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

NCT Number: NCT03488030

SAP Approve Date: 28th of August 2019

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

Statistical Analysis Plan

Version No. 1.0

28th of August 2019

Prepared by:

CCI [redacted]

Requested by:

Takeda Pharma S.A.

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Buenos Aires - Argentina

TITLE PAGE

Study title:	Real-world data of Moderate to Severe Inflammatory Bowel Disease in Argentina: a non-interventional, multicenter study to evaluate disease control, treatment patterns, burden of disease and quality of life (RISE AR)
Study code:	IBD-5004
Study type:	Observational
Study drug	Not applicable
Therapeutic area:	Moderate to Severe Inflammatory Bowel Disease - Crohn's Disease (CD) and Ulcerative Colitis (UC)
Sponsor:	Takeda Pharma S.A. Tronador 4890 C1430DNN Buenos Aires - Argentina
Version No., date:	Version No. 1.0, 28 August 2019
Statistical analysis plan performed by:	CCI [redacted]

SIGNATURE PAGE

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

PROTOCOL VERSION: Version 1.0

PROTOCOL DATE: 24January2018

SAP PREPARED BY:

CCI [redacted]

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SAP REVIEWED AND APPROVED BY:

CCI [redacted]

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dd/mmm/yyyy

REVISION LOG

Version No.	Version Date	Author	Changes from Previous Approved Versions
1.0	28 AUG 2019	CCI [redacted]	Not Applicable (First Version)

TABLE OF CONTENTS

1 RATIONALE

This Statistical Analysis Plan (SAP) was written in accordance with CTI Clinical Trial & Consulting Services' standard operating procedure (SOP) ST.CO.01-01 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, clarify issues which was not clarified in the protocol, expand statistical section of the protocol, provide basis for the statistical section of the statistical report and reduce the opportunity for bias by prospectively defining analysis. 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 here defined during the statistical analysis of the study data will be documented in the Statistical Report and in the Study Clinical Report.

This document was written in accordance with the information contained in the Study Protocol IBD-5004 - RISE AR, version 1.0, of 24 January 2018 and CRF Version 4.0, 18 December 2018.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary objective

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

2.1.2 Secondary objectives

- To characterize socio-demographic and clinical aspects of moderate to severe IBD.
- To characterize treatment patterns for IBD during the 3 years previous to Day 1, including the use of biologic therapies and failure to these therapies (if any).

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

2.2 Endpoints

2.2.1 Primary endpoints

- For Crohn's Disease: Proportion of patients with active disease (HBI score ≥ 8 or CDAI score ≥ 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.

2.2.2 Secondary endpoints

- Distribution of age, gender, smoking habits, professional status, family history, educational level, subject income by IBD type.
- Distribution of clinical variables (steroid behaviour, anthropometric information, medical history and comorbidities, clinical characterization of disease) by IBD type.
- Therapies for IBD (aminosalicylates, steroids, immunomodulators, immunosupressors biologics, antibiotics, probiotics and surgeries) and the length of these therapies during the previous 3 years.
- Proportion of biologic-experienced patients.
- Proportion of patients who have not responded previously to biologic therapies and reason.
- IBD treatment introduced at Day 1 (if applicable).
- Socio-demographic, clinical and treatment-related variables in patients with moderate to severe activity of CD (HBI score ≥ 8 or CDAI score ≥ 220 points) versus patients with mild or no activity (HBI score < 8 or CDAI score < 220 points).

- Socio-demographic, clinical and treatment-related variables in patients with moderate to severe activity of UC (9-point partial Mayo score ≥5) versus patients with mild or no activity (9-point partial Mayo score <5).
- Mean score of EQ-5D by IBD type.
- Mean score of different components of SF-36 by IBD type.
- Mean total score of IBDQ and by domain (bowel symptoms, systemic symptoms, emotional function and social function). Patients with ostomy will not be evaluated since this questionnaire is not validated to be used in this population.
- Mean total percentage of work impairment (WPAI).
- Mean work time missed (WPAI).
- Mean impairment while working (WPAI).
- Mean total activity impairment (WPAI).
- Healthcare resources (previous 3 years): drug therapies, imaging and laboratory testing, surgeries, hospitalizations and consultations.

