of remission of UC (11, 12). Immunosuppressors are effective in maintaining remission in CD and UC and while promoting corticosteroid withdrawal in corticosteroid-dependent patients (12). However, methotrexate is nowadays a second-line immunosupressor for patients resistant or intolerant to azathioprine or 6-mercaptourine, and cyclosporine seems to have no therapeutic value in treatment of CD (11).

Biological therapy has been increasingly used, namely for moderate to severe IBD or when there is no response to conventional treatments (12). In fact, infliximab (11,15), adalimumab (16,17) and vedolizumab (13,14) have shown to be effective in induction and maintenance of clinical remission of UC and CD. Side effects usually occur in less than 10% of cases, and it has been described that biological therapy can promote endoscopic and histologic improvement (12). Biologics have also the potential to improve QoL in IBD patients (18).

In face of IBD complexity and heterogeneity, treatment decision should consider the activity and severity level, the extension of inflammatory process and corticoid dependency (12). Furthermore, if the first-line immunosuppressive maintenance therapy fails, several other factors should be taken into account, including patient's wishes, fecundity and patient age (11).

2.1 Study Rationale

No studies have been conducted in Brazil 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, the burden of the disease, and understand their treatment patterns, particularly on the use of available biologic therapies.

3 Study Objective(s)

Primary Objective:

- To evaluate the disease activity in moderate to severe IBD patients (active CD defined as HBI ≥ 8 or CDAI ≥ 220 points at Day 1; active UC defined as 9-point partial Mayo score ≥5 at Day 1).

Secondary Objectives:

- To characterize socio-demographic and clinical aspects of moderate to severe IBD;
- To characterize treatment patterns for IBD in the previous 3 years, 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 at Day 1, regarding socio-demographic and clinical variables of interest and treatment patterns;
- For patients with active IBD at study appointment (Day 1):
    a) To assess clinical activity after 12 months of follow up;
    b) To describe physician's drivers for therapeutic decision during the 12-month follow up period;
- 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 health resources related with the management of IBD in the previous 3 years.
- To estimate UC or CD-related health care costs in data from the previous 3 years.

4 Study Administrative Structure

4.1 Study Sites

The study is planned to be conducted in approximately 20 sites in Brazil.

The selected sites are public and private institutions in Brazil recognized by their large experience in the IBD management, and that follow IBD patients in ambulatory care.

Global Research will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

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
	Clinical Science Lead
	Clinical Science
	LATAM Area Medical Head & Scientific Affairs Director - Brazil
	Regulatory Affairs Director Brazil & LATAM
	Regulatory Affairs Manager
	Pharmacovigilance Manager
	Pharmacovigilance Analyst
	Pharmacovigilance Analyst

4.3 Contract Research Organisation (CRO)

The CRO (CCI [redacted]) 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 Global Research before the study is initiated at a site:

- Written agreement between Takeda or 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 (ie, 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 Brazilian 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 Site Study 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, eg, Patient Report Outcome tools.

The appointed CRO or the Site Study 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.

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

Authorities

Global Research or the appointed Contract Research Organization (CRO) will send required documents to the competent authority (CA) and/or other national or regional authorities. Global Research 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 Site Study Responsible must give the subject (and if applicable, parent or legal guardian) oral and written information about the study in a form that the subject 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 it is stated that if consent is withdrawn, any data collected before withdrawal of consent will be kept. The original, signed Informed Consent Forms must be kept on the Site.

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

6 Study Design and Plan

This study is a 'non-interventional study' as defined in: G-STND-PV-006, G-SOP-MA-005, Directive 2001/20/EC (22) and will follow the guidelines for GPP (21).

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 multicentre, non-interventional study to determine the rate of control of disease activity. (Figure 1).

