



Title: Impact of co-morbidities on treatment response in inflammatory bowel disease: VERNE study

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## Impact of co-morbidities on treatment response in inflammatory bowel disease: VERNE study

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## Table of contents

Table of contents.....	3
1. Figures.....	6
2. List of abbreviations .....	6
3. Study Summary .....	7
3.1. Sponsor .....	7
3.2. Title.....	7
3.3. Study code .....	7
3.4. Scientific committee .....	7
3.5. Participating centers and investigators .....	7
3.6. Research ethics committee .....	7
3.7. Study objectives .....	7
3.8. Study design .....	8
3.9. Study disease .....	8
3.10. Study population.....	8
3.11. Study calendar.....	8
3.12. Coordination and monitoring.....	8
3.13. Study sponsor.....	8
4. Rationale and background .....	9
5. Study objectives.....	11
5.1. Primary objective .....	11
5.2. Secondary objectives .....	11
6. Methodology .....	11
6.1. Study design .....	11
6.1.1. Study Scheme .....	12
6.1.2. Study calendar.....	12
6.2. Investigator recruitment, training and site selection .....	12
6.2.1. Investigator recruitment .....	12
6.2.2. Investigator training .....	13
6.3. Patient selection.....	13
6.3.1. Study population.....	13

6.3.2. Inclusion criteria .....	13
6.3.3. Exclusion criteria.....	13
6.3.4. Discontinuation criteria .....	14
As it is a retrospective study, there is no possibility of early termination, hence no discontinuation criteria are considered.....	14
6.3.5. Informed consent.....	14
6.4. Study procedure.....	14
6.4.1. Study visits .....	14
6.4.2. Study site monitoring .....	14
6.4.3. Data collection .....	14
6.4.4. Study variables.....	15
6.4.5. Main outcome .....	20
7. Statistical Analysis.....	20
7.1. Sample size calculation .....	20
7.2. Analysis population.....	20
7.3. General statistical analysis considerations .....	20
7.4. Assessment of the primary objective: Evaluate the impact of the co-morbidities profile in IBD patients on treatment response to biological therapy .....	21
7.5. Percentage of IBD patients exhibiting co-morbidities.....	22
7.6. Co-morbidities profile according to the level of IBD severity.....	22
8. Data management.....	22
9. Practical considerations .....	23
9.1. Electronic case report form .....	23
9.2. Monitoring and quality of data.....	23
10. Ethical considerations .....	24
11. Confidentiality.....	25
11.1. Patient confidentiality .....	25
11.2. Data confidentiality.....	25
12. Study administration.....	25
13. Investigators compliance.....	26
14. Management and reporting of adverse events or adverse reactions .....	26
14.1. Definitions.....	26

14.1.1.	Definition of Adverse Event .....	26
14.1.2.	DefinItion of Adverse Drug Reaction .....	26
14.1.3.	DefinItion of Serious Adverse Event.....	27
14.1.4.	Special Situations.....	27
14.1.5.	Criteria for Causal Relationship to the (Study) Drug.....	28
14.2.	Handling of Adverse Events .....	29
14.2.1.	Reporting of Adverse Reactions.....	29
14.2.2.	Collection and Recording of Adverse Events.....	29
	Appendix 1: Patient's information sheet .....	31
	Appendix 2: Patient's written informed consent .....	34
	Appendix 5: Adverse event reporting form.....	36
	References.....	37

## 1. Figures

Figure 1. Study Scheme.....	12
Figure 2. Study calendar.....	12

## 2. List of abbreviations

Abbreviation	Description
<b>ADR</b>	Adverse Drug Reaction
<b>AE</b>	Adverse event
<b>AEMPS</b>	<i>Agencia Española del Medicamento y Productos Sanitarios</i>
<b>AR</b>	Adverse Reaction
<b>CD</b>	Crohn's Disease
<b>CDAI</b>	Crohn's Disease Activity Index
<b>eCRF</b>	Electronic Case Report Form
<b>EQ-5D</b>	EuroQoL Questionnaire
<b>HBI</b>	Harvey-Bradshaw Index
<b>HRQoL</b>	Health Related Quality of Life
<b>IBD</b>	Inflammatory Bowel Disease
<b>PMS</b>	Partial Mayo Score
<b>SAP</b>	Statistical Analysis Plan
<b>SAE</b>	Serious Adverse Event
<b>SIBDQ</b>	Short Inflammatory Bowel Disease Questionnaire
<b>UC</b>	Ulcerative Colitis
<b>UCDAI</b>	Ulcerative Colitis Disease Activity Index

### **3. Study Summary**

#### **3.1. Sponsor**

Takeda Farmacéutica España S.A.

#### **3.2. Title**

Impact of co-morbidities on treatment response in inflammatory bowel disease: VERNE study

#### **3.3. Study code**

Vedolizumab-5016 (MACS-2015-101162)

#### **3.4. Scientific committee**

Personal Protected Data



#### **3.5. Participating centers and investigators**

It is estimated that 25 gastroenterology sites will participate in the study in order to ensure representativeness of all the Spanish territory.

#### **3.6. Research ethics committee**

The study protocol and other relevant documents will be submitted to Hospital Universitario y Politécnico La Fe de Valencia ethic committee.