3 STUDY DESIGN

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

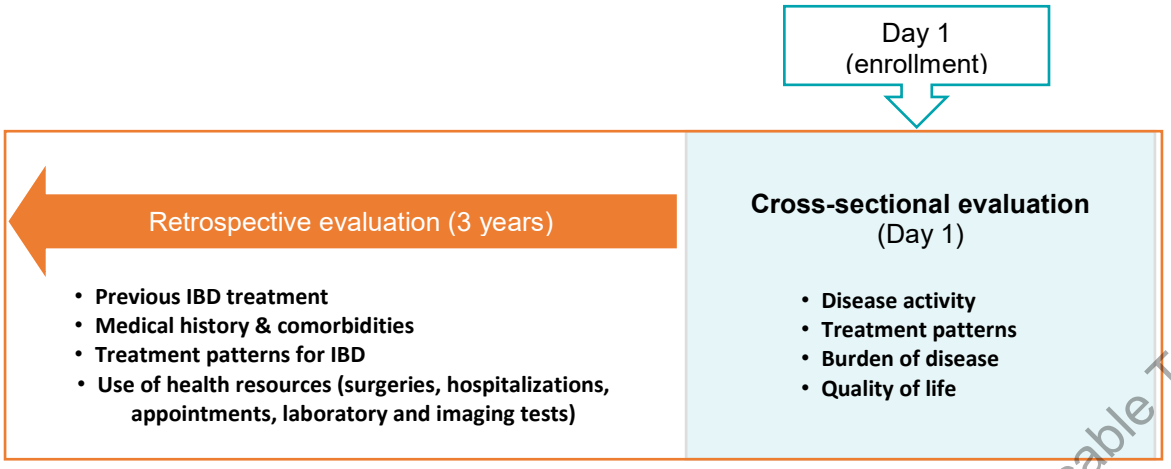

Figure 1. Study design scheme

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria:

1. Male or female subjects.
2. Subjects aged 18 years or older.
3. Diagnosis of moderate to severe CD or UC for at least 6 months prior to Day 1 appointment based on clinical or endoscopic or image criteria (please see protocol study – section 6.3.1).
4. Subjects who provided the written informed consent.

4.2 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.

5 PROTOCOL CLARIFICATIONS

The last secondary objective, estimation of healthcare resources cost, will not be calculated as stayed in section 3 of the protocol (3. Study objectives), since these variables were not collected in the CRF.

Adverse events were not collected in the study database and results regarding these variables will not be presented in the statistical report.

Secondary endpoint "*Proportion of patients who quit their job due to IBD and have not been able to return to work"* will not be calculated as stayed in section 10.1.1 of the protocol (10.1.1 Study endpoints), since these variables were not collected in the CRF.

In the protocol the analysis dataset was not defined. In this SAP the analysis dataset was defined according to section 6 *Definition of analysis subsets*.

The descriptive analysis for continuous variables will be summarized by mean, standard variation, median, maximum, minimum as stayed in the protocol and also by first quartile and third quartile.

6 DEFINITION OF ANALYSIS SUBSETS

Analysis dataset – All patients fulfilling selection criteria (section 4), who provided the written informed consent, without major study protocol deviations and who have completed the Day 1 assessment will be included in the statistical analysis dataset.

7 RATIONALE AND CALCULATION OF THE SAMPLE SIZE

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

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

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

Rate of uncontrolled disease (*p*) = 20%

Margin of error (ME) = 0.05

Expected recruitment period: 6 months

8 STATISTICAL METHODS

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

Statistical analysis will allow a characterization of the study population, the estimation of primary endpoints and to compare the subgroup of patients with mild or no activity of disease and those with moderate to severe activity. A descriptive analysis will be obtained for all relevant variables, with absolute and relative frequency for categorical variables and mean, standard variation, median, maximum, minimum, first quartile and third quartile, for continuous ones. For each study endpoint, data will be summarized by IBD type (CD or UC). Hence, for each IBD type, the patients with disease activity will be compared with patients with mild or no activity regarding socio-demographic, clinical and treatment variables of interest. The variable normality assumption will be tested using the Kolmogorov-Smirnov test or Shapiro-Wilk test as applicable. Non-parametric tests will be used whenever the assumptions for parametric tests are not accepted. 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. Variables with clinical significance or statistical significance ($p<0.200$) will be included in the initial logistic regression model, or otherwise specified by the sponsor. All tests will be two-sided considering a significance level of 5%.