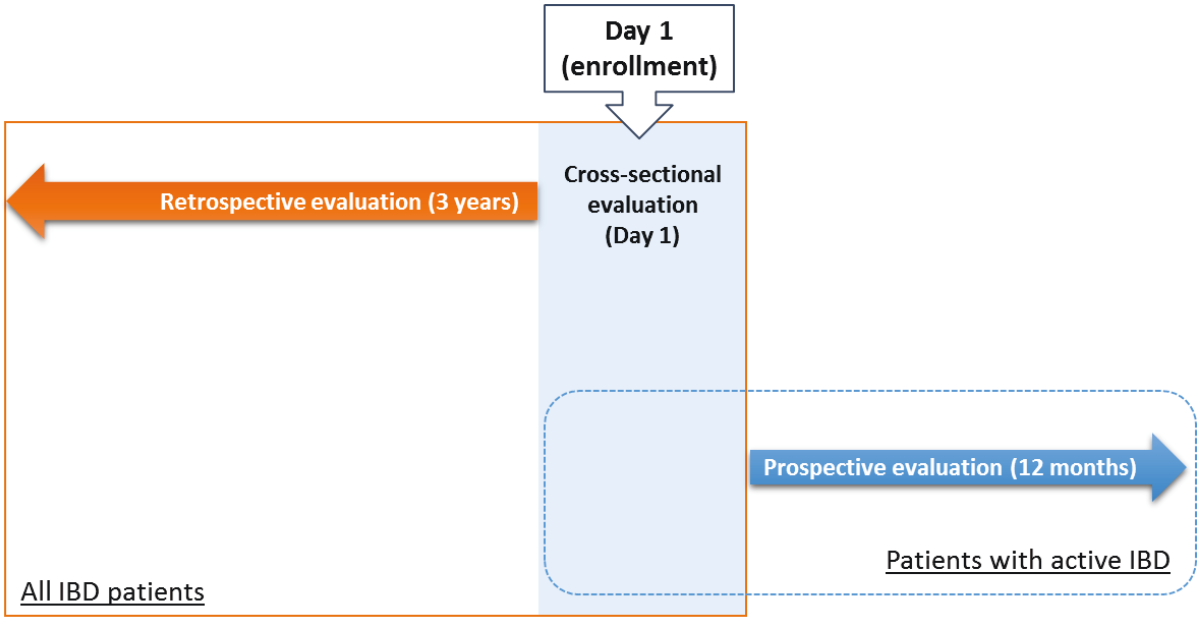

Figure 1. Study design scheme

During study appointment (Day1) data regarding disease activity, treatment patterns, burden of disease and quality of life will be collected (Figure 1). For patients with active disease at Day 1, a 12-month prospective evaluation will be conducted that will allow to follow the course of the disease.

At each site, eligible subjects will be identified consecutively as they attend scheduled clinical appointment (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 health resources related with the management of IBD.

UC patients with no or mild disease activity at Day 1 will not continue to 12-month follow up. CD patients with no or mild disease activity at Day 1 but with colonoscopy or calprotectin levels in the previous year suggestive of inadequate control of activity will progress to 12-month follow up.

6.1 Study Schedule

Planned Start of Study:	April 2016
Planned collection of first data point:	October 2016
Planned End of Study:	April 2018
Planned completion of the Study Report:	August 2018

This study will have duration of 6 months for the cross-sectional phase, with an additional follow-up of 12 months for the patients included in the prospective phase.

The Start of Study is defined as date of last protocol signature and planned to occur on April 2016. The collection of first data point (*first patient in*) will start during October 2016. The recruitment period is expected to last up to 6 months. The End-of-Study is defined as the date when the last subject completed follow-up period.

Takeda Brasil 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.

Global Research will ensure that results are posted on “clinicaltrials.gov” and as required by local authorities.

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 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. Furthermore, the inclusion of a prospective follow-up for patients with active disease will enable an insight on how active CD or UC are managed in Brazil and what are the factors associated to achieving disease control.

In terms of external validity, two major points should be considered. First, the 20 study sites will be selected among reference public and private institutions for IBD management. It is expected that their patients will be representative of patients with moderate to severe IBD in Brazil. In addition, the inclusion and exclusion criteria are not restrictive and will enable the assessment of real-world data about IBD control in Brazil. 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 and prospective evaluations. 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.

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 6 months. Disease control may be underestimated due to selection bias, since patients with active IBD are expected to have more medical appointments and may be more easily invited. Nevertheless, the 6-month period will also enable the inclusion of patients with no or mild active disease.

