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

SAP Approve Date: 30 January 2018

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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).

Statistical Analysis Plan

Version No. 3

30 January 2018

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TITLE PAGE

Study 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 code:	Vedolizumab_4008
Study type:	Observational
Studied Disease:	Inflammatory Bowel Disease (Crohn Disease and Ulcerative Colitis)
Sponsor:	Takeda Pharma Ltda.
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Statistical analysis plan performed by:	CCI [redacted]

SIGNATURE PAGE

STUDY 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)

PROTOCOL VERSION: Amendment 1

PROTOCOL DATE: October 17, 2016

PPD

VERSION CONTROL

Version No.	Version Date	Author	Changes from Previous Approved Versions
0.1	03MAY2017	PPD	Not Applicable (First Version)
0.2	24OCT2017		• Signature page: the sponsor responsible for SAP approval changed • Inclusion of the section 9. DISCREPANCY IN RETROSPECTIVE DATA AFTER DATABASE LOCK
0.3	30JAN2018		• Inclusion of the item 7) in the section 8. PROTOCOL CLARIFICATIONS/AMENDMENTS clarifying that in the longitudinal analysis a sensitivity analysis will be performed to determine the proportion of patients with active IBD after 12 months considering the activity disease assessment in a time window of 1 month

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
CD	Crohn Disease
CDAI	Crohn's Disease Activity Index
CPI	Consumer Price Index
CRF	Case Report Form
EQ-5D	EuroQol-5D
HBI	Harvey Bradshaw Index
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IRR	Incidence Rate Ratio
MS	Minimum Salary
OR	Odds Ratio
QoL	Quality of Life
SAP	Statistical Analysis Plan
SF-36	Short Form-36
UC	Ulcerative colitis
VAS	Visual Analog Scale
WPAI	Work Productivity and Activity Impairment Questionnaire

1 RATIONALE

This Statistical Analysis Plan (SAP) was written for Biostatistics and intends to provide guidelines from which the analysis will proceed, create a common and clear understanding of the planned analysis by all involved. This SAP was prepared by the biostatistician who will be further responsible (if possible) for the statistical analysis of the study data.

This SAP, in particular table shells and examples of figures/graphs, was reviewed and approved by the Sponsor's Representative previously to database locking and performance of the statistical analysis.

Any changes to the planned statistical methodology/definitions described on this SAP during the statistical analysis of the study data will be documented in the Statistical Report.

This document was written in accordance with the information contained in the Amendment 1 of Study Protocol Vedolizumab_4008 of October 17, 2016 and CRF version 3.0, 11OCT2016.

This version of the SAP is an amendment of the SAP approved on May 03, 2017.

2 LITERATURE REVIEW

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 0.5-24.5/105 inhabitants, while CD incidence varies between 0.1-16/105 inhabitants worldwide; IBD prevalence is estimated to reach up to 396 per 105 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 (5ASA)], corticosteroids, immunosuppressors (azathioprine, 6-mercaptourine, methotrexate, cyclosporine), and biologic treatment options (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).

3 STUDY OBJECTIVES

3.1 Primary objective

The **main objective** of this multicenter, non-interventional study is to evaluate disease activity in moderate to severe inflammatory bowel disease (IBD) patients [active Crohn's disease (CD) defined as the Harvey Bradshaw Index (HBI) score ≥ 8 or Crohn's Disease Activity Index (CDAI) ≥ 220 points at Day 1; active Ulcerative colitis (UC) defined as 9-point partial Mayo score ≥ 5 at Day 1].

3.2 Secondary objectives

The **secondary objectives** of the study include:

- Characterization of socio-demographic and clinical aspects of moderate to severe IBD;
- Characterization of treatment patterns for IBD in the previous 3 years, including the use of biologic therapies and failure to these therapies (if any);
- For each type of IBD: comparison of patients with moderate to severe disease activity with patients with no or mild disease activity, regarding socio-demographic and clinical variables of interest and treatment patterns;
- For patients with active IBD in the study appointment (Day 1):
    - Assess clinical activity after a 12 months of follow-up;
    - Description of physician's drivers for therapeutic decision during the 12-month follow up period;
- Evaluation of the quality of life (SF-36, EQ-5D and IBDQ) in moderate to severe IBD patients;
- Evaluation of the work productivity impairment (WPAI) experienced by moderate to severe IBD patients;
- Description of the use of health resources related with the management of IBD in the previous 3 years;
- Estimation of UC or CD-related health care costs in data from the previous 3 years.

3.3 Study Design

This is a multicenter, non-interventional study designed to evaluate disease control, treatment patterns, burden of disease and health related quality of life among patients with IBD.
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. 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.

