CLINICAL STUDY PROTOCOL

Grupo de Estudo da Doença Inflamatória Intestinal (GEDII)

A study in the real-world practice to evaluate the impact of biosimilar infliximab (**Rem**sima) in clinical outcomes in patients with inflammatory bowel diseases: a 2-year longitudinal analysis from the GEDII **Reg**istry.

Study code: **REMREGISTER**

Type of study: Observational

Date of protocol: *18Dec2014*

Version no.: 1

Name of Coordinating Investigator	Scientific Coordination: Prof. Fernando Magro Grupo de Estudo da Doença Inflamatória Intestinal (GEDII)
Signature and Date	_____ _____
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE *(to be signed by the PI from each participating center)*

Study Title: A study in the real-world practice to evaluate the impact of biosimilar infliximab (**Rem**sima) in clinical outcomes in patients with inflammatory bowel diseases: a 2-year longitudinal analysis from the GEDII **Reg**istry.

Study Code: REMREGISTER

Protocol Version/Date: 1, 18Dec2014

Center Name: _____

Principal Investigator:

Name:

Academic degree:

Address:

Phone:

Email:

I, the undersigned, am responsible for the conduct of the study at this site and affirm that:

I understand and will conduct the study according to the protocol, any approved protocol amendments, and all applicable Health Authority requirements and national laws.

I will not deviate from the protocol without prior written permission from the GEDII, except where necessary to prevent immediate danger to the subject.

Signature Date of Signature

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1. Sinopse

Title:	A study in the real-world practice to evaluate the impact of biosimilar infliximab (**Rem**sima) in clinical outcomes in patients with inflammatory bowel diseases: a 2-year longitudinal analysis from the GEDII **Reg**istry
Study Code:	**REMREGISTER**
Authors:	Prof. Fernando Magro
Disease/Condition	Inflammatory Bowel Disease (IBD)
Rational	Remsima became licensed in Portugal in September 2013, following the marketing authorization granted by EMA. Considering the absence of data regarding the use of Remsima in IBDs, it is pertinent to explore the impact of this biosimilar of infliximab on clinical outcomes and safety profile in this population in the real-world setting. Taking advantage of the valuable tool such as the GEDII Registry, the GEDII promoted a research to increase the knowledge about the use of Remsima. This study will follow a cohort of patients registered in the GEDII Registry and who initiated biosimilar infliximab (Remsima). The cohort will comprise both biologic-naïve patients and patients who previously received the originator infliximab (Remicade).
Primary Objectives:	• To evaluate the impact of Remsima in inducing clinical response among biologic-naïve patients with IBDs registered in the GEDII Registry followed for two years. • To evaluate the impact of Remsima in inducing clinical remission among biologic-naïve patients with IBDs registered in the GEDII Registry followed for two years. • To evaluate the impact of Remsima in promoting mucosal healing, among biologic-naïve patients registered in the GEDII Registry followed for two years. • To evaluate the impact of Remsima in promoting biomarkers remission by normalization of calprotectine.
Secondary Objective(s):	• To evaluate the impact of Remsima in maintaining clinical remission among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years. • To evaluate the impact of Remsima in maintaining endoscopic remission among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years. • To evaluate the impact of Remsima in maintaining steroid-free remissions among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years. • To evaluate the impact of Remsima in maintaining steroid-free remissions among biologic-naïve patients with IBDs registered in the GEDII Registry, followed for two years. • To evaluate the rate of Remsima persistence among patients with IBDs registered in the GEDII Registry after two years of follow up. • To evaluate the impact of Remsima in perianal manifestations measured by the Perianal Disease Activity Index (PDAI), among patients with perianal Chron's disease registered in the GEDII Registry, followed for two years. • To evaluate the immunogenicity of Remsima among patients registered in the GEDII Registry throughout the 2-year follow up. • To assess serum infliximab levels among patients registered in the GEDII Registry throughout the 2-year follow up. • To assess the safety profile of Remsima among patients registered in the GEDII Registry throughout the 2-year follow up. • To explore the correlation between fecal calprotectin levels with mucosal healing and clinical activity among patients with IBDs registered in the GEDII Registry treated with Remsima. • To explore the correlation of fecal calprotectin levels with serum infliximab levels throughout the 2-year follow up. • To explore the correlation of fecal calprotectin levels with the development of

	anti-drug antibodies throughout the 2-year follow up. • To evaluate the use of health resources among patients with IBDs registered in the GEDII Registry treated with Remsima.
Primary hypotheses (if applicable):	No research hypothesis is predefined.
Study Design:	Multicenter, prospective, observational study designed to gather and analyze data on a consecutive cohort of subjects with IBDs who are being treated with Remsima (biosimilar of infliximab) according to approved label in Portugal. There is no imposed experimental intervention and treatment with Remsima will be determined taking into account the therapeutic protocol adopted by each hospital.
Inclusion Criteria:	1. Male or female patients, 18 years or older; 2. Patients with IBD who are registered in the GEDII Registry, including: o Patients with moderate to severe, active Crohn's disease who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies, or o Patients with fistulising active Crohn's disease who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy), or o Patients with moderate to severe active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. 3. Patients who initiated Remsima according to physician's criteria, including: • Anti-TNF-alfa naïve patients or • Patients on treatment with Remicade with stable clinical response (defined as Harvey-Bradshaw Index < 5 – for CD patients; or Mayo score <2 – for UC patients) and who switched to Remsima 4. Remsima managed according to local SMPc; 5. Patients who gave their consent to be included in the GEDII Registry.
Exclusion Criteria:	1. Patients who are not eligible for anti-TNF-alfa therapy; 2. Patients who are being treated with any investigational agent; 3. Patients who are not willing to comply with routine clinical appointments.
Expected number of subjects:	100 patients
Expected number of sites:	A total of 16 centers are expected to participate.
Subject selection:	The study will analyze a consecutive sample of patients who are registered in the GEDII Registry and who fulfill the protocol's eligibility criteria. The overall duration of observation for each patient is two years from the time patient initiated Remsima (exposure of interest).
Exposure of interest:	Remsima (biosimilar of infliximab) is the exposure of interest. This product will be used according to the approved label (dose of 5 mg/kg, administered as a 2-hour infusion per dose)
Main data collected:	The GEDII Registry allows the collection of socio-demographic, clinical characteristics and outcomes of patients diagnosed with IBDs. Fecal calprotectin will be analysed at start of Remsima and throughout predefined time points up to month 24. The sample will be analyzed by a Central Laboratory. Blood samples for evaluation of serum levels of infliximab and antibodies against infliximab will be collected during scheduled appointments to the hospital and prior to infusion of Remsima.
Endpoints	**Primary endpoint:** **In the subset of biologic-naïve patients with active, moderate to severe CD:** • To determine the proportion of patients who had clinical response (3-point reduction in the Harvey-Bradshaw Index) at week 14 after induction therapy with Remsima. • To determine the proportion of patients with clinical remission (Harvey-Bradshaw Index < or =4 points) during maintenance therapy with Remsima at