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;
2) Subjects aged 18 years or older (at the time of diagnosis of moderate to severe UC or CD);
3) Diagnosis of moderate to severe CD or UC for at least 6 months prior to Day 1 appointment according the clinical or endoscopic criteria (23, 24, 25, 26, 27);
4) Subjects who provided the written informed consent.

In addition, for the prospective period, eligible patients should present at least one of the following criteria that will only be applied at Day 1:

- For CD patients:
    - HBI ≥ 8 or
    - CDAI ≥ 220 or

Considering that for CD patients, the disease activity may not be clearly documented only with clinical data, some objective criteria may be considered as entry criteria for the 12-month prospective period:

- colonoscopy in the previous year suggestive of inadequate control of activity or
- calprotectin levels in the previous year suggestive of inadequate control of activity (i.e, calprotectin >200ug/g) (28).

For UC: partial Mayo Score ≥5

***Note 1*:** UC patients with no or mild disease activity at Day 1 will not continue to follow up. CD patient with no or mild disease activity at Day 1 but with colonoscopy or calprotectin levels (i.e, calprotectin >200ug/g) in the previous year suggestive of inadequate control of activity will progress to 12-month follow up.

Patients that fulfill the above criteria (active disease) will be followed for 12 months, in order to explore patterns of care.

Note 2: Patients with colostomy and prospective period:

Although clinical scales defined above are impacted by colostomy these patients will not be excluded from the protocol to ensure the assessment of different clinical presentations of the IBD. In addition, patients with colostomy must follow the same criteria as above to be eligible to the prospective phase.

Note 3: Patients who are eligible for the prospective period, it means, with active disease at Day 1 but who during the 12 months period presents disease remission and/or no activity disease condition, mustcontinue in the study.

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.

4) Hospitalized patients at Day 1.
5) Current off label treatment with Vedolizumab.

6.3.3 Study Discontinuation Criteria

It will be considered a premature termination the situation in which the subject discontinues the participation, i.e. they are withdrawn from the study before completing the 12 months of follow up period (365 days ± 14 days from Day 1), due to any of the reasons listed below:

1. Withdrawal of consent: subjects who for any reason withdraw the free and informed consent;
2. Lost to follow-up (no return of the subject on the expected date of visit - drop-out from the protocol);
3. Death;
4. Study termination;
5. Any situation that places the subject within one of the exclusion criteria.

Note: Patients who are eligible for the prospective period, it means, with active disease at Day 1 but who during the 12 months period presents disease remission and/or no activity disease condition, are allowed to continue the participation in the study.

6.3.4 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.

After 2 and 4 months of enrolment, the overall proportion of patients with CD and UC will be reviewed. In case the expected ratio of IBDs (50%CD/50%UC) is not attained at 2 and 4 months of enrolment, the participating sites will be instructed to change future enrolments so

that this balance is achieved and that at least 30 UC patients and 30 CD patients with active disease enter the prospective follow-up.

6.4 Treatments

Non-interventional study – no treatments/pharmacotherapy are pre-defined in the protocol. All clinical decisions will be fully responsibility of the investigator.

7 Conduct

7.1 Data collection overview

Table 1. Study Flow Chart

Study variables	**Day 1**	**Prospective period* *(approx. 12 months)* *Collection data points***			
Timing of data collection	Day 1 visit	3-months (90 days ± 14 days)	6-months (180 days ± 14 days)	. 9-months (270 days ± 14 days)	End of fw-up (12 months) (365 days ± 14 days)
Informed consent	X				
Inclusion criteria	X				
Exclusion criteria	X				
Anthropometric Information (Weight, Height, BMI)	X				
IBD type (CD or UC)	X				
Socio-demographic variables	X				
Smoking habits	X				
Family history of IBD	X				
Medical history / Comorbidities	X				
Date of diagnosis of CD or UC	X				
Date of diagnosis of moderate to severe CD or UC	X				
Clinical Characterization of Disease – (location, behavior, EIM)	X				
Steroid behavior	X				
Disease activity: CD (HBI score or CDAI); UC (partial/total Mayo Score)	X				X
Eligibility for 12-month follow up	X				
SF-36	X				
EQ-5D	X				
IBDQ**	X				
WPAI	X				
Previous treatments or regimens [1, 2]	X				
Treatment started at Day 1	X				
Treatment at follow-up		X	X	X	X
Previous surgeries for IBD	X [2]				
Hospitalizations	X [2]				
Consumption of health resources related with IBD management	X [2]				
Previous imaging and laboratory testing form	X [2]				