#### **3.7. Study objectives**

The main objective of the present study is to evaluate the impact of the co-morbidities profile on treatment response in Inflammatory Bowel Disease (IBD) patients. The study also aims to describe the percentage of IBD patients exhibiting co-morbidities as well as the level of IBD severity according to the co-morbidities profile.

### **3.8. Study design**

A retrospective, non-interventional, multicentre, observational study that will include consecutive patients diagnosed with Ulcerative Colitis (UC) or Crohn's Disease (CD) who started treatment with biologics between June 2011 and June 2013.

### **3.9. Study disease**

Patients with IBD: UC and CD.

### **3.10. Study population**

Consecutive UC and CD patients that started treatment with biologics between June 2011 and June 2013 that attend a regular visit to the gastroenterology site will participate in the study. A minimum estimated sample of 200 UC patients and 200 CD patients is required. In order to avoid a biased sample (specially selection bias), patients will be recruited consecutively.

### **3.11. Study calendar**

In order to achieve the desired estimated sample, the work filed corresponding to the patients inclusion is estimated at four months. Also, time required for conducting data management, statistical analysis and preparation of the final report is estimated at three months after the inclusion of the last patient.

### **3.12. Coordination and monitoring**

The study will be coordinated by Apices Soluciones SL.

### **3.13. Study sponsor**

This study is funded by Takeda Farmacéutica España S.A.

## 4. Rationale and background

Inflammatory Bowel Disease (IBD) is a group of inflammatory disorders of the gastrointestinal tract whose etiology is believed to be a combination of genetic predisposition to gastrointestinal immune system dysregulation and environmental factors.<sup>1</sup> Crohn's Disease (CD) and Ulcerative Colitis (UC) are IBD major forms and have been empirically defined by clinical, pathological, endoscopic and radiological features, exhibiting a very heterogeneous clinical profile; particularly, CD has different clinical courses and a broad spectrum of patterns, thus making it difficult to choose the best treatment. The course of IBD is characterized by two phases: relapse and remission.<sup>2</sup>

UC is a relapsing non-transmural inflammatory disease that is restricted to the colon and, depending on anatomic extent, can be classified as proctitis, left-sided colitis, or pancolitis.<sup>3</sup> In gastroenterology clinical practice it is usually defined as mild, moderate or severe, depending on the frequency of bloody stools.<sup>4</sup> Many tools have been developed to assess UC severity.<sup>5</sup> Mayo score and Ulcerative Colitis Disease Activity Index (UCDAI or Sutherland Index) were developed in the early 1980s as simplified indexes to classify UC severity and considers three clinical variables and an endoscopy score.<sup>6,7</sup>

On the other hand, CD is a relapsing, transmural inflammatory condition that can affect the entire gastrointestinal tract, and is usually presented as discontinuous involvement of the different sections of the gastrointestinal tract which can lead to several complications (i.e. strictures, abscesses and fistulas). CD phenotype can be classified according to the Vienna criterion which is based on anatomical location and behavior of the disease.<sup>3,8</sup> Also, the Crohn's Disease Activity Index (CDAI) was developed to quantify the symptoms of patients with CD and has been broadly used in order to define response or disease remission when assessing therapeutic options. Index values of 150 and below are associated with quiescent disease; values above that indicate active disease, and values above 450 are reported for extremely severe disease.<sup>9</sup>

In terms of diagnosis, UC can be confirmed through endoscopic and histological studies, whereas CD has no definitive diagnostic, and it is usually conducted based on history, physical examination and findings from endoscopic, radiological, laboratory and histological studies.<sup>3</sup>

In terms of epidemiology, some of the CD and UC highest-incidence areas of the world are northern European countries, the United Kingdom and North America.<sup>1,10</sup> Although the incidence and prevalence of UC and CD are beginning to stabilize in these high-incidence areas, they continue to rise in low-incidence regions (i.e: southern Europe and Asia).<sup>1</sup> It is estimated that 1.4 million and 2.2 million people in the United States and Europe, respectively, suffer from IBD.<sup>1</sup> Spanish incidence of IBD seems to have increased in the last years, and is also variable across regions;<sup>11</sup> UC incidence is estimated at 0.6-8 patients per 100,000 inhabitants per year, whereas there seems to be 0.4-5.5 CD patients per 100,000

inhabitants per year. Spanish IBD prevalence, albeit very difficult to establish, is estimated at 87-110 cases per 100,000 inhabitants per year.<sup>12,13</sup>

The onset of IBD typically occurs in the late adolescence and beginning of adult stages of life and patients tend to progress to relapsing and chronic disease conditions.<sup>14</sup> IBD is known to exert a negative impact in patient's life both in terms of Health Related Quality of Life (HRQoL) and productivity, overall representing a major burden for society and health services.<sup>15,16,17,18,19</sup>