	each data collection time points (weeks 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102). • To determine the proportion of patients with mucosal healing (defined as absence of mucosal ulceration) during maintenance therapy with Remsima at weeks 54 and 102. • To determine the proportion of patients with biomarker remission, defined by calprotectine < 100 µg/g at weeks 2, 6, 14, 22, 38, 54, 70, 86 and 102. **In the subset of biologic-naïve patients with active, moderate to severe fistulising CD:** • To determine the proportion of patients who had clinical response (defined as a reduction of at least 50 percent in the number of draining fistulas present at baseline, confirmed at two or more consecutive study visits (a minimum of 21 days between consecutive visits is required), after induction therapy with Remsima. • To determine the rate of loss of response during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102). • To determine the median time to loss of response during maintenance therapy with Remsima Loss of response is defined as one of the following: a) recrudescence of draining fistulas; b) the need for a change in medication for CD or the need for additional therapy for persistent or worsening luminal disease activity; c) the need for a surgical procedure for CD for anal disease; d) discontinuation of the study medication owing to a perceived lack of efficacy. **In the subset of biologic-naïve patients with active, moderate to severe UC:** • To determine the proportion of patients who had clinical response (defined as a 3-point reduction in Partial Mayo score at week 14, after induction therapy with Remsima. Partial Mayo Score: Mayo score excluding the endoscopy subscore (range: 0-9). • To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) at week 14, after induction therapy with Remsima. • To determine the proportion of patients with mucosal healing (defined as Mayo endoscopy subscore ≤ 1) at week 14, after induction therapy with Remsima. • To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 38, 54, 70, 86 and 102). • To determine the rate of mucosal healing (defined as Mayo endoscopy subscore ≤ 1) during maintenance therapy with Remsima at weeks 54 and 102. • To determine the proportion of patients with biomarker remission, defined by calprotectine < 100 µg/g at weeks 2, 6, 14, 22, 38, 54, 70, 86, and 102. **Secondary Endpoints:** **In the subset of patients with CD who switched from Remicade to Remsima** • To determine the proportion of patients with clinical remission (defined as Harvey-Bradshaw Index < or =4 points) at each data collection time points up to week 102. **In the subset of patients with fistulising CD who switched from Remicade to Remsima** • To determine the rate of loss of response during maintenance therapy with Remsima at each data collection time points up to week 102. • To determine the median time to loss of response during maintenance therapy with Remsima • Loss of response is defined as one of the following: a) recrudescence of draining fistulas; b) the need for a change in medication for CD or the need for additional therapy for persistent or worsening luminal disease activity; c) the need for a surgical procedure for CD for anal disease; d) discontinuation of the study medication owing to a perceived lack of efficacy.

	In the subset of patients with UC who switched from Remicade to Remsima • To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) during therapy with Remsima at each data collection time points. • To determine the rate of mucosal healing (Mayo with endoscopy subscore ≤ 1) during therapy with Remsima at weeks 14, 54 and 102. The proportions found at each time point will be compared with the proportion found at baseline (time of Remsima initiation). **In the subset of biologic-naïve patients with perianal CD** • To assess the change in PDAI score at weeks 2, 6, 14, 22, 38, 54, 70, 86, and 102, comparing to baseline score. The PDAI is based on five variables (the presence or absence of discharge, pain or restriction of activities of daily living, restriction of sexual activity, the type of perianal disease, and the degree of induration. Overall score ranges from 0 to 20, with higher scores indicating more severe disease. **For all the above subsets:** • To determine the proportion of patients who withdrew Remsima during the two-year follow up, and reason for discontinuation (persistence on Remsima). • To determine the rates of steroid-free status and steroid-free remission at week 30, week 54 and week 102 - subset of patients taking corticosteroids at baseline). • To determine the incidence of adverse events (serious and non-serious) throughout the observation period, including AEs of special interest. AEs of interest include, among others: infusion-related reactions, opportunistic infections, laboratory abnormal values. • To evaluate the development of anti-drug antibodies (+ or -) at each data collection time points (baseline, weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102). • To determine serum infliximab levels at each data collection time points (baseline, weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102). • To correlate fecal calprotectin levels with mucosal healing (defined as Mayo endoscopy subscore ≤ 1) at each data collection time points among patients with UC. • To correlate fecal calprotectin levels with Harvey-Bradshaw Index score at each data collection time points among patients with CD. • Fecal calprotectin levels and serum infliximab levels at each data collection time points. • Fecal calprotectin levels and presence of anti-drug antibodies (+ or -) at each data collection time points. • To describe the use of health resources: o IBD-related hospitalizations (number of hospitalizations, and length of stay). o Type of surgery o Emergency room admissions (number of admissions). o Treatments (dose and duration of treatment). o Physician consultations (number of consultations and specialty). o Exams (type and number of exams).
Statistical methods	The association between two quantitative variables will be performed through Pearson correlation coefficient or Spearman correlation coefficient, in case the normality assumption is not verified. The association of two categorical variables will be tested through the Chi-Square test or Fisher Exact test (if applicable). The comparison of two independent samples in respect to quantitative variables will be performed through t-test for independent samples or the Mann-Whitney non-parametric test, according to the assumption validations of the statistical test (if applicable). For each subset, the proportion of patients with clinical response, clinical remission or mucosal healing and presence of anti-drug antibodies at each data collection time points will be summarized using 95% confidence intervals. Kaplan-Meier curves will be used to analyze the median time to loss of response.

