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

NCT Number: NCT02861118

SAP Approve Date: February 15, 2017

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# "Impact of co-morbidities on treatment response in inflammatory bowel disease"

## VERNE Study

## APICES Project No. TAK125008

## Statistical Analysis Plan

**Version 1.0**
**February 15th, 2017**

| | |
|---|---|
| **Prepared by:** | Personal Protected Data (PPD) |
| **Reviewed by:** | |
| **Approved by:** | |

## 1. HISTORY OF REVISION (Documentation of changes)

| SECTIONS | VERSION | DATE REVISED | REVISED BY | DESCRIPTION OF CHANGES |
|---|---|---|---|---|
| | | | | |
| | | | | |
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| | | | | |

## INDEX

## 2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis for VERNE study. In it is described all consideration over study data and are defined the tables, figures and listing (TLFs) that will be presented as result of the study.

Additionally includes definition of the different population and missing data consideration.

The statistical analysis plan will be signed and per protocol dataset will be defined before database lock.

Table of abbreviations

| | |
|---|---|
| CD | Crohn's Disease |
| UC | Ulcerative Colitis |
| IBD | Inflammatory Bowel Disease |
| HBI | Harvey-Bradshaw Index |
| PMS | Partial Mayo Score |
| PNR | Primary non-response |
| LOR | Secondary Loss of response |
| PR | Partial response |
| SE | Side Effects |
| 95% CI | 95% Confidence Interval |

# 3. SYNOPSIS

## 3.1. Study title

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

## 3.2. Study Code

MACS-2015-101162

## 3.3. Sponsor

Takeda Farmacéutica España S.A.
Address: C/ Alsasua 20, 28023 - Madrid (Spain)
Phone: +34 91 7149900
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## 3.4. 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.

## 3.5. Objectives

Primary:

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

Secondary:

- 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.

## 3.6. Total number of subjects

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.

### 3.7. Inclusion Criteria

- Adult patients (aged ≥18).
- Patients diagnosed with UC or CD according to the "World Gastroenterology Organization Practice Guidelines for the Diagnosis and Management of IBD in 2010".
- 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.

### 3.8. 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.

### 3.9. Study treatment

The patients participating in this retrospective, non-interventional, multicentre, observational study will not receive treatment in relation to the study aside from the treatment already prescribed by their usual physician. In order to fulfill current legislations regarding non-interventional studies, investigators will commit to follow usual clinical practice.

## 4. STUDY POPULATIONS

### 4.1. Definition of study populations to analyse

**Study Population:** All patients who meet the selection criteria and have given their informed consent will be included in the analysis.

### 4.2. Disposition of subjects

A flowchart will be provided to describe the total included patients in each part of analysis for patients with Crohn's Disease and Ulcerative Colitis separately. Discrepancies between the numbers of patients of each part of the analysis will be described by number of patient, site and the reason of the discrepancy.

### 4.3. Study Discontinuations

Not applicable.

# 5. SUBJECT DESCRIPTION

## 5.1. Demographic and baseline description. General considerations

All analysis will be described for patients with Crohn's Disease and Ulcerative Colitis separately.

The demographic and baseline description will be performed for all "analyzed patients".

Given the descriptive nature of the study, the statistical methodology used will be based primarily on an exploratory analysis of the data through the calculation of descriptive parameters.

The continuous variables will be summarized in a table showing the mean, median, standard deviation and maximum-minimum range and the categorical variables will be presented as absolute frequencies and percentages.

## 5.2. Subject Characteristics

The analysis of continuous variables will be described by the mean, median, standard deviation, minimum and maximum. This analysis included the age of patients and number pack-year in smoking habits.

The analysis of categorical variables will be described by the distribution of frequencies and percentages. This analysis included the following variables:

- 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 and smoker).
- Alcohol abuse (yes/no).

## 5.3. Disease characteristics

The analysis of continuous variables included the following variables:

- Time from diagnostic of disease (UC or CD) (time in months from the date of diagnostic until the date of informed consent).
- Charlson index.