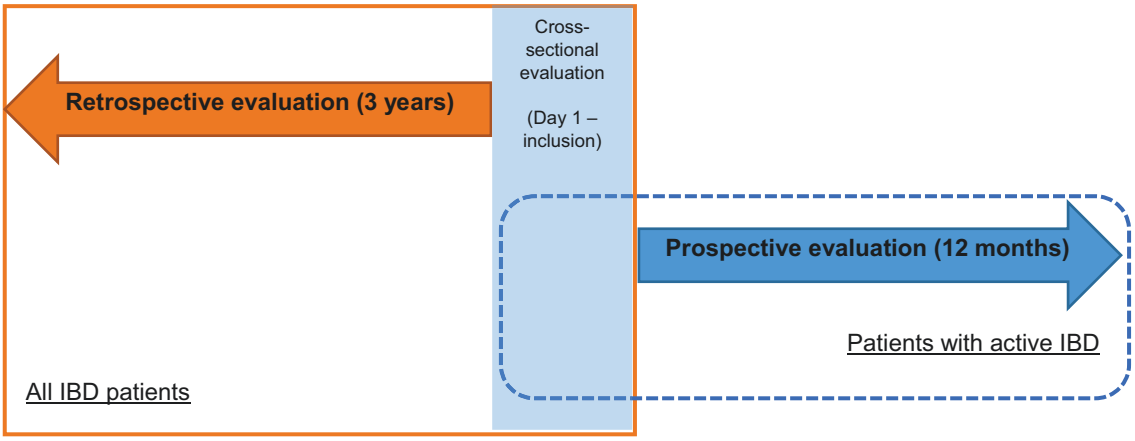


Figure 1 – Study Scheme.

4 STUDY POPULATION

Study population will include male or female patients aged 18 or older, diagnosed with CD or UC, who comply with all of the inclusion criteria and do not present any of the exclusion criteria.

4.1 Inclusion criteria

To be eligible to the subjects must meet all of the following 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 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 points;
  - CDAI ≥ 220 points 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 >200µg/g)

- For UC patients: partial Mayo score ≥ 5 points.

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, must continue in the study

4.2 Exclusion Criteria

Any subject that meets at least one or more of the following criteria is not eligible for the study:

1. Indeterminate colitis or not classified colitis;
2. Current or previous participation in interventional clinical trial (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.

4.3 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.

5 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints of the study are:

- For CD: Proportion of patients with active disease (HBI ≥ 8 or CDAI ≥ 220 points – based on the criteria used by the site) at Day 1;
- For UC: Proportion of patients with active disease (9-point partial Mayo score ≥ 5 points) at Day 1.

5.2 Secondary Endpoints

The secondary endpoints of the study are:

- Distribution of the age, gender, smoking habits, professional status, family history, educational level, subject income by IBD type;
- Distributions of clinical features (e.g.: type of IBD, steroid behavior, anthropometric information, medical history and comorbidities, clinical characterization of the disease) by IBD type;
- Therapies for IBD (aminosalicylates, steroids, immunomodulators, immunosuppressants, biologic products, antibiotics, probiotics, surgery) 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 CD (HBI ≥ 8 or CDAI ≥ 220 points) versus participants with no or mild activity (HBI < 8 or CDAI < 220 points);
- Socio-demographic, clinical and treatment-related variables in participants with moderate to severe activity of UC (partial Mayo score ≥ 5 points) versus participants with no or mild activity (partial Mayo score < 5 points);
- 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. 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): drug therapies, imaging and laboratory testing, surgeries, hospitalizations and consultations.

6 DETERMINATION OF SAMPLE SIZE

However, 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.

7 STATISTICAL ANALYSIS

7.1 General considerations

As the study is an observational study, epidemiologic methods will be performed in the data analysis.
A descriptive analysis will be obtained for all relevant variables, with absolute and relative frequency for categorical variables and mean, standard variation, median, maximum and minimum (or range) for continuous ones. For each study endpoint, data will be summarized by IBD type (CD or UC). The variable normality assumption will be tested using the Kolmogorov-Smirnov test. Non-parametric tests will be used whenever the assumptions for parametric tests are not accepted. Statistical tests will be performed considering bilateral tests and a significance level of 0.05.
All statistical analyses will be performed using the statistical software SAS® (version 9.4; SAS Institute Inc., Cary, USA).

The statistical analysis of the study include a cross-sectional analysis (at the end of the cross-sectional study) and a longitudinal analysis (at the end of the 12-month follow-up period). No interim analyses are planned.