Data analysis will be performed using SAS® (version 9.4; SAS Institute Inc, Cary, USA).

There will be no imputation of missing data for this study, unless otherwise specified.

In case of complete missing dates, date is to be considered as missing.

In case of partial dates:

- Missing day is to be considered as the 15th day of the month;
- Missing day and month are to be considered as the 1st day of July.

8.1 Primary Analyses

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 Crohn's Disease (CD):

$$p_{CD} = \frac{Number\ of\ patients\ with\ active\ CD\ (HBI\ score \geq 8\ or\ CDAI\ score \geq 220)}{Total\ number\ of\ CD\ patients}\ x\ 100$$

For Ulcerative Colitis (UC):

$$p_{UC} = \frac{Number\ of\ patients\ with\ active\ UC\ (9 - point\ partial\ Mayo\ score \geq 5)}{Total\ number\ of UC\ patients}\ x\ 100$$

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

8.2 Secondary Analyses

The following objectives will be addressed for all IBD patients:

- In order to characterize socio-demographic and clinical aspects of moderate to severe IBD, a summary table with the descriptive statistics of the selected variables, by CD and UC patients.
- Descriptive statistics will also be used to summarize treatment patterns for CD and UC in the previous 3 years, including the use of biologic therapies and failure to these therapies (if any), time between IBD diagnosis and initial treatment, first treatment after diagnosis of moderate to severe IBD, among other variables of interest.
- Within CD and UC groups, the patients with moderate to severe disease activity will be compared with patients with mild or no activity, regarding socio-demographic, clinical and treatment variables of interest:
    - Chi-square or Fisher exact tests will be used to compare qualitative variables, such as gender, smoking habits, professional status, family history of IBD, steroid behavior (dependent/refractory), previous treatment with biologic therapies, and previous surgery for IBD, among others.
    - The t-student or Mann-Whitney tests will be used for comparison of quantitative variables, such as age, time since diagnosis, and duration of treatment, among others.
    - If applicable, logistic regression models (for CD and UC patients) will be used to identify independent variables associated with disease control at Day 1, and odds ratios (OR) with 95% CI will be presented.
- For each IBD disease, a descriptive statistical analysis will be used to summarize patients' QoL (Quality of Life), overall and according to disease activity
    - The score of EQ-5D analog scale and responses to each item (Mobility, Self-care, Usual activity, Pain/discomfort, Anxiety/depression):

- Utilities will be configured such that 0 is associated with being dead and 100 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, Role Physical, Body pain, General health, Vitality, Social Functioning, Role-Emotional, Mental Health) and based on standardized scores, two summary scores are to be estimated (Physical Component Score and Mental Component Score). The standard scoring method for SF-36 questionnaire will be obtained using the QualityMetric Health Outcomes™ Scoring Software 4.5 provided by QualityMetric Incorporated.
- The IBDQ score and each of the four IBDQ domains (Bowel systems, Emotional health, Systematic systems and Social function). Total IBDQ score range from 32 to 224, with a higher score reflecting better quality of life. Response to each of the questions is graded from 1 to 7 ("1" being the worst situation and "7" the best). Please see section 9. *Data, derivations and transformations* for the IBDQ scores calculation. Note: The IBDQ is not validated for patients with ostomies and therefore should not be applied for these patients.

- The comparison of SF-36 scale scores or component summary scores, EQ-5D VAS scale and IBDQ domain scores or total score according to disease activity will be performed through the t-test for independent samples or Mann-Whitney test in case of non-normality of the quantitative variable distribution. The association between each EQ-5D dimension and disease activity will be determined for each IBD type using Chi-Square Test.

- To evaluate the work productivity impairment (WPAI) experienced by moderate to severe IBD patients, the following variables will be estimated and summarized, by CD or UC, overall and according to disease activity. In brief, the WPAI questions are: 1) if currently employed, 2) hours missed due to disease, 3) hours missed other reasons, 4) hours actually worked, 5) degree disease affected productivity while working, 6) degree disease affected regular activities. 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 will be calculated for each IBD type. Also percent work time missed due to IBD, percent impairment while working due to IBD and percent total activity impairment due to IBD will be calculated. Please see section 9. *Data, derivations and transformations* for the percentages' calculation formula. Additionaly, the proportions of patients reporting some absenteeism, some work impairment and some activity impairment due to IBD will be presented. Patients with moderate to severe disease will be compared with patients with no or mild disease regarding WPAI data (percent total work productivity impairment due to IBD, percent work time missed due to IBD, percent impairment while working due to IBD and percent total activity impairment due to IBD) through the t-test for independent samples or Mann-Whitney test in case of non-normality of the quantitative variable distribution.