[1] Excludes new treatments prescribed at Day 1 visit. [2] Retrospective data collection (approx. 3 years)

* Prospective follow-up only for patients with active IBD at Day 1. In this period, data collection is expected to occur quarterly for all registered medical appointments.

** 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;
- 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;
- Disease presentation [location, behavior, extraintestinal manifestations (EIM)];
- Steroid behavior (dependent or refractory);
- Colonoscopy in the previous year suggestive of inadequate control of activity (yes/no) (qualitative data/Mayo subscore);
- Calprotectin levels in the previous year suggestive of inadequate control of activity (i.e., calprotectin >200ug/g) (yes/no) (qualitative data);
- Eligibility for 12-month prospective follow up (yes/no).

Disease activity (at Day 1 and 12 months follow up appointment)

- 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 (29).

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 (30).

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) (31).

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 (32).

For more 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 (33). 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 quality of life (34). A Portuguese (Brazil) version was already validated (35). 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;
- Treatment started at Day 1 (name, dose);
- Previous surgeries for IBD.

At follow up appointment only:

- Therapeutic strategy: maintain current treatment vs discontinued;
- If discontinued, new treatment (name, dose, start date), and reason for discontinuation.

Other health care resources related with IBD management

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

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 reaction is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

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: There is a reasonable possibility that the drug caused the event. There is a reasonable temporal relationship between the drug administration and the event, and no other obvious alternative explanation for the occurrence of the event.

Not related: There is not a reasonable possibility that the drug caused the event. There is evidence for (an) alternative explanation(s) for the event (eg, the event is explained by one or more of the following: a) the subject's medical condition (medical history, disease progress, indication), b) a concomitant medication for which the event is labelled, or c) AE occurrence prior to the introduction of the medicinal product.

The investigator must make an assessment of causality using the above definition. Causality cannot be assumed in the absence of the investigator's assessment.

8.2 Collection and Recording of Adverse Events

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

If during the conduct of the study a member of the research team is spontaneously informed of an AE, ADR, SSR, beneficial event or product quality issue, where the event/issue pertains to a Takeda/ Multilab product (or unbranded generic which active principle is also manufactured by Multilab), such information should be reported to the Sponsor within 24 hours of Investigator´s team awareness, including the Investigator itself. The investigator should assess the causality for the adverse events and the causality should not be assumed if there is no investigator's assessment.

<u>Follow-up information</u>

After notification of the initial AE Report form, the Investigator may be contacted by the Sponsor to obtain additional information on the event or for data clarification. The investigator shall make best effort to obtain the requested additional information. All new additional information obtained on the event should be recorded on an AE Report form and notified to the Sponsor within 24 hours of Investigator awareness of the new information.

8.3 Reporting of Adverse Reactions

The Sponsor is responsible for submission of adverse reactions to regulatory authorities in accordance with local reporting requirements or the Sponsor's post marketing commitments, with the exception of Individual Case Safety Reports s not collected as part of the study and reported spontaneously by investigator or study participant to national competent authorities as in 12.2 above.

8.4 Other Safety Information

If the investigator becomes aware of any of the following events associated with a Takeda product during the study, whether or not associated with an AE, the event should be recorded on an AE Report form /Pregnancy Report form and submitted to the Sponsor within 24 hours of investigator awareness.

- **Use during pregnancy**
- **Overdose:** This refers to the administration of a quantity of a drug given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.
- **Off-label use:** This relates to situations where the drug is intentionally used for a medical purpose not in accordance with the authorised product information.
- **Misuse:** This refers to situations where the drug is intentionally and inappropriately used not in accordance with the authorised product information.
- **Abuse:** This corresponds to the persistent or sporadic, intentional excessive use of a drug, which is accompanied by harmful physical or psychological effects.