	Generalized Estimated Equations will be used to investigate maintenance of clinical remission (homogeneity) throughout data collection time points (time-effect). The incidence of adverse events (percentage of subjects with at least one AE) and serious adverse events (SAE) will be presented as well as the frequency distribution of AE and SAE by means of total number of observations (n) and relative frequency (%). The correlation between fecal calprotectin levels with clinical and endoscopic activity of disease will be analyzed through the Pearson or Spearman (in case the normality assumption is not verified) correlation coefficient at each data collection time point.
Overall Study Duration:	The overall duration of the study is three years (1 year of recruitment + 2-year observation period).
Study timelines:	The study is expected to start during the 1st Quarter of 2015. Study closure is expected to occur 2nd Quarter of 2018.

2 INTRODUCTION

2.1 INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is a chronic and disabling condition with an increasing incidence in southern Europe. The etiology of IBD remains unknown, but the characteristic disproportionate inflammatory response in the gut may develop through various mechanisms at the cellular and subcellular level.[1] Ulcerative colitis (UC) and Crohn's disease (CD) represent the two main types of IBD.

Ulcerative colitis is a relapsing non-transmural inflammatory disease that is restricted to the colon. Patients typically present with bloody diarrhoea (often nocturnal and postprandial), passage of pus, mucus, or both, and abdominal cramping during bowel movements. Crohn's disease is a relapsing, transmural inflamatory disease of the gastrointestinal mucosa that can affect the entire gastrointestinal tract from the mouth to the anus. Typical presentations include the discontinuous involvement of various portions of the gastrointestinal tract and the development of complications including strictures, abscesses, or fistulas.[2]

In Portugal, the prevalence of IBDs increased from 86 to 146 persons per 100 000 inhabitants between 2003 and 2007. Within the same timeframe, the prevalence of UC and CD increased from 42 to 71 persons per 100 000 inhabitants and from 43 to 73 persons per 100 000 inhabitants, respectively. IBDs are more prevalent among women.[3]

Tumor necrosis factor α (TNF) is a proinflammatory cytokine that plays a central role in the pathogenesis of CD and UC.[4] Abundantly expressed in the gastrointestinal tracts of patients with IBD[5], TNF is believed to contribute to intestinal mucosal inflammation through several mechanisms, including disruption of the epithelial barrier, induction of apoptosis of the villous epithelial cells, and secretion of chemokines from intestinal epithelial cells.[4]

Over the past decade, anti-TNF agents have dramatically influenced the treatment of patients with refractory IBD. These agents have been developed as monoclonal antibodies (mAbs) or fragments thereof that are directed against TNF molecules.

Infliximab (IFX, Remicade) is a chimeric immunoglobulin G (IgG) human (75%)/murine (25%) mAb administered by intravenous infusion (5 mg/kg), indicated for induction and maintenance of remission in adult and pediatric CD and for induction and maintenance of remission of UC.[6] IFX is also approved for other chronic inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

2.2 BIOSIMILARS

The recent expiry of patents for some biologic therapies prompted the development of biosimilars. Biosimilars are biological medicines similar to other, already authorized, biological medicines that are able to enter the market once the patent for the original product, the reference product, has expired. Unlike chemically synthesized small-molecules, biologics have complex structures of high molecular weight. Therefore, slight changes in the production processes may lead to differences in the final product. Indeed, even different batches of the same product may show a certain level heterogeneity.

In 2005 the European Medicines Agency (EMA) established a specific legal pathway for the approval of biosimilars, in which it is recognized that biosimilars cannot be identical to the primary compound, but must be similar to the original EU-approved molecules in terms of quality, safety, and efficacy.[7] Regulators evaluate biosimilars cautiously, and a biosimilar is only registered if the applicant has demonstrated in sufficient detail that the biosimilar is of good quality and equivalent in efficacy and safety to its reference medicinal product.[8]

The development of a biosimilar should comprise a step-wise and comprehensive comparability exercise using the same reference product throughout the development program. The comparability should be performed in terms of quality, efficacy and safety. With few exceptions, the clinical development of a biosimilar should at least include a Phase I and a pivotal (confirmatory) phase III study. The phase III

study should be an equivalence or non-inferiority trial, using a homogeneous population. In addition, the most sensitive clinical model should be used which should represent the patient population or therapeutic indication where differences between biosimilar and reference products can be most easily detected. Extrapolation to other indications may be granted, based on the totality of evidence gathered throughout the biosimilar development program.[7]

In Europe, the first biosimilar was approved in 2006 and so far the experience accumulated with marketed biosimilars has been successful.

In June 2013, EMA licensed the first biosimilar monoclonal antibodies (mAbs) in the EU (two biosimilars of infliximab). This decision was based on the robust comparisons of the physicochemical and *in vitro* and *ex vivo* biological analyses, leading to the conclusion that both mAbs were biosimilar to the reference product Remicade. In the case of Remsima (one of the biosimilar of infliximab), as part of the comparability exercise it was shown that all major physicochemical characteristics and biological activities of Remsima were comparable to those of Remicade. The clinical evidence submitted by the applicants was substantiated by a pivotal equivalence clinical trial conducted in rheumatoid arthritis patients, supported by a pivotal pharmacokinetic trial in patients with ankylosing spondylitis. EMA extended the licensing to the other indications of the originator, including adult and pediatric CD and UC, ankylosing spondylitis, psoriatic arthritis and psoriasis.[9]

2.3 THE GEDII REGISTRY

Patient registries are a powerful tool to observe the course of disease, understand variations in treatment and outcomes, to assess effectiveness, to monitor safety and harm and to examine factors that influence prognosis and quality of life. It also allows to describe care patterns and to measure quality of care.

From a clinician's perspective, registries can collect data about disease presentation and outcomes on large numbers of patients rapidly, thereby producing a real-world picture of disease, current treatment practices, and outcomes. A registry might also provide data that can be used to assess the degree to which clinicians are managing a disease in accordance with evidence based guidelines, focus attention on specific aspects of a particular disease that might otherwise be overlooked, or provide data for clinicians to compare themselves with their peers. Overall, the use of patient registries appears to be active and growing.[10]

The "Grupo de Estudo da Doença Inflamatória Intestinal" (GEDII) Registry was created on 2005 and allows the regular and systematic capture of socio-demographic and clinical characteristics of patients diagnosed with IBDs (DC, UC and indeterminate UC). The Registry also captures the clinical and safety outcomes, treatments and the use of health resources.

So far, the Registry covers 20 gastroenterology departments of public hospitals. As of April 2014, the Registry comprised a total of 2500 patients, the vast majority of which belonged to CH São João, Porto.