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

9 DATA, DERIVATIONS AND TRANSFORMATIONS

Analysis dataset: A dichotomous variable (yes/no) will be calculated.

Yes – Patients who meet all inclusion criteria, not meet any of the exclusion criteria, sign the informed consent, without major study protocol deviations and who have completed the Day 1 visit.

No – Otherwise

Age at Day 1 (years): The difference between the Day 1 date and the patient's birth date, in years.

Moderate to severe Crohn's disease (active CD disease): A dichotomous variable (yes/no) will be calculated.

Yes – Patients with HBI score ≥ 8 or CDAI score ≥ 220 at Day 1 visit.

No – otherwise.

Moderate to severe Ulcerative Colitis disease (active UC disease): A dichotomous variable (yes/no) will be calculated.

Yes – Patients with 9-point partial Mayo score≥ 5 at Day 1.

No – otherwise.

Time since IBD diagnosis and Day 1(years) – time between the IBD diagnosis and Day 1 visit, in years.

Time since first treatment after IBD diagnosis and Day 1 (years) - time between the start date of first IBD treatment after diagnosis and date of Day 1 visit, in years.

Time since diagnosis of moderate to severe IBD and Day 1 (years) - time between the date of moderate to severe IBD and date of Day 1 visit, in years.

Time since first treatment (or treatment change) after moderate to severe IBD diagnosis and Day 1 (years) - time between the start date of first IBD treatment/treatment change after moderate to severe diagnosis and date of Day 1 visit, in years.

BMI - The following formula must be considered: $\frac{Weight\ (Kg)}{Height\ (m)^2}$.

BMI categories – The BMI will be recoded according to the following cut-offs:

Underweight – BMI <18.50 kg/m^2

Normal range – BMI between 18.50 and 24.99 kg/m^2

Overweight – BMI between 25.00 and 29.99 kg/m^2

Obese – BMI ≥ 30.00 kg/m^2

Total number of extra intestinal manifestation conditions per patient – Sum of all of extra intestinal manifestation conditions by each patient in the previous 3 years.

Total number of not extra intestinal manifestation conditions per patient – Sum of all not extra intestinal manifestation conditions by each patient in the previous 3 years.

Harvey Bradshaw Index cut-off - A dichotomous variable will be calculated:

HBI score ≥ 8 points – Patients with Harvey Bradshaw Index equal or higher than 8 points.

HBI score < 8 points – Patients with Harvey Bradshaw Index lower than 8 points.

Crohn´s Disease Activity Index cut-off - A dichotomous variable will be calculated:

CDAI score ≥ 220 points – Patients with Crohn´s Disease Activity Index equal or higher than 220 points.

CDAI score < 220 points – Patients with Crohn´s Disease Activity Index lower than 220 points.

HBI and CDAI cut-offs - A trichotomous variable will be calculated:

HBI score ≥ 8 points and CDAI score ≥ 220 points (Moderate to severe) – Patients with HBI equal or higher than 8 points and CDAI equal or higher than 220 points.

HBI score < 8 points and CDAI score < 220 points (No or mild) – Patients with HBI lower than 8 points or CDAI lower than 220 points.

HBI score < 8 points and CDAI score ≥ 220 points OR HBI score ≥ 8 points and CDAI score < 220 points (Moderate to severe) – Patients with HBI lower than 8 points and CDAI equal or higher than 220 points OR patients with HBI equal or higher than 8 points and CDAI lower than 220 points.

Patients with only HBI score assessed at Day 1 - A dichotomous variable (yes/no) will be calculated.

Yes – Patients with HBI score assessed at Day 1 and without CDAI score assessed at Day 1.

No – Patients with HBI score and CDAI score evaluated at Day 1 **and** patients with only CDAI score evaluation at Day 1.