In the recent years, the aim of IBD treatment has evolved from symptomatic control to deep remission, which is defined as the absence of symptoms, markers of inflammatory activity, and endoscopic lesions, and is associated with fewer admissions to hospital, surgeries and better HRQoL.<sup>20,21</sup> Main current treatment modalities for UC and CD include 5-aminosalicylates, corticosteroids, immunomodulators (including thiopurines, methotrexate, tacrolimus, cyclosporine, and biological therapies), and surgery. Conventional treatment with corticosteroids and immunomodulators has not been able to reduce the complications of the disease or modify its course.<sup>22,23</sup> Over the last decade, biologic treatments, such as infliximab, adalimumab, certolizumab pegol, golimumab and vedolizumab has been used in patients with moderate to severe CD, and in those with acute severe UC who failed to respond to corticosteroids.<sup>24</sup>

At present, early introduction of immunomodulators and biologic agents in patients with more serious disease is probably the most widely accepted management strategy.<sup>18-25</sup> Treatment of IBD with anti-TNF $\alpha$  since IBD diagnosis, albeit capable of inducing and maintaining mucosal healing and reducing surgery and hospitalization rates, may imply overtreatment of patients with milder forms of disease, thus emphasizing the need for accurate prognostic markers to guide patient selection.<sup>18,20</sup> It is worth mentioning that although anti-TNF $\alpha$  therapy is thought to be an effective approach for IBD, up to 30% of patients do not respond to induction therapy (primary non-response) and a significant proportion loses response over time (secondary non-response).<sup>26,27</sup> Very often patients profile in randomized controlled trials is quite restrictive and not representative of patients routinely treated under usual clinical conditions, especially, in terms of presence co-morbidities, concomitant treatments and previous use of biologics.<sup>28</sup>

Previous studies and reviews have been conducted in order to determine the impact of co-morbidities on treatment response in diseases like chronic obstructive pulmonary disease.<sup>29,30</sup> However, to the best of our knowledge, this type of correlation has not been subject of study in IBD patients. Varkas *et al.*<sup>31</sup> evaluated the impact of spondyloarthritis on IBD patients, but the co-morbidities profile was not analyzed. Also, Ha *et al.*<sup>32</sup> conducted a study aiming to evaluate IBD management within aging population and identified previous co-morbidities as a variable related to disease progression but, again, the impact of co-morbidities profile on treatment response was not assessed.

In this context, the present study aims to study the effect of certain co-morbidities profile on treatment response by developing a co-morbidity scale to predict response to biological treatment in UC and CD patients.

## 5. Study objectives

### 5.1. Primary objective

- Evaluate the impact of the co-morbidities profile in IBD patients on treatment response to biological therapy.

### 5.2. Secondary objectives

- Evaluate the impact of Extraintestinal Manifestations profile in IBD patients on treatment response to biological therapy.
- Describe the percentage of IBD patients exhibiting co-morbidities.
- Determine the co-morbidities profile according to the level of IBD severity.

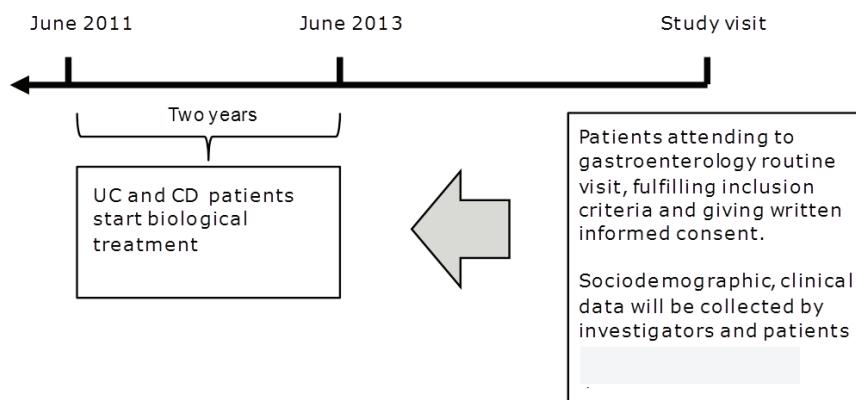
## 6. Methodology

### 6.1. Study design

In order to meet the objectives of the present study, a retrospective, non-interventional, multicentre observational study including 25 gastroenterology sites from all around Spain has been designed. Participating investigators will be gastroenterologists and will include consecutive patients diagnosed with UC or CD that started treatment with biologics between June 2011 and June 2013, after giving written informed consent. The study will consist of one only visit in which investigators will collect patients' sociodemographic (age, gender, race, level of education, smoking habits alcohol intake) and clinical (concomitant diseases, date of diagnosis, previous treatment, current treatment, disease activity when starting treatment with biologics and at the study visit, current situation in terms of treatment with biologics) data from medical charts or directly from patients (in case of discrepancy, the information coming from medical charts will be preferable). Time since patients started biological treatment until study visit or until lack of treatment response or until treatment change will constitute the reference period for the study. In order to fulfill current legislations regarding non-interventional studies, investigators will commit to follow usual clinical practice.

### 6.1.1. Study Scheme

Each investigator will recruit consecutive patients diagnosed with UC or CD that started biological treatment between June 2011 and June 2013, which fulfill inclusion criteria and give written informed consent. Investigators will inform patients about the study objectives and methodology and will fill in electronic Case Report Forms (eCRF) with sociodemographic and clinical data Figure 1 summarizes the study scheme.