- Cross-sectional analysis: it is expected to obtain a characterization of the study population, the estimation of primary endpoints and the comparison of the subgroups of patients with no or mild 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 mild activity regarding socio-demographic, clinical and treatment variables of interest. Further details of this analysis are described in Section 7.5 and 7.6.
- Longitudinal analysis will be calculated the proportion of controlled patients after 12-month follow up assessment, as well 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. Further details of this analysis are described in Sections 7.5 and 7.6.

7.2 Analysis Sets

In this study, they will be analyzed two populations:

- The cross-sectional population will include all patients who have completed the Day 1 assessment (expected to occur 6 months after start of enrolment).
- The longitudinal population will include all patients included in the prospective period (patients with active IBD in Day 1).

7.3 Disposition of Subjects

The number of screening failures as well as number of subjects included in this study will be described in this section. The number (n) and % (frequency distribution) of patients who were included or not in prospective phase, patients who completed the study, subjects who discontinued the study and distribution for each study dataset by IBD type will be also summarized.

7.4 Demographic and other characteristics

A descriptive statistical analysis will be performed for cross-sectional dataset for socio-demographic, anthropometric and clinical data: gender and age, weight, height, body mass index (BMI), professional situation, education level, income, smoking habits, medical history, comorbidities and extra intestinal manifestations, among other variables. A descriptive statistical analysis will be performed for longitudinal dataset for socio-demographic and anthropometric data, clinical and treatment-related features. Descriptive statistical analysis will be performed for each IBD type.

7.5 Primary Analysis

The primary endpoint analysis will be performed calculating the proportion of patients with active disease at Day 1. The results will be presented as percentage and calculated as.

- For CD:

$$p_{CD} = \frac{\#\ patients\ with\ active\ CD\ (HBI \geq 8\ or\ CDAI > 220)}{\#\ total\ of\ patients\ with\ CD} \times 100$$

- For UC:

$$p_{UC} = \frac{\#\ patients\ with\ active\ UC\ (Mayo\ partial\ score \geq 5)}{\#\ total\ of\ patients\ with\ UC} \times 100$$

The 95% confidence interval will be computed for each estimate. In this study, the primary endpoint will be analyzed for cross-sectional dataset.

7.6 Secondary Analysis

The secondary analysis include both a cross-sectional analysis and a longitudinal analysis.

The cross-sectional will be performed for cross-sectional analysis dataset:

- A descriptive statistical analysis will be performed for socio-demographic, anthropometric and clinical aspects of IBD by type (CD and UC);

- A descriptive statistical analysis will be performed for the 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.

- For each type of IBD (CD or UC), a comparison of patients with moderate to severe activity and patients with no or mild activity disease regarding socio-demographic, clinical and treatment variables of interest will be performed:

    - For 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, the assessment of a significant difference between groups will be done using the Chi-Square Test or the Fisher's Exact Test depending if the assumption of cell frequency to be made;
    - For quantitative variables, such as age, time since diagnosis, and duration of treatment, such as age, time since diagnosis, and duration of treatment, the assessment of a significant difference between groups will be made through the t-test

for independent samples or Mann-Whitney test in case of non-normality of the quantitative variable distribution;

- If applicable, for CD and UC patients, the assessment of independent variables which can be associated with disease control at day 1 will be performed using a logistic regression model. The odds ratios (ORs) estimates and the respective 95% confidence intervals will be presented.

- For each IBD (CD and UC), a descriptive statistical analysis (global and according to disease activity) for the quality of life data will be performed:
  - EuroQoL questionnaire (EQ-5D-5L) considers five attributes of quality of life evaluation:
    - Mobility;
    - Self-care;
    - Usual activity;
    - Pain/discomfort;
    - Anxiety/depression.

    Each dimension has five possible levels, 1-no problems, 2 slight problems, 3-moderate problems, 4-severe problems, 5-extreme problems.

    The resulting score of EQ-5D analog scale:
    - A value of 100 in VAS EQ-5D score indicate the best health imagined and a value of 0 means the worst health imagined;
    - 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;
  - 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;

    For each score estimate the 95% confidence interval will be computed.
  - The IBDQ score and each of the four IBDQ domains:
    - Bowel function – Sum of questions 1, 05, 09, 13, 17, 20, 22, 24, 26, 29;

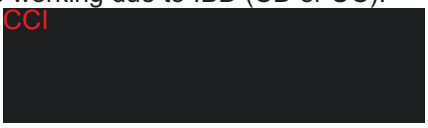
- Emotional status – Sum of questions 03, 07, 11, 15, 19, 21, 23, 25, 27, 30, 31, 32;
- Systematic symptoms – Sum of questions 02, 06, 10, 14, 18;
- Social function – Sum of questions 04, 08, 12, 16, 28;

For each score estimate the 95% confidence interval will be computed.