Patients with missing information in both scores will be considered as a missing value in this new variable.

Patients with only CDAI score assessed at Day 1 - A dichotomous variable (yes/no) will be calculated.

Yes – Patients with CDAI score assessed at Day 1 and without HBI score assessed at Day 1.

No – Patients with HBI score and CDAI score evaluated at Day 1 **and** patients with only HBI score evaluation at Day 1.

Patients with missing information in both scores will be considered as a missing value in this new variable.

Patients with HBI score and CDAI score assessed at Day 1 - A dichotomous variable (yes/no) will be calculated.

Yes – Patients with CDAI score and HBI score assessed at Day 1.

No – Patients with only one score (CDAI or HBI) assessed at Day 1.

Patients with missing information in both scores will be considered as a missing value in this new variable.

HBI score and CDAI score not assessed at Day 1 - A dichotomous variable (yes/no) will be calculated:

Yes – Patients without CDAI score and without HBI score assessments at Day 1.

No – Patients with only one score (CDAI or HBI) assessed at Day 1.

Patients with missing information in both scores will be considered as a missing value in this new variable.

Location of CD (Montreal classification) at Day 1- A dichotomous variable will be calculated:

L1/L1+L4/L2/L2+L4 – Patients with location of CD classified as "L1 – ileal", "L1 + L4 – ileal + isolated upper GI tract disease", "L2 – colonic disease" or "L2+L4 – colonic disease + isolated upper GI tract disease"

L3/L3+L4/L4 – Patients with location of CD classified as "L3 – ileocolic", "L3+L4 – ileocolic + isolated upper GI tract disease" or "L4 – isolated upper GI tract disease".

Behavior (Montreal classification) at Day 1 - The Behavior (Montreal classification) at Day 1 will be recoded according to the following cut-offs:

B1/B1+P – Patients with behavior classified as 'B1 – Non stenosing/non penetrating' or 'B1 + P – Non stenosing/non penetrating + perianal disease'

B2/B2+P – Patients with behavior classified as 'B2 – Stenosing' or 'B2 + P – Stenosing + perianal disease'.

B3/B3+P – Patients with behavior classified as 'B3 – Penetrating' or 'B3 + P – Penetrating + perianal disease'

P – Patients with behavior classified as 'P – perianal disease'

9-point Partial Mayo score cut-off - A dichotomous variable will be calculated:

Partial Mayo score ≥ 5 points – Patients with 9-point partial Mayo score equal or higher than 5 points

Partial Mayo score < 5 points – Otherwise

Extent of inflammation (Montreal classification) at Day 1 - A dichotomous variable will be calculated:

E1 proctitis/ E1 proctosigmoiditis – Patients with extent of inflammation classified as "E1 - distal UC: proctitis" or "E1 - distal UC: proctosigmoiditis".

E2/E3 – Patients with extent of inflammation classified as "E2 - left-sided: mucosa inflammation extending up to splenic flexure" or "E3 - pancolitis: mucosa inflammation up to proximal transverse colon and beyond"

Severity of UC (Montreal classification) at Day 1 - A dichotomous variable will be calculated:

S0/S1 – Patients with severity of UC classified as "S0 - Clinical remission (asymptomatic)" or "S1 - Mild UC (passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers)"

S2/S3 – Patients with severity of UC classified as "S2 - Moderate UC (passage of more than four stools per day but with minimal signs of systemic toxicity)" or "S3 - Severe UC (passage of at least 6 bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37,5°C, hemoglobin of less than 10,5 g/100ml, and ESR of at least 30mm/h)".

IBDQ score and IBDQ domains at Day 1 - The following formulas must be considered:

$$Bowel\ systems = \frac{Sum\ of\ scores: Questions\ 01,\ 05,\ 09,\ 13,\ 17,\ 20,\ 22,\ 24,\ 26\ and\ 29}{10}$$

$$Emotional\ health\ = \frac{Sum\ of\ scores: Questions\ 03, 07, 11, 15, 19, 21, 23, 25, 27, 30, 31\ and\ 32}{12}$$

$$Systematic\ systems\ = \frac{Sum\ of\ scores: Questions\ 02, 06, 10, 14\ and\ 18}{5}$$

$$Social\ function\ = \frac{Sum\ of\ scores: Questions\ 04, 08, 12, 16\ and\ 28}{5}$$