- **Medication error:** This refers to any unintentional error in the prescribing, dispensing, or administration of a drug while in the control of the healthcare professional or patient.
- **Accidental occupational exposure:** This refers to exposure to a drug, as a result of one's professional or non-professional occupation.

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 (SDV) will include the check of the Signed Informed Consent for all subjects. Source documents (e.g., medical records, original laboratory records) and Signed Informed Consent should be available to study monitors whenever possible, and consent to such access will be explicitly included in the Informed Consent Form.

Additional details will be specified in the Monitoring Plan.

9.2 Audit from Quality Assurance Unit

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

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 designated CRO, CCI Data Management will be carried out according to a Data Management Plan, which must be written and

approved before the design of the study database is 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 CCI and concomitant medication PPD 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 7 should be signed off separately by a physician who may or may not be involved in the study.

Data collection will be implemented by means of a study-specific eCRF. 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 EDC system database for site resolution and closed by the sponsor reviewer.

CCI will also be responsible for study's follow up, including regular contacts with investigators and in-house monitoring (review of data collected and support on queries resolution). 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.

10 Statistical Methods and Determination of Sample Size

Statistical analyses will be performed by the designated CRO, CCI 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:

<u>Primary Endpoints:</u>

- 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.

<u>Secondary Endpoints:</u>

- Distribution of age, gender, smoking habits, professional status by IBD type.
- Distribution of clinical variables by IBD type.

- Therapies for IBD (aminosalicylates, steroids, immunomodulators, immunossupressors, biologics, antibiotics, probiotics, surgeries) within 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.
- 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 light 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 light or no activity (partial Mayo <5).
- Among patients who had moderately to severely active CD at Day 1: HBI or CDAI score after 12 months.
- Among patients who had moderately to severely active UC at Day 1: Partial Mayo score after 12 months.
- Among patients who had moderately to severely active CD or UC at Day 1: Treatment after 12 months; in case of change of current treatment: reason for change
- 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). The IBDQ is not validated for patients with ostomies and therefore should not be applied for these patients.
- Mean of subjects total percentage of work impairment (WPAI).
- Mean work time missed (WPAI).
- Mean impairment while working (WPAI).
- Mean total activity impairment (WPAI).
- Health resources (previous 3 years) imaging and laboratory testing, surgeries, hospitalizations, consultations and adverse events.

10.1.2 Statistical analyses overview

Descriptive statistics will be calculated for all variables, including mean, median, standard deviation and range for numerical variables and absolute and relative frequencies for categorical variables. Whenever relevant, 95% confidence intervals (CI) will be computed. For each study endpoint, data will be summarized by IBD type (CD and UC).

Cross-sectional analysis

The cross-sectional analysis will be conducted once all patients have completed the Day 1 assessment (expected to occur 6 months after start of enrolment).

This analysis will allow a characterization of the study population, the estimation of primary endpoints and to compare the subgroup of patients with no or light 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 no or light 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%.

Longitudinal analysis

The longitudinal analysis will be performed once all the patients that were included in the prospective period have completed the 12-month follow up.

The proportion of controlled patients will be presented as well as the 95%CI at the 12-month follow up assessment. If applicable, logistic regression will be used for calculating odd ratios and 95% confidence intervals for the patient control at month 12 determined by independent variables. All tests will be two-sided considering a significance level of 5%.

In case the expected ratio of IBDs (50%CD/50%UC) is not attained at 2 and 4 months of enrolment, the participating sites will be instructed to change future enrolments so that this balance is achieved and that at least 30 UC patients and 30 CD patients with active disease enter the prospective follow-up.

For details of the statistical analyses please refer to the Statistical Analysis Plan.