2.4 RATIONALE

Remsima became licensed in Portugal in September 2013, following the marketing authorization granted by EMA. Considering the absence of data regarding the use of Remsima in IBDs, it is pertinent to explore the impact of this biosimilar of infliximab on clinical outcomes and safety profile in this population in the real-world setting. Taking advantage of the valuable tool such as the GEDII Registry, the GEDII promoted a research to increase the knowledge about the use of Remsima. This study will follow a cohort of patients registered in the GEDII Registry and who initiated biosimilar infliximab (Remsima). The cohort will comprise both biologic-naïve patients and patients who previously received the originator infliximab (Remicade).

No research hypothesis is predefined.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

- To evaluate the impact of Remsima in inducing clinical response among biologic-naïve patients with IBDs registered in the GEDII Registry followed for two years.
- To evaluate the impact of Remsima in inducing clinical remission among biologic-naïve patients with IBDs registered in the GEDII Registry followed for two years.
- To evaluate the impact of Remsima in promoting mucosal healing, among biologic-naïve patients registered in the GEDII Registry followed for two years.
- To evaluate the impact of Remsima in promoting biomarkers remission by normalization of calprotectine.

3.2 SECONDARY OBJECTIVES

- To evaluate the impact of Remsima in maintaining clinical remission among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years.
- To evaluate the impact of Remsima in maintaining endoscopic remission among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years.
- To evaluate the impact of Remsima in maintaining steroid-free remissions among patients with IBDs registered in the GEDII Registry who switched from Remicade to Remsima, followed for two years.
- To evaluate the impact of Remsima in maintaining steroid-free remissions among biologic-naïve patients with IBDs registered in the GEDII Registry, followed for two years.
- To evaluate the rate of Remsima persistence among patients with IBDs registered in the GEDII Registry after two years of follow up.
- To evaluate the impact of Remsima in perianal manifestations measured by the Perianal Disease Activity Index (PDAI), among patients with perianal Chron's disease registered in the GEDII Registry, followed for two years.
- To evaluate the immunogenicity of Remsima among patients registered in the GEDII Registry throughout the 2-year follow up.
- To assess serum infliximab levels among patients registered in the GEDII Registry throughout the 2-year follow up.
- To assess the safety profile of Remsima among patients registered in the GEDII Registry throughout the 2-year follow up.
- To explore the correlation between fecal calprotectin levels with mucosal healing and clinical activity among patients with IBDs registered in the GEDII Registry treated with Remsima.
- To explore the correlation of fecal calprotectin levels with serum infliximab levels throughout the 2-year follow up.
- To explore the correlation of fecal calprotectin levels with the development of anti-drug antibodies throughout the 2-year follow up.

- To evaluate the use of health resources among patients with IBDs registered in the GEDII Registry treated with Remsima.

4 STUDY DESIGN

This is a multicenter, prospective, observational study designed to gather and analyze data on a consecutive cohort of subjects with IBDs who are being treated with Remsima (biosimilar of infliximab) according to approved label in Portugal. There is no imposed experimental intervention and treatment with Remsima will be determined taking into account the therapeutic protocol adopted by each hospital.
A prospective, observational study is considered an appropriate tool to assess treatment effects, safety and tolerability, including rare adverse drug reactions, in a heterogeneous group of individuals in a real-life setting.
The study will analyze a consecutive sample of 100 patients who are registered in the GEDII Registry throughout a period of 24 months and who fulfill the protocol's eligibility criteria. The overall duration of observation for each patient is two years from the time patient initiated Remsima (exposure of interest).
In the context of real clinical practice, patients with IBDs attend to the consultation every 2 weeks during induction period and approximately every 8 weeks during maintenance period, in average. Therefore, data collection time points in this study will reflect this routine schedule and will take into account the condition being studied (DC, fistulising CD or UC)

Blood samples for evaluation of serum levels of infliximab and antibodies against infliximab will be collected during scheduled appointments to the hospital as follows:

- CD patients initiating induction with Remsima at study inclusion: Day 1 (basal), week 2, 6 and then every 8 weeks up to week 102 (or every 6 weeks, if required);
- CD patients in maintenance with Remsima at study inclusion: Week 2, 6 (number of weeks since patient started infliximab) and every 8 weeks thereafter, until completing the 24-month follow up period (or every 6 weeks, if required);
- UC patients initiating induction with Remsima at study inclusion: Day 1 (basal), week 2, 6 and then every 8 weeks up to week 102 (or every 6 weeks, if required);
- UC patients in maintenance with Remsima at study inclusion: Week 2, 6 (number of weeks since patient started infliximab) and every 8 weeks thereafter, until completing the 24-month follow up period (or every 6 weeks, if required).

Blood samples should always be collected prior to infusion with Remsima, during the scheduled appointment.

In this study, fecal calprotectin will be analyzed at:
CD patients - start of Remsima, week 2, 6, 14, 22, 38, 54, 70, 86 and 102.
UC patients - start of Remsima, week 2, 6, 14, 22, 38, 54, 70, 86 and 102.
Stool samples should always be collected during the scheduled appointment

A total of 16 centers are expected to participate.

5 STUDY TIMELINES

The study is expected to start during the 1st Quarter of 2015.

The overall duration of the study is three years (1 year of recruitment + 2-year observation period).

6 STUDY POPULATION

6.1 INCLUSION CRITERIA

Study subjects must fulfill the following criteria:

1. Male or female patients, 18 years or older;
2. Patients with IBD who are registered in the GEDII Registry, including:
    - Patients with moderate to severe, active Crohn's disease who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies, or
    - Patients with fistulising active Crohn's disease who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy), or
    - Patients with moderate to severe active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.
3. Patients who initiated Remsima according to physician's criteria, including:
    - Anti-TNF-alfa-naïve patients or
    - Patients on treatment with Remicade with stable clinical response (defined as Harvey-Bradshaw Index < 5 – for CD patients; or Mayo score <2 – for UC patients) and who switched to Remsima
4. Remsima managed according to local SMPc;
5. Patients who gave their consent to be included in the study

6.2 EXCLUSION CRITERIA:

Subjects will be excluded if at least one of the following criteria is met:

1. Patients who are not eligible for anti-TNF-alfa therapy;
2. Patients who are being treated with any investigational agent;
3. Patients who are not willing to comply with routine clinical appointments.