The analysis of categorical variables included the following variables:

- Disease location (L1=terminal ileum; L2= colon; L3=ileum and colon; L4=upper gastrointestinal track; E1=proctitis; E2=left colitis; E3=extensive colitis).
- Disease behavior (only for CD patients) (B1=inflammatory; B2=stenosis; B3= fistulizing; B1p; B2p; B3p (p=perineal)).
- Extraintestinal manifestations:
    - Arthropathy and arthritis (yes/no).
    - Metabolic bone disease (yes/no).
    - Eye disease (yes/no).
    - Oral, aural and nasal disease (yes/no).

- Skin disease (yes/no).
- Hepato-pancreato-biliary disease (yes/no).
- Neurological disease (yes/no).
- Cardiovascular manifestations of IBD (yes/no).
- Pulmonary manifestations of IBD (yes/no).

## 6. TREATMENT DESCRIPTION

All analysis will be described for patients with Crohn's Disease and Ulcerative Colitis separately.

### 6.1. Biological treatment

We will describe the treatments administered to the patients:

- Number and percentage of patients who received each biological treatment (infliximab, adalimumab, golimumab and others).
- Number and percentage of patients who intensified the biological treatment and the reason (increased doses, decreased intervals between doses or both) according to the different biological treatment specified.
- Number and percentage of patients who discontinued the treatment and the reason (PNR, LOR, PR, SE, remission and others) according to the different biological treatment specified.
- Number and percentage of patients who received a second biological treatment and the description of the different biological treatments and the number of biological treatments received after discontinuation.
- Number and percentage of patients who received concomitant treatment with corticosteroids or immunosuppressives during induction phase. Description of the different concomitant treatment received.

### 6.2. Treatments received before the reference period

- Number and percentage of patients who received at least one treatment before the reference period.
  - Number and percentage of patients who received aminosalicylates and the description of the treatments received (mesalazine, sulfasalazine, others).
  - Number and percentage of patients who received corticosteroids and the description of the treatments received (prednisone, hydrocortisone, methylprednisolone, Beclomethasone, budesonide, others).
  - Number and percentage of patients who received Immunosuppressives and the description of the treatments received (ciclosporin, methotrexate, azathioprine, mercaptopurin, others).
  - Number and percentage of patients who received anti-diarrheal drugs.
  - Number and percentage of patients who received pain medications.
  - Number and percentage of patients who received antidepressants.
  - Number and percentage of patients who received antibiotics.

- Number and percentage of patients who used alternative medicine and the description of the therapy received (acupuncture, relaxation therapy, Qigong, herbal therapy, others).
- Number and percentage of patients who received cannabis.
- Number and percentage of patients who received other treatments and the description of the treatment received.

### 6.3. Treatments received during the reference period (maintenance phase).

- Number and percentage of patients who received at least one concomitant treatment during the reference period (maintenance phase).
  - Number and percentage of patients who received aminosalicylates and the description of the treatments received (mesalazine, sulfasalazine, others).
  - Number and percentage of patients who received corticosteroids and the description of the treatments received (prednisone, hydrocortisone, methylprednisolone, Beclomethasone, budesonide, others).
  - Number and percentage of patients who received Immunosuppressives and the description of the treatments received (ciclosporin, methotrexate, azathioprine, mercaptopurin, others).
  - Number and percentage of patients who received anti-diarrheal drugs.
  - Number and percentage of patients who received pain medications.
  - Number and percentage of patients who received antidepressants.
  - Number and percentage of patients who received antibiotics.
  - Number and percentage of patients who used alternative medicine and the description of the therapy received (acupuncture, relaxation therapy, Qigong, herbal therapy, others).
  - Number and percentage of patients who received cannabis.
  - Number and percentage of patients who received others treatments and the description of the treatment received.

## 7. EFFICACY ASSESSMENT

### 7.1. Efficacy Assessment; general considerations

Non responders will be those patients not achieving a reduction in HBI of at least 2 points from baseline for CD and a decrease in the PMS of at least 2 points for UC.

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 [*primary response and primary non-response*]) and at long term (at least 6 months after starting the anti-TNF [*primary response maintenance and loss of response*]).