**Figure 1.** Study Scheme

### 6.1.2. Study calendar

The expected calendar is as follows:

Months	1	2	3	4	5	6	7
Field work							
Data management							
Data Analysis							
Report							

**Figure 2.** Study calendar

## 6.2. Investigator recruitment, training and site selection

25 gastroenterology centers, representative from all the Spanish territory will be selected. One investigator (gastroenterologist) per center is expected to participate in the study in order to recruit the estimated sample.

### 6.2.1. Investigator recruitment

Study sites will be identified and selected across all the Spanish geographies in order to provide patients representativeness of the Spanish population and in order to enable

fulfillment of the objectives of the study. The study will be conducted among hospital- and office-based gastroenterologists specialized in UC and CD care management.

#### **6.2.2. Investigator training**

A training phone call will be performed to all participant investigators in order to explain the protocol and to train them and their personnel in the eCRF.

### **6.3. Patient selection**

#### **6.3.1. Study population**

The present study will include patients diagnosed with UC or CD that started biological treatment between June 2011 and June 2013, attending physician gastroenterology services in Spain. In order to avoid a biased sample, investigators will recruit consecutive patients. It is estimated that a period of 4 months will be necessary to achieve the desired sample of 200 UC and 200 CD patients.

#### **6.3.2. Inclusion criteria**

- Adult patients (aged  $\geq 18$ )
- Patients diagnosed with UC or CD according to the "World Gastroenterology Organization Practice Guidelines for the Diagnosis and Management of IBD in 2010"<sup>33</sup>
- Patients naive to biologics that started treatment with biologics between June 2011 and June 2013
- Patients in whose biological treatment was prescribed according to daily clinical practice.
- Patients that gave written informed consent

#### **6.3.3. Exclusion criteria**

- Patients that were participating in a clinical trial during the study reference period.
- Patients that, according to investigator's criteria is not capable to understand and fill in the study questionnaires or to give written informed consent

#### 6.3.4. Discontinuation criteria

As it is a retrospective study, there is no possibility of early termination, hence no discontinuation criteria are considered.

#### 6.3.5. Informed consent

Following the current local regulations, patients will be informed on study objective and methodology through a patient's information sheet (appendix 1) and will also have to give written informed consent before data collection begins (appendix 2).

### 6.4. Study procedure

#### 6.4.1. Study visits

The study will consist of only one visit in which investigators will inform patients about the study objective and methodology and the possibility to take part of it. All data will be collected during the study visit or retrospectively from patients' clinical chart after giving written informed consent. More detail on data collection is given on sections 6.4.3, 6.4.4 and 6.4.5.

#### 6.4.2. Study site monitoring

Regular fortnightly phone calls will be made by study monitors in order to check inclusion status, solve any potential recruitment issues, check data plausibility etc.

As the CRFs will be electronic, filters in the eCRF design may limit the number of queries. Nevertheless, study monitors will check the entered data and deal with any possible queries which may arise in relation with the core data set. If electronic queries are subsequently generated, these will be resolved with physicians by study monitors before completion and validation of the database. The corrections to data will be included in the eCRF either by the investigators or the study monitors. Any correction to data will be recorded in the system together with the automatic identification of the person who performed it and the corresponding date (audit trail). Ongoing eCRF review will be done by the CRO during the study field work.

#### 6.4.3. Data collection

25 gastroenterology centers (one investigator per center) from all around Spain will participate in the study. In order to achieve the minimum sample, each gastroenterology specialist will have 4 months to include approximately 8 UC and 8 CD consecutive patients that fulfill the inclusion/exclusion criteria specified on sections 6.3.2 and 6.3.3. Investigators will inform patients about the study objectives and

methodology and patients will have to give written informed consent before inclusion in the study as specified on section 6.3.5.

Investigators will collect sociodemographic and clinical data from patients' records specified on section 6.4.3 and will introduce it in the eCRF.

#### 6.4.4. Study variables

The following **sociodemographic variables** will be collected from patients' medical records or directly from patients during the study visit, straight after their inclusion in the study:

- Age
- Gender
- Race (caucasian, asiatic, latin, black, other)
- Level of education (uneducated, primary education, secondary education, university education)
- Working status (student, self-employed, employed by other, retired, housework, unemployed, temporarily unable to work, permanently unable to work, other)
- Smoking habits (non-smoker, ex-smoker, smoker, number of cigarettes per day)
- Alcohol intake (units per week).