6.3 DISCONTINUATION FROM OBSERVATION PERIOD

In this study patients will be followed up to a maximum period of 24 months. However, observation may be stopped prior to the 24 months for different reasons including, but not limited to:

- Patient discontinues the exposure of interest (Remsima)
- Protocol violation
- Lost to follow up
- Patient withdrawal of consent
- Pregnancy
- Death

In the case observation period is stopped prior to the 24 months, the date of study discontinuation, last intake of Remsima, and the reason for discontinuation should be recorded in the electronic CRF. In addition, all efforts should be made to assess calprotectin levels, serum drug levels and anti-infliximab antibodies as closest as possible to the date of discontinuation.

7 INFORMATION TO BE COLLECTED

7.1 VARIABLES CAPTURED BY THE GEDII REGISTRY

The GEDII Registry allows the collection of socio-demographic, clinical characteristics and outcomes of patients diagnosed with IBDs.

The following basal variables will be collected:

- Date of birth
- Sex
- Height
- Weight
- BMI
- Smoking status
- Pregnancy status (if applicable)
- Diagnosis (UC, CD)
- Date of start of symptoms
- Familial history of IBDs
- Disease presentation (abdominal, constitutional, abdominal + constitutional, anal disease, acute abdomen, fever, anemia, extra-intestinal manifestation, abdominal mass, similar presentation to UC)
- Clinical course
- Steroid-dependent or steroid-refractory disease
- CD Patients: Harvey Bradshaw score – CD activity (5 items: general well-being, abdominal pain, number of liquid or soft stools per day, abdominal mass and complications)
- Perianal disease activity index (PDAI) score: discharge, pain/restriction of activities, restriction of sexual activity, type of perianal disease, degree of induration – only for patients with perianal disease.
- Routine laboratory parameters (hemoglobin, leukocytes, neutrophils, eosinophiles, basophiles, monocytes, lymphocytes, erythrocyte sedimentation rate, CRP, ferritin, iron and transferrin)
- UC patients: Mayo score (UC activity): stool frequency, rectal bleeding, findings of endoscopy, physician's global assessment.
- Colitis location (rectum, rectum-sigmoide, colon distal, pancolitis)
- First episode (Montreal classification)
- Location of CD
- Location of CD, by segment
- CD classification, based on prognosis
- Anal lesion (strictures, abscesses, or fistulas)
- Number of draining fistulaes
- Ileal disease (achievement ≥ 1m, <1m)
- Extra-abdominal manifestations
- Dose of Remsima, date of start (first infusion - Day 1)
- Concomitant therapies (since the first infusion - Day 1)

- Assessment of serum levels of infliximab (prior to infusion) - µg/mL
- Assessment of anti-infliximab antibodies (prior to infusion)
- Assessment of fecal calprotectin levels (µg/g)

Information to be collected during induction therapy with Remsima and maintenance therapy (every 8 weeks until completion of the 24-month follow up period)* see Chronogram A and B:

- Weight and BMI
- Extra-abdominal manifestations
- Clinical activity:
  Harvey Bradshaw Index – CD: at week 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102
  Partial Mayo score – UC: at week 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102
- For patients with perianal disease only: PDAI score at weeks 2, 6, 14, 22, 38, 54, 70, 86, and 102.
- Endoscopic activity (CD: weeks 54 and 102; UC: weeks 14, 54, 102)
- Number of draining fistulaes (fistulizing CD)
- Dose of Remsima
- Concomitant therapies, if changed since previous appointment
- Routine laboratory parameters (hemoglobin, leukocytes, neutrophils, eosinophiles, basophiles, monocytes, lymphocytes, erythrocyte sedimentation rate, CRP, ferritin, iron and transferrin)
- Adverse reactions: drug (start date, end date), description of event (start and end date), action taken, outcome, causality assessment and severity.
- Assessment of serum levels of infliximab (prior to infusion)
  CD patients: at week 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102.
  UC patients: at week 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102.
- Assessment of anti-infliximab antibodies (prior to infusion)
  CD patients: at week 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102.
  UC patients: at week 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102.
- Assessment of fecal calprotectin levels (prior to infusion)
  CD patients, week 2, 6, 14, 22, 38, 54, 70, 86, and 102.
  UC patients, week 2, 6, 14, 22, 38, 54, 70, 86, and 102.
- Use of health resources (colonoscopy, other imaging techniques), surgeries and occurrences (consultations, admission to emergency rooms, hospitalizations)
- Status: ongoing/discontinuation. If discontinued, reason.

* data collection may occur every 6 weeks, if required.

7.2 ASSESSMENT OF BIOLOGICAL MARKER - FECAL CALPROTECTIN

Faecal calprotectin has been shown to be useful in the diagnosis of IBD, correlates with mucosal disease activity and can help to predict response to treatment or relapse. In IBD, the presence of active gut inflammation is associated with migration of leucocytes, including neutrophils, to the gut mucosa.[11] As a result the faecal stream contains increased levels of these inflammatory proteins including calprotectin. Faecal calprotectin has been shown to differentiate quiescent from active disease in both patients with CD and UC.[12,13]
This biological marker is not routinely assessed in the medical practice and therefore is not collected in the GEDII Registry.

The fecal samples will be analyzed by a Central Laboratory (Dept. de Farmacologia FMUP) using Quantum Blue. Report with the results will be provided to Investigators by mail.

7.3 ASSESSMENT OF SERUM INFLIXIMAB LEVELS AND ANTIDRUG ANTIBODIES

Serum infliximab levels and antidrug antibodies will be assessed immediately prior to drug infusion and at the scheduled appointment to the hospital. Overall, each patient will have a maximum of 14 determinations.

Blood from infliximab (IFX) treated patients will be collected prior to infliximab infusion. Blood will be collected to blood clotting tubes. One hour after collection, blood will be centrifuged at 10 min at 3000 RPM. Sera will be transferred into fresh tubes and stored at -20C.
Infliximab and anti-infliximab levels will be determined with an ELISA assay. Both assays employ the quantitative enzyme immunoassay technique. A monoclonal antibody specific for IFX has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any IFX present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for IFX is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of IFX bound in the initial step. The color development is stopped and the intensity of the color is measured by a spectrophotometer.

8 EXPOSURE OF INTEREST

Remsima (biosimilar of infliximab) is the exposure of interest. This product will be used according to the approved label (dose of 5 mg/kg, administered as a 2-hour infusion per dose) (EMA/CHMP/589422/2013).