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:

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

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

At the cross-sectional analysis, 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 no or light 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 no or light 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' quality of life, 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 (raw score) - sum of Q3a, Q3b, Q3c, Q3d, Q3e, Q3f, Q3g, Q3h, Q3i, Q3J
    - Role Physical (raw score) - sum of Q4a, Q4b, Q4c, Q4d
    - Body Pain (raw score) - sum of Q7,Q8
    - General Health (raw score) - sum of Q1, Q11a, Q11b, Q11c, Q11d
    - Vitality (raw score) - sum of Q9a, Q9e, Q9g, Q9i
    - Social Functioning (raw score) - sum of Q6, Q10
    - Role-Emotional (raw score) - sum of Q5a, Q5b, Q5c
    - Mental Health (raw score) - sum of Q9b,Q9c,Q9d,Q9f,Q9h
    - Based on SF-36 standardized scores, two summary scores are estimated, the Physical Component Score and the Mental Component Score
  - The IBDQ score and each of the four IBDQ domains:
    - 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.
- 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.
- Health 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.
- Health Care 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 by in Brazilian 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.

For patients with active IBD at study appointment (Day 1), and included in the prospective period, the following analysis will be conducted:

- Descriptive statistics will be presented in a summary table, for the main socio-demographics, clinical characteristics and treatment regimen of the included patients at Day 1 (baseline), by IBD disease.
- The proportion of patients with active CD after 12 months among patients who had moderately to severely active CD at Day 1 (baseline) will be expressed as percentage and determined as

$$\frac{CD\ patients\ with\ HBI \geq 8\ or\ CDAI > 220\ after\ 12\ months}{Total\ CD\ patients\ with\ HBI \geq 8\ or\ CDAI > 220\ at\ Day\ 1}\ x\ 100$$

- Similarly, the proportion of patients with active UC after 12 months among those who had moderately to severely active UC at Day 1 (baseline) will be expressed as percentage and determined as:

$$\frac{UC\ patients\ with\ partial\ Mayo\ score\ \geq 5\ after\ 12\ months}{Total\ UC\ patients\ with\ partial\ Mayo\ score\ \geq 5\ at\ Day\ 1}\ x\ 100$$

- Patients that had light or no activity of disease at the end of the 12-month follow-up will be compared with patients that remained with active disease, regarding socio-demographic, clinical and treatment variables of interest. Similarly to the cross-sectional analysis, the comparison of categorical variables will be conducted with Chi-square or Fisher exact tests and t-student or Mann-Whitney tests will be used to compare quantitative variables.
- If applicable, variables associated with having light or no activity 12 months after baseline will be identified through logistic regression models for each IBD disease and OR (95%CI) will be presented.

- In addition, survival analysis with Kaplan Meier curves and Cox regression models will be used (if applicable) to identify factors associated with achieving light or no activity with baseline treatment (continued or initiated at baseline), during follow-up. In this analysis, patients that remained with active disease or that change treatment due to lack of disease control will be censored and, conversely, success will be defined as having light or no active disease. Time to success will be considered as dependent variable in survival analysis methods.
- The number and reason for treatment changes during follow-up will be summarized and treatment patterns during prospective period will also be described. Patients with treatment changes will be compared with those without changes, regarding main socio-demographic, clinical and treatment baseline variables. The comparison of categorical variables will be conducted with Chi-square or Fisher exact tests and t-student or Mann-Whitney tests will be used to compare quantitative variables.
- If aplicable, Poisson regression models based on generalized linear equations will be used to examine the relationship between variables of interest and the incidence of the treatment changes during follow-up.

10.4 Interim Analyses

No interim analyses are planned for this study. The planned analyses will be conducted in two moments, at the end of the cross-sectional study and at the end of the 12-month follow-up period.

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 approximately 400 patients regardless of IBD type. This sample size will allow estimates with 95% confidence interval and a margin of error less than 5%.
Based on the above and considering an expected ratio of CD/UC of approximately 50%/50%, and that the rate of inadequate control of disease activity varies from 20-30% (regardless of the IBD type), it is expected to analyze 40-60 patients with CD and 30-50 patients with UC during the 12-month follow up.

11 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point, 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 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 Site Responsible must as a minimum store the list of participating subjects and the signed Informed Consent Forms on site for 5 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

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