The following **clinical variables** will be collected from patients' medical records (when available) or directly from patients during the study visit, straight after their inclusion in the study:

- Date of diagnosis (UD or CD).
- Disease activity at the beginning of the reference period and at the study visit through collection of the following variables:
  - For UC patients:
    - Partial Mayo Score (PMS) (9 point scale that excludes the endoscopic appearance of the mucosa)<sup>34</sup>
    - General disease activity:<sup>2</sup>
      - Mild: up to four bloody stools daily and no systemic toxicity
      - Moderate: four to six bloody stools daily and minimal toxicity
      - Severe: more than six bloody stools daily and signs of toxicity, such as fever, tachycardia, anaemia, raised erythrocyte sedimentation rate.
      - Fulminant: More than ten bloody stools daily, continuous bleeding, anaemia requiring blood transfusion, abdominal tenderness and colonic dilatation on plain abdominal radiographs.
    - Disease anatomic extent: proctitis, left-sided colitis or pancolitis.
    - Endoscopy findings:

- Normal or inactive disease
- Mild disease (erythema, decreased vascular pattern, mild friability)
- Moderate disease (marked erythema, lack of vascular pattern, friability erosions)
- Severe disease (spontaneous bleeding, ulceration).
- For CD patients:
  - Harvey-Bradshaw Index (HBI) (a simplified version of CDAI)<sup>35</sup>
  - General disease activity:<sup>2</sup>
    - Mild to moderate: ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity, abdominal tenderness, painful mass, obstruction or >10% weight loss.
    - Moderate to severe: failure to respond to treatment for mild disease, more prominent symptoms of fever, weight loss, abdominal pain or tenderness, intermittent nausea and vomiting without obstruction, or significant anemia.
    - Severe to fulminant: persisting symptoms on corticosteroids, high fevers, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of abscess.
  - Disease behaviour: non-stricting and non-penetrating, stricturing and penetrating (fistulas and abscesses),
  - Disease location: terminal ileum.
- For CD and UC patients:<sup>2,33</sup>
  - Stool frequency (normal number for this patient, 1-2 stools more than normal, 3-4 more stools than normal, 5 or more stools than normal)
  - Rectal bleeding (no blood seen, streaks of blood with stool less than half the time, obvious blood with stool most of the time, blood alone passes)
  - Urgency (hurry, immediately, incontinence)
  - Nocturnal stools (yes/no)
  - Need for antidiarrheal drugs (yes/no)
  - Constipation (yes/no)
  - Abdominal tenderness (none, mild and localized, mild to moderate and diffuse, severe or rebound)
  - Abdominal pain or cramping (none, mild, moderate, severe)
  - Anorexia (yes/no)
  - Nausea (yes/no)
  - Vomiting (yes/no)
  - Fever (yes/no)
  - Appetite loss
  - Weight loss (yes/no)
  - Fatigue (yes/no)
  - Night sweats (yes/no)

- Stunted growth (yes/no)
- Primary amenorrhoea (yes/no)
- General well-being (generally poor, fair, poor, terrible)
- Physician's global assessment (normal or quiescent disease severity, mild disease activity, moderate disease activity, severe disease activity)
- Other complications: severe profuse bleeding, massive bleeding due to ulceration, presence of stomach or duodenum ulceration, intestinal perforation, intraabdominal abscesses, stenosis, obstruction, fistulas, megacolon, others.
- Extraintestinal manifestations in UC and CD patients to be chosen from the following list according to ECCO guidelines:<sup>33</sup>
  - Arthropathy and arthritis
  - Metabolic bone disease
  - Eye disease
  - Oral, aural and nasal disease
  - Skin disease
  - Hepato-pancreato-biliary disease
  - Neurological disease
  - Cardiovascular manifestations of IBD
  - Pulmonary manifestations of IBD
- Urogenital manifestations of IBDComorbidities in UC and CD patients (defined as the coexistence of another medical condition alongside IBD, and does not imply causation) at the time of diagnosis and at the study visit, will be listed according to chosen according to the Charlson index:<sup>36</sup>

<b>Comorbidity Component</b>	<b>Score</b>
Myocardial Infarction	1
Congestive Heart Failure	1
Peripheral Vascular Disease	1
Cerebrovascular Disease	1
Dementia	1
Chronic Obstructive Pulmonary Disease	1
Connective Tissue Disease	1
Peptic Ulcer Disease	1
Diabetes Mellitus	1 (mild), 2 (moderate- severe)
Moderate-Severe      Chronic      Kidney Disease	2
Hemiplegic	2
Leukemia	2
Malignant Lymphoma	2
Solid Tumor	2 (tumor), 6 (if metastasis)
Liver Disease	1 (mild), 3 (moderate-severe)
Acquired immunodeficiency syndrome (AIDS)	6

- Biological treatment/s for UC or CD followed during the reference period:
  - Starting date
  - Posology
  - Intensification of biological treatment: date and type of intensification
  - Continuing with the treatment
  - Date and reason for discontinuation, if applicable
  - New biological treatment prescribed after discontinuation, starting date, posology, continuing with the treatment, date and reason for discontinuation.
- Concomitant treatment with corticosteroids (e.g. prednisone, hydrocortisone, betamethasone, methylprednisolone, etc,) or immunosuppressives (e.g. Ciclosporin, Methotrexate, etc) during induction phase
  - Starting date, number of cycles

Other treatments followed before the reference period to be chosen from the following list:

- Aminosalicylates (e.g. mesalazine, Sulfasalazine, 5-ASA, etc), oral, enema, suppository.
- Corticosteroids (e.g. prednisone, hydrocortisone, betamethasone, methylprednisolone, etc), oral, enema, suppository.
- Thiopurines (e.g. azathioprine, mercaptopurine, etc).
- Immunosuppressives (e.g. Ciclosporin, Methotrexate, etc).
- Anti-diarrheal drugs.
- Pain medications.
- Antidepressants.
- Antibiotics.
- Use of alternative medicine (e.g. acupuncture, relaxation therapy, Qigong, herbal therapy, etc).
- Other (specify)

- Other treatments followed during the reference period to be chosen from the following list:
  - Aminosalicylates (e.g. mesalazine, Sulfasalazine, 5-ASA, etc), oral, enema, suppository.
  - Corticosteroids (e.g. prednisone, hydrocortisone, betamethasone, methylprednisolone, etc), oral, enema, suppository. Number of cycles
  - Thiopurines (e.g. azathioprine, mercaptopurine, etc).
  - Immunosuppressives (e.g. Ciclosporin, Methotrexate, etc).
  - Anti-diarrheal drugs.
  - Pain medications.