9 ENDPOINTS

9.1 PRIMARY ENDPOINT

In the subset of biologic-naïve patients with active, moderate to severe CD:

- To determine the proportion of patients who had clinical response (3-point reduction in the Harvey-Bradshaw Index) at week 14 after induction therapy with Remsima.
- To determine the proportion of patients with clinical remission (Harvey-Bradshaw Index $\leq$4 points) during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102).
- To determine the proportion of patients with mucosal healing (defined as absence of mucosal ulceration) during maintenance therapy with Remsima at weeks 54 and 102.
- To determine the proportion of patients with biomarker remission, defined by calprotectine < 100 µg/g at weeks 2, 6, 14, 22, 38, 54, 70, 86 and 102.

In the subset of biologic-naïve patients with active, moderate to severe fistulising CD:

- To determine the proportion of patients who had clinical response (defined as a reduction of at least 50 percent in the number of draining fistulas present at baseline, confirmed at two or more consecutive study visits (a minimum of 21 days between consecutive visits is required), after induction therapy with Remsima.
- To determine the rate of loss of response during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102).
- To determine the median time to loss of response during maintenance therapy with Remsima

Loss of response is defined as one of the following: a) recrudescence of draining fistulas; b) the need for a change in medication for CD or the need for additional therapy for persistent or worsening luminal disease activity; c) the need for a surgical procedure for CD for anal disease; d) discontinuation of the study medication owing to a perceived lack of efficacy.

In the subset of biologic-naïve patients with active, moderate to severe UC:

- To determine the proportion of patients who had clinical response (defined as a 3-point reduction or more in Partial Mayo score) at week 14, after induction therapy with Remsima.
  Partial Mayo Score: Mayo score excluding the endoscopy subscore (range: 0-9).

- To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) at week 14, after induction therapy with Remsima.

- To determine the proportion of patients with mucosal healing (defined as Mayo endoscopy subscore ≤ 1) at week 14, after induction therapy with Remsima.

- To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) during maintenance therapy with Remsima at each data collection time points (weeks 14, 22, 38, 54, 70, 86 and 102).

- To determine the rate of mucosal healing (defined as Mayo endoscopy subscore ≤ 1) during maintenance therapy with Remsima at week 54, 102.

- To determine the proportion of patients with biomarker remission, defined by calprotectine < 100 µg/g at weeks 2, 6, 14, 22, 38, 54, 70, 86 and 102.

9.2 SECONDARY ENDPOINTS

In the subset of patients with CD who switched from Remicade to Remsima

- To determine the proportion of patients with clinical remission (defined as Harvey-Bradshaw Index < or =4 points) at each data collection time points up to week 102.

In the subset of patients with fistulising CD who switched from Remicade to Remsima

- To determine the rate of loss of response during maintenance therapy with Remsima at each data collection time points up to week 102.

- To determine the median time to loss of response during maintenance therapy with Remsima

  Loss of response is defined as one of the following: a) recrudescence of draining fistulas; b) the need for a change in medication for CD or the need for additional therapy for persistent or worsening luminal disease activity; c) the need for a surgical procedure for CD for anal disease; d) discontinuation of the study medication owing to a perceived lack of efficacy.

In the subset of patients with UC who switched from Remicade to Remsima

- To determine the proportion of patients with clinical remission (defined as Partial Mayo score ≤ 2 with no individual subscore >1) during therapy with Remsima at each data collection time points.

- To determine the rate of mucosal healing (Mayo with endoscopy subscore ≤ 1) during therapy with Remsima at weeks 14, 54 and 102. The proportions found at each time point will be compared with the proportion found at baseline (time of Remsima initiation).

In the subset of biologic-naïve patients with perianal CD

- To assess the change in PDAI score at weeks 2, 6, 14, 22, 38, 54, 70, 86 and 102 comparing to baseline score.

  The PDAI is based on five variables (the presence or absence of discharge, pain or restriction of activities of daily living, restriction of sexual activity, the type of perianal disease, and the degree of induration. Overall score ranges from 0 to 20, with higher scores indicating more severe disease.

For all the above subsets:

- To determine the proportion of patients who withdrew Remsima during the two-year follow up, and reason for discontinuation (persistence on Remsima).
- To determine the rates of steroid-free status and steroid-free remission at week 30, week 54 and week 102 - subset of patients taking corticosteroids at baseline.
- To determine the incidence of adverse events (serious and non-serious) throughout the observation period, including AEs of special interest. AEs of interest include, among others: infusion-related reactions, opportunistic infections, laboratory abnormal values.
- To evaluate the development of anti-drug antibodies (+ or -) at each data collection time points (baseline, weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102).
- To determine serum infliximab levels at each data collection time points (baseline, weeks 2, 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102).
- To correlate fecal calprotectin levels with mucosal healing (defined as Mayo endoscopy subscore ≤ 1) at each data collection time points among patients with UC.
- To correlate fecal calprotectin levels with Harvey-Bradshaw Index score at each data collection time points among patients with CD.
- Fecal calprotectin levels and serum infliximab levels at each data collection time points
- Fecal calprotectin levels and presence of anti-drug antibodies (+ or -) at each data collection time points
- To describe the use of health resources:
  - IBD-related hospitalizations (number of hospitalizations, and length of stay).
  - Type of surgery
  - Emergency room admissions (number of admissions).
  - Treatments (dose and duration of treatment).
  - Physician consultations (number of consultations and specialty).
  - Exams (type and number of exams).

10 STATISTICAL ANALYSIS

10.1 GENERAL CONSIDERATIONS

All quantitative variables will be summarized through descriptive statistics namely mean, median, standard deviation and range (minimum and maximum) and qualitative variables though absolute (n) and relative frequencies (%) and 95% confidence intervals (if applicable). The statistical analysis will be performed through frequency tables for qualitative variables and tables with descriptive statistics for quantitative variables.

The association between two quantitative variables will be performed through Pearson correlation coefficient or Spearman correlation coefficient, in case the normality assumption is not verified.
The association of two categorical variables will be tested through the Chi-Square test or Fisher Exact test (if applicable).
The comparison of two independent samples in respect to quantitative variables will be performed through t-test for independent samples or the Mann-Whitney non-parametric test, according to the assumption validations of the statistical test (if applicable).