$$IBDQ\ score\ = Sum\ of\ all\ scores\ of\ all\ questions$$

WPAI Questionnaire (for Crohn's Disease and Ulcerative Colitis) at Day 1 - The following formulas must be considered:

$$TWPI\ (Absenteeism\ and\ Presenteeism\ combined) = \frac{Q2}{(Q2+Q4)} + \left[1 - \left(\frac{Q2}{Q2+Q4}\right) \times \frac{Q5}{10}\right] \times 100$$

$$Percent\ work\ time\ missed\ due\ to\ IBD\ (Absenteeism) = \frac{Q2}{(Q2+Q4)} \times 100$$

$$Percent\ impairment\ while\ working\ due\ to\ IBD\ (Presenteeism\ ) = \frac{Q5}{10} \times 100$$

$$Percent\ total\ activity\ impairment\ due\ to\ IBD = \frac{Q6}{10} \times 100$$

Absenteeism due to Crohn's disease/Ulcerative Colitis - A dichotomous variable (yes/no) will be calculated:

Yes – Patients with percent work time missed due to IBD (absenteeism) higher than 0%.

No – Patients with percent work time missed due to IBD (absenteeism) equal to 0%.

Work impairment due to Crohn's disease/Ulcerative Colitis - A dichotomous variable (yes/no) will be calculated:

Yes – Patients with percent impairment while working due to IBD (presenteeism) higher than 0%.

No – Patients with percent impairment while working due to IBD (presenteeism) equal to 0%.

Activity impairment due to Crohn's disease/Ulcerative Colitis - A dichotomous variable (yes/no) will be calculated:

Yes – Patients with percent total activity impairment due to IBD higher than 0%.

No – Patients with percent total activity impairment due to IBD equal to 0%.

Total number of surgeries per patient – Sum of all previous surgeries due to IBD realized by each patient in the previous 3 years.

Total number of hospitalizations per patient – Sum of all previous hospitalizations due to IBD for each patient in the previous 3 years.

Time of hospitalization – The difference between the start date and end date of each hospitalization, in days. For each patient all hospitalized time will be summed. Time of hospitalization will only be calculated if start date and end date of hospitalization is complete.

Total number of medical appointments per patient – Sum of all previous medical appointments for IBD by each patient in the previous 3 years.

Any change in IBD treatment during medical appointments in the previous 3 years per patient – A dichotomous variable (yes/no) will be calculated:

Yes – Patients with at least one medical decision regarding any IBD classes classified as: Introduced a new therapeutic class, Discontinuation (no switch), Drug change (same therapeutic class) or Switched of therapeutic class or Dose changed (same drug).

No – Patients without medical decisions regarding any IBD classes classified as: Introduced a new therapeutic class, Discontinuation (no switch), Drug change (same therapeutic class), Switched of therapeutic class or Dose changed (same drug).

Total number of IBD treatment changes per patient during medical appointments in the previous 3 years – Sum of all medical decisions classified as Introduced a new therapeutic class, Discontinuation (no switch), Drug change (same therapeutic class), Switched of therapeutic class or Dose changed (same drug) for all medical appointments and any IBD classes, in the previous 3 years, for each patient.

Height (in the previous 3 years, not considering Day 1) – For each patient, height in the previous 3 years will be calculated by the mean of all heights collected in that period.

Weight (in the previous 3 years, not considering Day 1) – For each patient, weight in the previous 3 years will be calculated by the mean of all weight collected in that period.

IBM (in the previous 3 years, not considering Day 1) – The following formula must be considered:

$$IBM\ (in\ the\ previous\ 3\ years) = \frac{Mean\ weight\ in\ the\ previous\ 3\ years\ not\ considering\ Day\ 1\ (Kg)}{Mean\ height\ in\ the\ previous\ 3\ years\ ,not\ considering\ Day\ 1\ \ (m)^2}$$

BMI categories (in the previous 3 years, not considering Day 1) – The BMI (in the previous 3 years, not considering Day 1) will be recoded according to the following cut-offs:

Underweight – BMI <18.50 kg/m^2

Normal range – BMI between 18.50 and 24.99 kg/m^2

Overweight – BMI between 25.00 and 29.99 kg/m^2

Obese – BMI ≥ 30.00 kg/m^2

Total number of fecal calprotectin levels per patient – For each patient, fecal calprotectin levels in the previous 3 years will be calculated by the mean of all fecal calprotectin levels collected in that period.