We will calculate the following variables:

- **Lack response during the induction phase (primary non response):** Those patients who 10 weeks after starting the anti-TNF not achieving a reduction in HBI of at least 2 points from baseline for CD and a decrease in the PMS of at least 2 points for UC. In the cases where these indexes are not available, clinical response will be evaluated according to physician criteria at short term (*primary response and primary non-response*).
- **Loss of response during the maintenance phase (secondary loss of response):** Those patients who at least 6 months after starting the anti-TNF not achieving a reduction in HBI of at least 2 points from baseline for CD and a decrease in the PMS of at least 2 points for UC. In the cases where these indexes are not available, clinical response will be evaluated according to physician criteria at short term (*primary response maintenance and loss of response*).

## 7.2. Primary efficacy endpoint

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

  The analysis that will be performed to answer the objective will be the following:

  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** and the **loss of response during the maintenance phase**. In both models independent variables will include all comorbidities, as well as sociodemographic and clinical variables as covariates.

  - The following potential variables will be considered for the analysis:
    - Crohn's Disease or Ulcerative Colitis.
    - Myocardial Infarction (yes/no).
    - Congestive Heart Failure (yes/no).
    - Peripheral Vascular Disease (yes/no).
    - Cerebrovascular Disease (yes/no).
    - Dementia (yes/no).
    - Chronic Obstructive Pulmonary Disease (yes/no).
    - Connective Tissue Disease (yes/no).
    - Peptic Ulcer Disease (yes/no).
    - Mild Chronic Hepatopathy (yes/no).
    - Diabetes Mellitus (yes/no).
    - Hemiplegic (yes/no).
    - Moderate-Severe Chronic Kidney Disease (yes/no).
    - Diabetes with lesions in target organs (yes/no).
    - Solid Tumor (yes/no).
    - Leukemia (yes/no).
    - Lymphoma (yes/no).

- Moderate-Severe Chronic Hepatopathy (yes/no).
- Solid tumor with metastases (yes/no)
- Acquired immunodeficiency syndrome (AIDS) (yes/no).
- 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 and smoker).
- Alcohol abuse (yes/no).
- Time from diagnostic of disease.
- Disease location.
- Discontinuation the biological treatment (yes/no)

- Each one of the variables will be compared between the subjects with primary non-response vs primary response and primary response maintenance vs loss of response and those variables whose p-value is lower than 0.1 are considered potential variables for performing a logistic regression analysis.
  - For the comparison of the variables between subjects, the following criteria will be considered: dichotomous or categorical variables will be compared between the two groups using the Chi-squared test. Continuous variables will be compared between the two groups using the Student's T-test for independent samples.
- The logistic regression models will be assessed and the results will be submitted for any statistically significant model, providing the following results: Odds Ratio, 95%CI, p-value, sensitivity and specificity. The models will be assessed using stepwise automatic variable Wald entry (backward and forward) techniques and entry also assessing the specificity and sensitivity of the final model.

## 7.3. Secondary efficacy endpoints

- Secondary endpoint: **Evaluate the impact of Extraintestinal Manifestations profile in IBD patients on treatment response to biological therapy.**

  The analysis that will be performed to answer the objective will be the following:

  To evaluate the impact of extraintestinal manifestations profile in IBD patients on treatment response to biological therapy, a logistic regression analysis will be performed, in which **lack of response during the induction phase** will be used as the dependent variable and patient disease (CD or UC) and different extraintestinal manifestations variables (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) will be used as independent variables, yielding the following results: Odds Ratio, 95%CI, p-value, sensitivity and specificity.

We will repeat this analysis with the **loss of response during the maintenance phase variable** as dependent variable.

- Secondary endpoint: **Describe the percentage of IBD patients exhibiting co-morbidities.**
  The analysis that will be performed to answer the objective will be the following:
  We will provide the frequencies, percentages and 95%CI of the following comorbidities for patients with Crohn's Disease and Ulcerative Colitis separately:
  - Myocardial Infarction (yes/no).
  - Congestive Heart Failure (yes/no).
  - Peripheral Vascular Disease (yes/no).
  - Cerebrovascular Disease (yes/no).
  - Dementia (yes/no).
  - Chronic Obstructive Pulmonary Disease (yes/no).
  - Connective Tissue Disease (yes/no).
  - Peptic Ulcer Disease (yes/no).
  - Mild Chronic Hepatopathy (yes/no).
  - Diabetes Mellitus (yes/no).
  - Hemiplegic (yes/no).
  - Moderate-Severe Chronic Kidney Disease (yes/no).
  - Diabetes with lesions in target organs (yes/no).
  - Solid Tumor (yes/no).
  - Leukemia (yes/no).
  - Lymphoma (yes/no).
  - Moderate-Severe Chronic Hepatopathy (yes/no).
  - Solid tumor with metastases (yes/no)
  - Acquired immunodeficiency syndrome (AIDS) (yes/no).