For each subset, the proportion of patients with clinical response, clinical remission or mucosal healing and presence of anti-drug antibodies at each data collection time points will be summarized using 95% confidence intervals.
Kaplan-Meier curves will be used to analyze the median time to loss of response.
Generalized Estimated Equations will be used to investigate maintenance of clinical remission (homogeneity) throughout data collection time points (time-effect).

The impact of immunogenicity on the efficacy of Remsima will also be exploratory assessed by associating serum drug levels concentration and anti-drug antibodies in respect to the outcomes, need for dose escalation, and discontinuation rate at the predetermined time points.

A total cost associated to treatment with Remsima until the end of observation period for each patient will be computed considering the sum of the following product for each health resource: nº of consumed units of the health resource x unitary cost of the health resource.
The use of health resources will be descriptively summarized by means of number of observations, mean, standard deviation, median, range and 95% confidence intervals, if applicable.

Safety Analysis

The incidence of adverse events (percentage of subjects with at least one AE) and serious adverse events (SAE) will be presented as well as the frequency distribution of AE and SAE by means of total number of observations (n) and relative frequency (%). Frequency distribution of AE by severity and degree of relationship with study drug will be summarized by total number of observations (n) and relative frequency (%).
AEs will be listed individually with severity, severity, degree of relationship with study drug, duration (for solved AEs and calculated as the difference between end date and start date), actions taken and outcome.
All deaths will be listed, regardless of being attributed to an AE.

Results for hemoglobin, leukocytes, erythrocyte sedimentation rate, CRP, iron, transferrin and fecal calprotectin will be summarized by total number of observations (n), mean, median, standard deviation, minimum and maximum.

Correlation of fecal calprotectin with endoscopic and clinical outcomes

- The correlation between fecal calprotectin levels with clinical and endoscopic activity of disease will be analyzed through the Pearson or Spearman (in case the normality assumption is not verified) correlation coefficient at each data collection time point:

    - Fecal calprotectin levels will be correlated with endoscopy Mayo subscore and partial Mayo score among patients with UC.

    - Fecal calprotectin levels will be correlated with Harvey-Bradshaw Index score among patients with CD.

Correlation of fecal calprotectin with serum infliximab and anti-infliximab antibodies levels

Exploratory Generalized Estimated Equations with AR1 correlation structure in time, to account for the within-subject correlations, will be used to explore the association between fecal calprotectin levels and serum drug levels (dependent variable) as well as the association of fecal calprotectin levels with the presence of antidrug antibodies (dependent variable), throughout the follow up period.

10.2 SAMPLE SIZE

The sample size is not based on formal statistical assumptions. This study will analyze all patients who are registered in the GEDII Registry and initiated Remsima, during a recruitment period of 12 months. In this circumstance it is expected to analyze a total of 100 patients. This sample will allow a descriptive analysis of clinical characteristics and outcomes among this population with an exploratory analytical component regarding maintenance of clinical remission during the follow period.
Regarding the correlation analysis of fecal calprotectin with clinical and endoscopy outcomes, with this sample size there is a power probability greater than 95% that the lower limit of a one-sided 95% confidence interval is higher than 0.50, if the observed correlation coefficient is at least 0.75.

11 PHARMACOVIGILANCE

New safety findings that can potentially affect the risk/benefit profile of a medicinal product identified during the conduct of epidemiological studies will be reported promptly to the Health Authorities, according to local pharmacovigilance regulations.

12 ETHICAL AND LEGAL ASPECTS

12.1 ETHICS

The study will be conducted according to the ethics principles originated from the Declaration of Helsinki and the Portuguese Clinical Research law (Law #21/2014, 16th April 2014)..
A copy of the protocol, proposed informed consent form and other written subject information will be submitted to the local Ethics Committee for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Investigator before recruitment of subjects and data collection.
The investigator will submit and, where necessary, obtain approval from the competent Ethics Committee for all subsequent protocol amendments and changes to the informed consent document.

12.2 INFORMED CONSENT

Before any protocol specific procedures are performed, the investigator is responsible for obtaining written informed consent from the subject (or authorized representative) and after an adequate and clear explanation of the aims, methods, anticipated benefits, and potential hazards of the study.
The informed consent process should be documented in the subject's medical charts, and the informed consent form should be signed and personally dated by the subject (or authorized representative, if applicable) and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or authorized representative.

12.3 STUDY DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the ethics committee, or at the discretion of the GEDII. If GEDII decides to terminate

prematurely the study, GEDII or designee will promptly notify the appropriate IEC and regulatory authority (if applicable).

13 QUALITY CONTROL

The study will involve a study monitor who will be responsibility to ensure that the study is conducted according to the protocol and to the local regulatory/ethical requirements.
Before the start of activities a study monitor will conduct Initiation Visits at the sites in order to train the investigational team on the protocol, safety reporting and other protocol-related procedures.
During the study the monitor will also be responsible for conducting periodic monitoring visits at the sites to ensure that the protocol is being followed and the data recorded is accurate and collected according to the defined procedures.
The sites may be subject to review by the Independent Ethics Committee and/or to quality assurance audits performed by GEDII designated representative, and/or to inspection by appropriate regulatory authorities. The Investigator(s) and their relevant staff should be available during the monitoring visits and possible audits or inspections. The investigator and institution will allow the appropriate regulatory authorities direct access to source documents to perform this verification.
Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to monitors, auditors, Ethics Committees, and regulatory authorities, as required.

14 DATA HANDLING

14.1 CONFIDENTIALITY

The investigator is responsible for ensuring that the subject's confidentiality is maintained.
Questionnaires, database and other documents generated in this study will be identified by a unique subject identification number only. This number will be assigned sequentially, based on subject's recruitment schedule. Each center will also be assigned a predefined two-digit number.
The GEDII Registry received the authorization of Comissão Nacional para Protecção de Dados for the purpose of data processing under the scope of "Lei de Protecção de Dados de Carácter Pessoal Dec. 67/98 de 26 de Outubro".

14.2 DATA COLLECTION

All study data will be obtained from the GEDII Registry and, when relevant, will be complemented by subject's interview or other medical sources (as appropriate).
The investigator will be responsible for ensuring that all findings and data are accurately and reliably recorded in the case report form.

All eligible subjects who are not enrolled in the study will be recorded in a specific form. No personal data will be collected in this form, only the date of assessment of eligibility criteria and reason for non-enrollment. This form will be kept exclusively at each site.