- Antidepressants.
- Antibiotics.
- Use of alternative medicine (e.g. acupuncture, relaxation therapy, Qigong, herbal therapy, etc).
- Other (specify)

All patients' data will be handled in a manner that preserves confidentiality.

#### 6.4.5. Main outcome

Non responders will be those patients not achieving a reduction in HBI of at least 2 points from baseline for CD,<sup>35</sup> and a decrease in the PMS of at least 2 points for UC<sup>34</sup>.<sup>37</sup>. In the cases where these indexes are not available, clinical response will be evaluated according to physician criteria at short term (10 weeks after starting the anti-TNF) and at long term (at least 6 months after starting the anti-TNF). Primary non-responders (PNR) were defined as patients with no clinical response at short term. Loss of response (LOR) was defined as loss of the effect of the drug along the follow up in a patient with initial response<sup>37</sup>.

Reasons to stop the drug will be classified as follows: PNR, LOR, side effects (SE), remission and other<sup>37</sup>.

## 7. Statistical Analysis

### 7.1. Sample size calculation

Response to treatment with biologics is estimated at 50%, meaning that half of included patients are expected to be non-responders. Considering a minimal sample of 10 patients that present the event of interest per independent variable included in the logistic regression model and a maximum of 10 independent variables per model, a minimum estimated sample of 200 UC patients and 200 CD patients is required.

### 7.2. Analysis population

All patients participating in the study that fulfill inclusion criteria, not presenting a major deviation of the study protocol will be included in the analysis.

### 7.3. General statistical analysis considerations

This section describes the main analyses that will be performed. Further information about detailed analyses, the methods of handling missing data, analysis methods and a list of table shells will be documented in a Statistical Analysis Plan (SAP) that will be

agreed with Takeda. All data analyses will be performed using SAS statistics software version 9.1 (SAS Institute Inc., Cary, NC) or SPSS for Windows version 19. All analyses will be performed in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines<sup>24</sup> and applicable sections of the Consolidated Standards of Reporting Trials (CONSORT) guidelines<sup>25</sup>.

All analyses will be primarily performed by descriptive statistical methods.

Continuous variables will be described with number of patients with valid / missing observations, mean, standard deviation, median, minimum and maximum. Additional descriptive statistics may be calculated as needed (e.g. quartiles other than the median, coefficient of variation, etc.). In particular, for non-normally distributed data, the median and interquartile range will be calculated. Categorical variables will be described by frequencies and related percentages per class level. Summaries will be reported overall.

In addition to descriptive analysis, many of the endpoints will undergo statistical testing to provide inferential summaries of subgroup comparisons (i.e. p-values, confidence limits).

Inter-individual comparisons will be performed: 2 sample t-test, Mann-Whitney test, ANOVA or Kruskall-Wallis test will be used to compare quantitative variables between study groups or categories or categorical variables; chi-square test or the exact Fisher test will be used to compare categorical variables between them.

#### **7.4. Assessment of the primary objective: Evaluate the impact of the co-morbidities profile in IBD patients on treatment response to biological therapy**

In order to determine the level of correlation between the co-morbidities profile and treatment response, adjusting for sociodemographic and clinical profile of patients, two logistic regression models will be conducted. The dependent variable of the models will be the lack of response during the induction phase (primary non response) and the loss of response during the maintenance phase (secondary loss of response) (see section 6.4.6). In both models independent variables will include all comorbidities included in the study, as well as sociodemographic and clinical variables as covariates. The maximum number of independent variables included in the model will be defined according to the number of patients per response category in the dependent variable. The maximum number of variables will be defined to ensure a minimum of 10 patients per independent variable and response category in the dependent one.

Depending on the volume of patients that have discontinued a biological treatment and started treatment with a different biologic during the reference period, this sample may be separately analyzed.

## **7.5. Percentage of IBD patients exhibiting co-morbidities**

The number, percentage, and 95% confidence interval of IBD patients with each co-morbidity will be described.

## **7.6. Co-morbidities profile according to the level of IBD severity**

The percentage of patients reporting each co-morbidity at treatment initiation will be compared according to the IBD severity assessed using the PMS and the general disease activity for UC patients and the HBI and the general disease activity for CD patients. Multivariable regression models will be used to assess the relationship between the co-morbidities profile and the level of IBD severity.

# **8. Data management**

Patients' data will be collected through an eCRF specially designed for this study. The eCRF will constitute the analysis data source and will consist of a web application accessible from any computer with internet access. The SSL (128 bites) protocol will be used for web communication, ensuring confidentiality for all communication between servers and investigators computers by encrypting all data sent (safe connection).