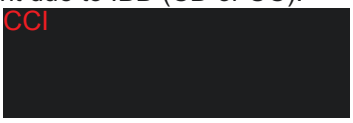
- For each IBD (CD and UC), a descriptive statistical analysis (global and according to disease activity) for the following WPAI data will be performed:
  - In brief, the WPAI questions are: 1) if currently employed, 2) hours missed due to disease, 3) hours missed other reasons, 4) hours actually worked, 5) degree disease affected productivity while working, 6) degree disease affected regular activities.
  - Percent total work productivity impairment due to IBD (TWPI) defined as the mean of subjects total percentage of work impairment associated with IBD that results from both absenteeism and presenteeism:

  - Percent work time missed due to IBD (CD or UC):

  - Percent impairment while working due to IBD (CD or UC):



  - Percent total activity impairment due to IBD (CD or UC):



- For each IBD (CD and UC), a descriptive statistical analysis (global and according to disease activity) of health resources (the previous 3 years) will be performed 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.
- A description of the health care resource costs will be presented. 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.
- Multivariate cost models may be developed where the observation time is divided into intervals of equal length.

The longitudinal analysis will be performed for the longitudinal analysis dataset (patients with active IBD at Day 1 included in the 12 months follow-up period):

- A descriptive statistical analysis will be performed for the main socio-demographic, clinical characteristics and treatment regimen of the included patients at Day 1 (baseline) , by IBD type (CD and UC);

- The proportion of patients with active IBD after 12 months among patients who had moderately to severely active IBD at Day 1 (baseline) will be calculated. The results will be presented as percentage.

    - For CD:

CCI [redacted]

    - For UC:

CCI [redacted]

The 95% confidence interval will be calculated for each estimate

- For each type of IBD (CD or UC), a comparison of patients that remained with active disease with patients that had mild or no activity of disease, after 12 months follow-up, regarding socio-demographic, clinical and related-treatment variables of interest will be performed:

    - For qualitative variables, the assessment of a significant difference between groups will be done using the Chi-Square Test or the Fisher's Exact Test depending if the assumption of cell frequency to be made;
    - For quantitative variables, the assessment of a significant difference between groups will be made through the t-test for independent samples or Mann-Whitney test in case of non-normality of the quantitative variable distribution;
    - If applicable, for patients with CD and UC, the assessment of independent variables which can be associated with the disease control (no or mild activity) after 12 months

follow-up will be performed using a logistic regression model. The ORs estimates and the respective 95% confidence intervals will be presented.

- If applicable, a survival analysis, with Kaplan Meier curves and Cox regression models to identify factors associated with the time of achieving mild or no activity with baseline treatment (continued or initiated at baseline) (dependent variable) will be performed for each type of IBD. The event of interest will be: have mild activity or no active disease. Thus, patients who remained with active disease or who change treatment due to lack of disease control will be censored and, conversely, success will be defined as having mild or no active disease. The survival analysis will include:
    - A non-parametric estimation of the survival function using the Kaplan-Meier estimator (global and stratified by categories for each categorical variable).
    - A comparison of estimated survival function curves of the different categories in each variable using the Log-Rank non-parametric test.
    - If applicable, the semi-parametric Cox proportional hazards model will be adjusted to identify potential factors associated with the time of achieving mild or no activity with baseline treatment (continued or initiated at baseline). The hazard ratios (HR) estimates and the respective 95% confidence intervals will be presented.
- A descriptive statistical analysis will be performed for the number and reason for treatment changes, as well for treatment patterns during the 12 month follow-up period by IBD type (CD and UC);
- For each type of IBD (CD or UC), a comparison of patients with treatment changes with those without changes 12 month follow-up, regarding main socio-demographic, clinical and treatment-related variables (at baseline) will be performed

    - For qualitative variables, the assessment of a significant difference between groups will be done using the Chi-Square Test or the Fisher's Exact Test depending if the assumption of cell frequency to be made;
    - For quantitative variables, the assessment of a significant difference between groups will be made through the t-test for independent samples or Mann-Whitney test in case of non-normality of the quantitative variable distribution;
    - If applicable, Poisson regression models based on generalized linear equations will be adjusted to investigate the relationship between variables of interest and the incidence of the treatment changes during follow-up. The incidence rate ratios (IRRs) estimates and the respective 95% confidence intervals will be presented.

7.7 Missing data

Missing values will not be replaced in this study.