Fecal calprotectin results suggestive of inadequate activity control at least one time – A dichotomous variable (yes/no) will be calculated:

Yes – Patients with at least one fecal calprotectin suggestive of inadequate control of activity collected in the previous 3 years.

No – Patients without fecal calprotectin suggestive of inadequate control of activity collected in the previous 3 years.

Colonoscopy results suggestive of inadequate activity control – A dichotomous variable (yes/no) will be calculated:

Yes – Patients with at least one colonoscopy suggestive of inadequate control of activity collected in the previous 3 years.

No – Patients without colonoscopy suggestive of inadequate control of activity collected in the previous 3 years.

Total number of previous imaging and laboratory testing due to IBD per patient – Sum of all previous imaging and laboratory testing due to IBD for each patient, in the previous 3 years.

Classes of IBD therapy – IBD therapies during the previous 3 years will be recoded according to the following categories:

Salicylic derivates: 1.1. sulphassalazine (SSZ), 1.2 Mesalazine (5-ASA), 1.3 Olsalazine and 1.4 Mesalazine extended release.

Corticosteroids: 2.1 Hydrocortisone, 2.2 Prednisone, 2.3 Prednisolone, 2.4 Budenoside and 2.5 Methylprednisolone.

Immunosuppressors: 3.1 Azathioprine, 3.2 6-Mercaptopurine, 3.3 Methotrexate, 3.4 Cyclosporine and 3.5 Tacrolimus.

Biologic therapy: 4.1 Infliximab, 4.2 Adalimumab, 4.3 Vedolizumab, 4.4 Certolizumab, 4.5 Golimumab and 4.6 Ustekimumab.

Antibiotics: 5.1 Metronidazole and 5.2 Ciprofloxacin.

Nutritional support: 6.1 Enteral nutrition and 6.2 Parenteral nutrition.

Others: rest of the IBD therapies.

Frist treatment start/change after moderate to severe IBD diagnosis per patient – A dichotomous variable (yes/no) will be calculated:

Yes – Patients with at least one first treatment start/change after moderate to severe IBD diagnosis.

No – Patients without first treatment start/change after moderate to severe IBD diagnosis or first IBD treatment after moderate to severe IBD diagnosis not applicable.

First IBD treatment combinations after moderate to severe IBD diagnosis – First IBD therapies after moderate to severe IBD diagnosis will be recoded according to the following categories

Only salicylic derivates – Patients with only salicylic derivates (sulphassalazine, mesalazine, olsalazine or mesalazine extended release) for IBD first treatment after moderate to severe IBD diagnosis.

Only corticosteroids – Patients with only corticosteroids (hydrocortisone, prednisone, prednisolone, budenoside or methylprednisolone) for IBD first treatment after moderate to severe IBD diagnosis.

Only immunosuppressors – Patients with only immunosuppressors (azathioprine, mercaptopurine, methotrexate, cyclosporine or tacrolimus) for IBD first treatment after moderate to severe IBD diagnosis.

Only biologic therapy – Patients with only biologic therapy (infliximab, adalimumab, vedolizumab, certolizumab, golimumab or ustekimumab) for IBD first treatment after moderate to severe IBD diagnosis.

Only antibiotics – Patients with only antibiotics (metronidazole or ciprofloxacin) for IBD first treatment after moderate to severe IBD diagnosis.

Only nutritional support – Patients with only nutritional support (enteral nutrition or parenteral nutrition) for IBD first treatment after moderate to severe IBD diagnosis.

Only other IBD type – Patients with only “other” IBD type for IBD first treatment after moderate to severe IBD diagnosis.

Corticosteroids and antibiotics combination – Patients with corticosteroids and antibiotics combination for IBD first treatment after moderate to severe IBD diagnosis.

Corticosteroids and salicylic derivates combination– Patients with corticosteroids and salicylic derivates combination for IBD first treatment after moderate to severe IBD diagnosis.

Corticosteroids and immunosupressors combination – Patients with corticosteroids and immunosupressors combination for IBD first treatment after moderate to severe IBD diagnosis.