Each investigator will have a user name and password to guarantee that data is not accessible to anyone else. Each investigator or designated person will be responsible for registering and verifying accuracy of patients' data introduced in the eCRF. By signing this protocol, investigators accept their digital signature to be legally equivalent and binding to its written form. When introducing their digital signature, investigators confirm all data has been reviewed and is considered accurate.

All data recorded by investigators will be reviewed by CRO personnel to detect missing information and data inconsistencies and indicate the corresponding queries in the monitoring reports. If any inconsistency is detected and resolved before locking the database, corrections will be included in the database.

Once the field work has been completed data collected will be validated for quality control and the statistical analysis of the results will be performed by the CRO.

The eCRF will allow defining filters in collected variables in order to avoid mistakes, as well as to obtain statistics about the main outcomes in real time. The eCRF will include specific logic checks and filters for collected variables in an effort to minimize errors in data entry. The eCRF will also allow the study team to obtain statistics on recruitment and eCRF completion progression in 'real-time'. The web application will be developed with the following technology:

- ASP.NET 2.0
- RDBMS My SQL v.5.0
- IIS 6.0
- SSL (128bits) validated by Verisign
- WEB server O.S. Windows 2003

The SSL technology implemented guarantees that all data transferred to the CRO database server will be encrypted and protected from external attacks. An audit trail process will ensure control of every movement made to the data stored. Information registered for every value stored in the database includes: the event date, responsible party, variable, old value, new value, and the type of action taken (creation, updating or deleting). This audit process provides an additional security mechanism for stored data and may also be useful in answering data entry questions by site personnel.

The two questionnaires to be filled in by patients during the study visit will be sent to investigators together with all the study documents. Investigators will have to send all questionnaires completed by included patients at their site to the CRO.

## 9. Practical considerations

### 9.1. Electronic case report form

An eCRF will be specifically designed for the present study and will include all the study variables required to meet the primary and secondary objectives of the study. The eCRF will consist of a web application accessible from any computer with internet access. Each investigator will have a unique access code to introduce patients' information in the eCRF.

Each patient will be assigned a 4-digit code: the two first digits will correspond to the site in which the patient has been recruited and the two last digits will be consecutively assigned after patient's inclusion in the study.

### 9.2. Monitoring and quality of data

On-site monitoring will not be conducted in the context of this study. Regular fortnightly phone calls will be made by study monitors in order to check inclusion status, solve any potential recruitment issues, check data plausibility etc. Investigators will receive all documents before the study begins. The CRO will provide instructions to investigators on how to introduce data in the eCRF when data collection starts; these instructions will also be briefly reminded to investigators every time they access the eCRF. During the

entire duration of the study, The CRO will provide technical support to investigators participating in the study.

Each investigator will be responsible for ensuring the accuracy of data entered in the eCRF as well as for completing all sections included in the eCRF. Each investigator commits to enter all data following their usual clinical practice.

The CRO will be responsible for supervising patients' recruitment through eCRF. During data collection period, standard monthly emails will be sent to investigators to inform about its progression, deal with any issues and remind investigators on their responsibilities. The CRO will guarantee database quality, compliance and accuracy of data introduced in the eCRF. The CRO will review the information entered through the web application weekly to guarantee data is being introduced correctly. If an inconsistency is detected during eCRF data review, the CRO will contact investigators via fax or email so that information can be clarified.

Investigators will guard original documents from each patient. All the information introduced in the eCRF will need to be traceable from original medical charts. Participating investigators from each site will keep a patient tracking sheet that will contain patients name together with assigned consecutive numbers and date of birth to allow identification. Investigators must also keep the original signed written informed consent from all patients included in the study.

When the CRO receives the completed questionnaires they will be handed to data entry department personnel that will introduce questionnaire answers in the study data base. Patients' questionnaires will be kept in the CRO office until statistical final report is completed. After that, they will be kept by the study sponsor.

## **10. Ethical considerations**

Investigators participating in the study will follow the principles described in the latest version of the Helsinki Declaration. Copies of the Helsinki Declaration and subsequent revisions will be supplied on request or can be obtained from the World Medical Association website (<http://www.wma.net/e/policy/17-c.html>). The study will follow the International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences-CIOMS-Ginebra, 2009) and local recommendations.

The study will be reviewed and approved by the appropriate Ethics Committee(s) according to their specific legal requirements. The study follows Spanish data protection laws; patient and data confidentiality will be respected.

The type of approvals required and the estimated time to receive approvals depends on requirements of the local ethical committees.

## 11. Confidentiality

### 11.1. Patient confidentiality

Information on patients' identity shall be considered as confidential for all effects and purposes. Each site and patient will have a study code. Sites will be automatically coded in the study website through the identification code and password assigned to each investigator. Patients will be assigned a sequential number by the study website upon meeting all inclusion and no exclusion criteria. Confidential patient tracking sheets, listing patient sequential numbers together with patient name and date of birth, will be kept by investigators at the study site for identification.