- Secondary endpoint: **Determine the co-morbidities profile according to the level of IBD severity.**
  The analysis that will be performed to answer the objective will be the following:
  We will classify to the patients into IBD severe or non-severe at baseline based on the HBI and PMI scores according the following criteria:

  Harvey-Bradshaw Index score
  - Non severe (Remission <5; Mild disease 5-7; Moderate disease 8-16)
  - Severe disease >16

  Partial Mayo Index Score
  - Non severe (Remission = 0-1; Mild Disease = 2-4; Moderate Disease = 5-7)
  - Severe Disease =8-9

We will compare the percentage of patients reporting each co-morbidity between IBP severe or non-severe using Chi-Square.

A logistic regression analysis will be performed, in which **IBP severe or non-severe at baseline** will be used as the dependent variable and patient disease (CD or UC) and different comorbidities variables will be used as independent variables, yielding the following results: Odds Ratio, 95%CI, p-value, sensitivity and specificity.

## APPENDIX 1: INDEX OF SECTION 14 FOR THE CLINICAL REPORT

The following proposal for section 14 is done according to the pre-defined ICH-format. Minor changes from this planned index do not need to be amended in the SAP.

Comments in Italics will not be printed in table headers or footers.

Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.

| | TITLE | TABLE TYPE | ANALYSIS SET | *COMMENT* |
|---|---|---|---|---|
| **14.** | **TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT** | | | |
| **14.1** | **DEMOGRAPHIC AND BASELINE DATA** | | | |
| 14.1.1 | Subject disposition | CAT2 | General population | |
| 14.1.2 | Subject characteristics | | | |
| 14.1.2.1 | Gender, Race | CAT2 | Study population | |
| 14.1.2.2 | Level of education | CAT2 | Study population | |
| 14.1.2.3 | Working status | CAT2 | Study population | |
| 14.1.2.4 | Smoking habits / Alcohol abuse | CAT2 | Study population | |
| 14.1.3 | Disease characteristics | | | |
| 14.1.3.1 | Time from diagnostic of disease | CONT2 | Study population | |
| 14.1.3.2 | Charlson index | CONT2 | Study population | |

| | TITLE | TABLE TYPE | ANALYSIS SET | COMMENT |
|---|---|---|---|---|
| 14.1.3.3 | Disease location | CAT2 | Study population | |
| 14.1.3.4 | Disease behavior | CAT2 | Study population | |
| 14.1.3.5 | Extraintestinal manifestations | CAT2 | Study population | |
| **14.2** | **TREATMENT DESCRIPTION** | | | |
| 14.2.1 | Biological Treatment | | | |
| 14.2.1.1 | Biological treatment description | CAT2 | Study population | |
| 14.2.1.2 | Intensification of the biological treatment | CAT2 | Study population | |
| 14.2.1.3 | Discontinuation of the biological treatment | CAT2 | Study population | |
| 14.2.1.4 | Second biological treatment description | CAT2 | Study population | |
| 14.2.1.5 | Concomitant treatments during induction phase | CAT2 | Study population | |
| 14.2.2 | Treatments received before the reference period | | | |
| 14.2.2.1 | Aminosalicylates | CAT2 | Study population | |
| 14.2.2.2 | Corticosteroids | CAT2 | Study population | |
| 14.2.2.3 | Immunosuppressives | CAT2 | Study population | |
| 14.2.2.4 | Anti-diarrheal, pain medications, antidepressants, antibiotics | CAT2 | Study population | |
| 14.2.2.5 | Alternative medicine, cannabis, other treatments | CAT2 | Study population | |