Corticosteroids and biologic therapy combination – Patients with corticosteroids and biologic therapy combination for IBD first treatment after moderate to severe IBD diagnosis.

Immunosupressors and biologic therapy combination – Patients with immunosupressors and biologic therapy combination for IBD first treatment after moderate to severe IBD diagnosis.

Corticosteroids, immunosupressors and biologic therapy – Patients with corticosteroids, immunosupressors and biologic therapy combination for IBD first treatment after moderate to severe IBD diagnosis.

Corticosteroids, immunosupressors and salicylic derivates – Patients with corticosteroids, immunosupressors and salicylic derivates combination for IBD first treatment after moderate to severe IBD diagnosis.

First treatment start/change after moderate to severe IBD diagnosis with only biologic therapy – A dichotomous variable (yes/no) will be calculated.

Only biologic therapy – patients with only biologic therapy treatment in the first IBD treatment after moderate to severe IBD diagnosis.

Other IBD treatments and combinations – patients without biologic therapy treatment or IBD treatment combinations with biologic therapy in the first IBD treatment after moderate to severe IBD diagnosis.

IBD treatment started/with dose changed at Day 1– A dichotomous variable (yes/no) will be calculated.

Yes – Patients with at least one IBD treatment (just IBD class of salicylic derivates, corticosteroids, immunosuppressors or biologic therapy) with start date equal to Day 1 date.

No – Patients without any IBD treatment (just IBD class of salicylic derivates, corticosteroids, immunosuppressors or biologic therapy) with start date equal to Day 1 date.

IBD treatment discontinuation at Day 1– A dichotomous variable (yes/no) will be calculated.

Yes – Patients with at least one IBD treatment (just IBD class of salicylic derivates, corticosteroids, immunosuppressors or biologic therapy) with end date equal to Day 1 date and reason for end of IBD treatment classified as “Discontinued”.

No – Patients without any IBD treatment (just IBD class of salicylic derivates, corticosteroids, immunosuppressors or biologic therapy) with end date equal to Day 1 date and reason for end of IBD treatment classified as “Discontinued”.

IBD treatment dose changed at Day 1– A dichotomous variable (yes/no) will be calculated.

Yes – Patients with at least one IBD treatment (just IBD class of salicylic derivates, corticosteroids, immunosuppressors or biologic therapy) with end date equal to Day 1 date and reason for end of IBD treatment classified as “Dose changed”.

No – Patients without any IBD treatment (just IBD class of salicylic derivates, corticosteroids, immunosuppressors or biologic therapy) with end date equal to Day 1 date and reason for end of IBD treatment classified as “Dose changed”.

Total number of IBD treatments during retrospective period (previous 3 years and at Day 1) per patient – Sum of IBD treatments reported during retrospective period (3 years) for each patient in the previous 3 years and including IBD treatment starting at Day 1.

IBD treatment duration – Time between the beginning of the IBD treatment until the end of the treatment (in months). For patients with ongoing IBD treatment at Day 1, stop date will be considered as Day 1 date visit.

Salicylic derivates treatment duration per patient – Sum of all IBD salicylic derivate treatments duration for each patient (in months). If the patient has two IBD salicylic derivate treatments taking in simultaneous, it will only be considered the treatment with the longest duration.

Corticosteroids treatment duration per patient – Sum of all IBD corticosteroid treatments duration for each patient (in months). If the patient has two IBD corticosteroids treatments taking in simultaneous, it will only be considered the treatment with the longest duration.

Immunosuppressors treatment duration per patient – Sum of all IBD immunosuppressor treatments duration for each patient (in months). If the patient has two IBD immunosuppressors treatments taking in simultaneous, it will only be considered the treatment with the longest duration.

Biologic therapy treatment duration per patient – Sum of all IBD biologic therapy treatments duration for each patient (in months). If the patient has two IBD biologic therapies taking in simultaneous, it will only be considered the treatment with the longest duration.

Antibiotics treatment duration per patient – Sum of all IBD antibiotic treatments duration for each patient (in months).

Nutritional support treatment duration per patient – Sum of all IBD nutritional support treatments duration for each patient (in months).

Other treatment duration per patient – Sum of all other IBD treatments duration for each patient (in months).

10 APPENDIX

External document: RISE AR TLFs Version No. 1.0, 28Aug2019