8 PROTOCOL CLARIFICATIONS/AMENDMENTS

As the amendments will not affect the data collection plan, this SAP was written in accordance with the information contained in Amendment 1 of study protocol, Version 17 Oct 2016. Since the Amendment was implemented at the end of the recruitment period at only one center and after the recruitment for the remaining centers, the section “Disposition of Subjects” will specify how many subjects were included based on the eligibility criteria described in the Amendment.

The following statistical analysis not described in the protocol should be considered:

1) General considerations: for each study endpoint, data will be summarized by study sites. Study sites can be classified as region: PI, BA, MG, GO, SP, PR, RS and RJ (Figure 2). The study sites/region should be considered as independent variable to be included in the regression models for the comparison of patients with no or mild activity with patients with disease activity.

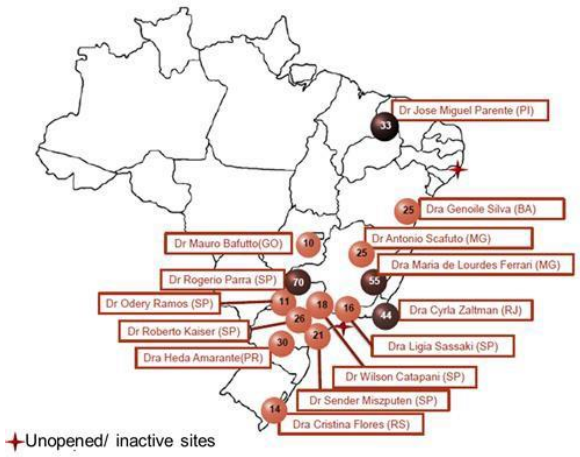


Figure 2 – Study sites by region.

2) Subject’s disposition: The study deposition should also be presented by IBD type and regions.
3) Demographic and other characteristics: The descriptive statistical analysis should also be performed by regions.
4) Primary Analysis: The proportion of patients with moderate to severe CD or UC should be calculated and compared by regions.
5) Secondary Analysis: For cross-sectional analysis dataset the descriptive statistical analysis will be performed also by region. The multivariate logistic regression model should include as independent variables all variables with $p<0.020$ in bivariate analysis. Optimized model present only variables with statistical significant OR (Odds Ratio). The region should be included as independent variable. For longitudinal analysis dataset the proportion of patients with moderate to severe CD or UC after 12 month follow-up should be calculated and compared by region. As for cross-sectional analysis dataset, the multivariate logistic

regression model should include as independent variables all variables with p<0.020 in bivariate analysis. Optimized model present only variables with statistical significant OR (Odds Ratio). The region should be included as independent variable.

For cross-sectional analysis dataset, 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. If applicable, if the number of patients in the levels of each dimension is small, the severity of each dimension will correspond to: have problems (group moderate, severe and unable/extreme problems) and have no problems (group slight or no problems). The correlation of scales scores of IBDQ and EQ-5D dimensions or VAS scale with SF-36 scales scores will be determined for each IBD type using Pearson or non-parametric Spearman's correlation coefficient.

Also for cross-sectional dataset, 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.

6) Other analysis: The influence of demographic characteristics, comorbidities and extra-intestinal manifestations on the quality of life will be assessed. For each type of IBD, a comparison of patients using biologic treatment and patients who not use biologic treatment regarding quality of life data will be done. Same analysis will be performed for patients who were hospitalized and patients who were not hospitalized.

   IBD treatment-related procedures in the previous 3 years will be described for patients using biologic treatment and patients who not use biologic treatment.

Note: Regions variable should be considered as independent variable for the regression analysis.

7) Longitudinal analysis: A sensitivity analysis will be performed to determine the proportion of patients with active IBD after 12 months, among patients who had moderately to severely active IBD at Day 1 (baseline), considering the CDAI/ HBI (for CD patient) or Mayo (for UC patients) scores collected during the IBD specialist appointments, allowing a time window of 1 month (30 days) to assess disease activity (M12 = (Day1 + 365 days) or (Day1 + 365 days) – (30 – 1 days)). The results will be presented as percentage and the 95% confidence interval will be calculated.

9 DISCREPANCY IN RETROSPECTIVE DATA AFTER DATABASE LOCK

Any discrepancy in retrospective IBD medication data found after the database lock will be corrected in case of: primary analysis is affected, there is more than 5% of error on data used for secondary analysis. The impact on published information should also to be weighted. The percentage of discrepancies at study medication will be evaluated and a re-analysis will be performed only if previous criteria apply. The new analysis will be included in the final report which includes the updated (new version) retrospective analysis and prospective analysis and results.

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