| | TITLE | TABLE TYPE | ANALYSIS SET | COMMENT |
|---|---|---|---|---|
| 14.2.3 | Treatments received during the reference period | | | |
| 14.2.3.1 | Aminosalicylates | CAT2 | Study population | |
| 14.2.3.2 | Corticosteroids | CAT2 | Study population | |
| 14.2.3.3 | Immunosuppressives | CAT2 | Study population | |
| 14.2.3.4 | Anti-diarrheal, pain medications, antidepressants, antibiotics | CAT2 | Study population | |
| 14.2.3.5 | Alternative medicine, cannabis, other treatments | CAT2 | Study population | |
| **14.3** | **EFFICACY DATA** | | | |
| 14.3.1 | Primary efficacy parameter | | | |
| 14.3.1.1 | Comparison of subjects presenting comorbidities, sociodemographic and clinical variables based on the lack of response during the induction phase (primary response vs primary non-response) | COMP1 / COMP4 | Study population | |
| 14.3.1.2 | Logistic regression: Lack of response during the induction phase | RL | Study population | |
| 14.3.1.3 | Comparison of subjects presenting comorbidities, sociodemographic and clinical variables based on the loss of response during the maintenance phase (primary response maintenance vs loss of response) | COMP1 / COMP4 | Study population | |
| 14.3.1.4 | Logistic regression: Loss of response during the maintenance phase | RL | Study population | |

| | TITLE | TABLE TYPE | ANALYSIS SET | COMMENT |
|---|---|---|---|---|
| 14.3.2 | Secondary efficacy parameters | | | |
| 14.3.2.1 | Logistic regression: Lack of response during the induction phase based on the extraintestinal manifestations | RL | Study population | |
| 14.3.2.2 | Logistic regression: Loss of response during the maintenance phase based on the extraintestinal manifestations | RL | Study population | |
| 14.3.2.3 | Comorbidities description according to IBD | CAT2 | Study population | |
| 14.3.2.4 | Comparations of comorbidities between IBD severe vs non-severe at baseline | COMP1 | Study population | |
| 14.3.2.5 | Logistic regression: IBD severe or non-severe at baseline based on the comorbidities and patient disease | RL | Study population | |

## TYPES OF TABLES

Examples for descriptive analysis of categorical variables:

**CAT2**

| | | Variable 2 | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Value a | | Value b | | ... | | |
| | | N | % | N | % | N | % | Total |
| Variable 1 | Value a | | | | | | | |
| | Value b | | | | | | | |
| | ... | | | | | | | |
| | Total | | | | | | | |

Examples for descriptive analysis of continuous variables:

**CONT2**

| | | Variable 1 | | | | | |
|---|---|---|---|---|---|---|---|
| | | N | Mean | Median | Standard deviation | Minimum | Maximum |
| Variable 2 | Value a | | | | | | |
| | Value b | | | | | | |
| | ... | | | | | | |

Examples for multivariable analysis or comparations:

Chi-square results

**COMP1**

| | Value | df | Asym. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|---|---|---|---|---|---|
| Pearson Chi-square | | | | | |
| Continuity correction | | | | | |
| Likelihood Ratio | | | | | |
| Fisher's Exact Test | | | | | |
| Linear by linear association | | | | | |
| N of valid cases | | | | | |

T-test results

**COMP 4**

**Independent Samples Test**

| | | | Variable | |
|---|---|---|---|---|
| | | | Equal variances assumed | Equal variances not assumed |
| Levene's Test for Equality of variances | F | | | |
| | Sig. | | | |
| t-test for Equality of means | t | | | |
| | df | | | |
| | Sig. (2-tailed) | | | |
| | Mean Difference | | | |
| | Std. Error Difference | | | |
| | 95% Confidence Interval of the difference | Lower | | |
| | | Upper | | |

Logistic regression results

**LR**

| | | B | S.E. | Wald | df | Sig. | Exp(B) | 95% C.I. for EXP(B) Lower | Upper |
|---|---|---|---|---|---|---|---|---|---|
| Step X | Variable 1 | | | | | | | | |
| | Variable 2 | | | | | | | | |
| | .... | | | | | | | | |
| | Constant | | | | | | | | |