Patients' identity should not be revealed nor published under any circumstances. Patient data recorded in the eCRF will be documented anonymously, coded with a patient number in such a way that only the investigator and site staff may associate particular data with an identified or identifiable individual or his/her medical record. All other parties involved in data management, analysis and storage will receive, and subsequently analyze, non-identifiable patient data.

### 11.2. Data confidentiality

By signing the investigator's confidentiality agreement, the investigator affirms to Takeda that information furnished by Takeda to the investigator will be kept in confidence and such information will be divulged to any expert committee, affiliated institution, and employees only under an appropriate understanding of confidentiality with such committee, affiliated institution and employees.

Data security will be maintained by data being recorded in a central database and tracked using an audit trail. The system will allow retrieving all entered data at any time, and will include security elements to prevent others than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A security copy of the database and the application files will be made outside the server housing the web-based study. Security copies will be periodically made and stored outside this server. A copy of the data stored in the database will be transferred to Takeda at the end of the study.

## 12. Study administration

The entire study will be managed by a project coordinator at the CRO who will coordinate the project and maintain fluid communication with the study sponsor and the study team at the CRO.

As part of the monitoring plan, regular phone calls (at least every two weeks) will be made by local study monitors in order to check inclusion status, resolve any issues, check data plausibility, etc.

## **13. Investigators compliance**

By signing the investigator's agreement, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of good clinical practice and all applicable laws, rules and regulations relating to the conduct of the study.

The investigator shall prepare and maintain complete and accurate study documentation in compliance with applicable national and local laws, rules and regulations and, for each patient participating in the study, promptly record all data in the eCRF as required by this protocol.

## **14. Management and reporting of adverse events or adverse reactions**

### **14.1. Definitions**

#### **14.1.1. Definition of Adverse Event**

An AE is defined as any untoward medical occurrence in a patient administered a drug or has undergone procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

#### **14.1.2. Definition of Adverse Drug Reaction**

An Adverse Drug Reaction (ADR) is defined as 'Any noxious and unintended response associated with the use of a drug in humans, at any dose, where a causal relationship (drug-event) is at least a reasonable possibility'. x Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

#### 14.1.3. Definition of Serious Adverse Event

An adverse event is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an adverse event is considered “life-threatening” if, in the view of either the investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of existing hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events (Including transmission of an infectious agent)

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

#### 14.1.4. Special Situations

The following special situations, although not necessarily considered to be AEs or ADR must be reported in the same way as ADR, or even in the same way as SAEs.

- Off-label use: situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
- Overdose (accidental or intentional): administration of a quantity of a medicinal product given per administration or cumulatively which is above

the maximum recommended dose according to the authorized product information.

- Misuse of a medicinal product: situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
- Abuse of a medicinal product: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Drug exposure during pregnancy and/or breast-feeding. Exposure during pregnancy is considered either through maternal exposure or via semen following paternal exposure.
- Lack of efficacy/effectiveness
- Medication errors: are broadly defined as any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not.
- Occupational exposure: this refers to the exposure to a medicinal product, as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting
- Falsified product: this refers to the use of a fake or counterfeit medicine, that passes itself off as a real, authorized medicine

#### 14.1.5. Criteria for Causal Relationship to the (Study) Drug

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 (eg, 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.

## **14.2. Handling of Adverse Events**

### **14.2.1. Reporting of Adverse Reactions**

According to the Order SAS/3470/2009, of 16 December, with published guidelines on post-authorization studies of drugs for human use, those studies in which it is not possible or not appropriate to do an individual assessment of the causal relation between clinical events and drugs of interest, individual reporting of suspected adverse reactions is not required. Studies labelled PAS-OD fall into this category and they do not require expedited reporting of suspected adverse reactions, unless otherwise specified by the AEMPS at the time of registration of the study.

In addition to that specified in the preceding paragraph, any relevant safety problem found during the course of the study will be made known to the AEMPS and the competent bodies of the Autonomous Communities involved, regardless of study design and documentation.

However, it is the responsibility of the investigator to report suspected serious adverse reactions that are detected during the course of the study to the contact point designated by the competent body on pharmacovigilance of the autonomous community in which the investigator reporting the case operates.

### **14.2.2. Collection and Recording of Adverse Events**

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

Information on all AEs or special situations, associated with the use of any product marketed by Takeda, whether initial or follow-up, serious or non-serious, that come to the attention of the investigator during the study visit should be recorded on the Takeda AE reporting form (see APPENDIX 5) and notified to the Sponsor within 24 hours of the Investigator's first awareness, using the following email address: [farmacovigilancia@takeda.com](mailto:farmacovigilancia@takeda.com)

In case the CRO is aware of any AE or special situation associated with the use of any product marketed by Takeda, it shall be the responsibility of the CRO to send such information recorded on the Takeda AE reporting form (see APPENDIX 5) to the pharmacovigilance department at Takeda within 24 hours from reception through the email address [farmacovigilancia@takeda.com](mailto:farmacovigilancia@takeda.com)

On a quarterly basis Takeda Pharmacovigilance will send a list of the adverse events received to the CRO in order to perform the corresponding reconciliation process. Then the CRO will send back the discrepancies to Takeda Pharmacovigilance for resolution.

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