14.3 STUDY ARCHIVE

The investigator will keep an adequate archive of all study documentation with access restricted to study team. The study archive will be kept at each site for at least 15 years from the study close out.

14.4 PUBLICATION POLICY

All documents and results generated from this clinical study are exclusive property of Coordinating Investigator. Any related publications must be previously approved in written by the Coordinating Investigator and GEDII.
For all publications related to this study, the GEDII will comply with recognized ethical standards concerning publications and authorship established by the International Committee of Medical Journal Editors (*Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals - Updated December 2013*).
The study results can only be published after the clinical study is terminated, the data analysis is completed and only upon the agreement of the study's scientific board. The publication should include the results from all the centers which have participated in the clinical investigation, The publication of results should be agreed by all participating investigators and in strict adherence to the principles originated from the Helsinki Declaration and according to Portuguese Clinical Research law (Law #21/2014, 16th April 2014).

For all publications related with this clinical study, the order of the authors is as follows:

1. The first author position will correspond to the Coordinating Investigator;
2. The subsequent author's positions will correspond to the principal investigator from each center, who will be ranked decreasingly according to the number of patients included in the study, as far as the number of co-authors allowed by the journal is not exceeded;
3. All the participating investigators not figuring in the authorship (due to journal's limitations in the number of co-authors) will be cited in the acknowledgment section of the publication.
4. The last author position will correspond to a GEDII member.

15 REFERENCES

1. Magro F, Portela F. Management of inflammatory bowel disease with infliximab and other anti-tumor necrosis factor alpha therapies. *BioDrugs*. 2010;24 Suppl 1:3-14.

2. Baumgart DC, Sandborn WJ. Inflammatory bowel disease: clinical aspects and established and evolving therapies. *Lancet*. 2007;369(9573):1641-57.

3. Azevedo LF, Magro F, Portela F, Lago P, Deus J, Cotter J, et al. Estimating the prevalence of inflammatory bowel disease in Portugal using a pharmaco-epidemiological approach. *Pharmacoepidemiol Drug Saf*. 2010;19(5):499-510.

4. Bosani M, Ardizzone S, Porro GB. Biologic targeting in the treatment of inflammatory bowel diseases. *Biologics*. 2009;3:77-97.

5. Breese EJ, Michie CA, Nicholls SW, Murch SH, Williams CB, Domizio P, et al. Tumor necrosis factor alpha-producing cells in the intestinal mucosa of children with inflammatory bowel disease. *Gastroenterology*. 1994;106(6):1455-66.

6. Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. *Inflamm Bowel Dis*. 2009;15(8):1264-75.

7. EMA. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues; EMA: London, UK, 2006; EMEA/CHMP/BMWP/42832.

8. Schneider CK. Biosimilars in rheumatology: the wind of change. *Ann Rheum Dis*. 2013;72(3):315-8.

9. Committee for Medicinal Products for Human Use (CHMP). Assessment Report - Remsima. EMA/CHMP/589422/2013.

10. Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 201.

11. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut*. 2006;55(3):426-31.

12. Sipponen T, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Farkkila M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis*. 2008;14(1):40-6.

13. Xiang JY, Ouyang Q, Li GD, Xiao NP. Clinical value of fecal calprotectin in determining disease activity of ulcerative colitis. *World J Gastroenterol*. 2008;14(1):53-7.

CHRONOGRAM A (applicable for CD or fistulising CD patients)

	Infliximab															
	Induction period*			Maintenance period - data collection time points (24-month follow up)												
Information to be collected	**Day1 or basal**	**W2**	**W6**	**W14**	**W22**	**W30**	**W38**	**W46**	**W54**	**W62**	**W70**	**W78**	**W86**	**W94**	**W102**	**Or completion of Fup[3]**
Date of birth	X[4]															
Sex	X[4]															
Height	X[4]															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking status	X[4]															
Medical history	X[4]															
Comorbidities	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease presentation	X[4]															
Diagnosis CD, location, steroid behavior, prognostic classification.	X[4]															
Clinical activity (HBI)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nr of draining fistulaes (fistulizing CD)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PDAI (perianal CD)	X	X	X	X	X		X		X		X		X		X	X
Dose of Remsima administered	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy	X								X						X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory parameters	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum infliximab levels[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal sample (calprotectin levels)[2]	X	X	X	X	X		X		X		X		X		X	X
Adverse reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Use of health resources	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Data related with induction period **will only be collected** for biologic-naïve patients starting Remsima. Data related with maintenance period is applicable both to biologic-naïve patients and patients who switched from Remicade. W = week, HBI = Harvey Bradshaw Index, PDAI, Perianal Disease Activity Index.

[1] Blood sample to be collected prior to each infusion of Remsima at the scheduled appointment. Sample will be analyzed by Central Laboratory.

[2] Stool sample to be collected and sent for Central Laboratory

[3] Patients in maintenance with Remsima at study inclusion will be followed every 8 weeks (or every 6 weeks, if required) until completing the 24-month follow up period;

[4] Basal data to be collected, regardless of the patient's treatment status at study inclusion.

CHRONOGRAM B (applicable for UC patients)

	Infliximab															
	Induction period*			Maintenance period - data collection time points (24-month follow up)												
Information to be collected	**Day1 or basal**	**W2**	**W6**	**W14**	**W22**	**W30**	**W38**	**W46**	**W54**	**W62**	**W70**	**W78**	**W86**	**W94**	**W102**	**Or completion of Fup[3]**
Date of birth	X[4]															
Sex	X[4]															
Height	X[4]															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking status	X[4]															
Medical history	X[4]															
Comorbidities	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease presentation	X[4]															
Diagnosis UC, location, steroid behavior, prognostic classif.	X[4]															
Clinical activity (Partial Mayo)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dose of Remsima administered	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy	X			X					X						X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Routine laboratory parameters	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum infliximab levels[1]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies[1]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Fecal sample (calprotectin levels)[2]	X	X	X	X	X		X		X		X		X	X	X	X
Adverse reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Use of health resources	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Data related with induction period **will only be collected** for biologic-naïve patients starting Remsima. Data related with maintenance period is applicable both to biologic-naïve patients and patients who switched from Remicade.

[1] Blood sample to be collected prior to each infusion of Remsima at the scheduled appointment. Sample will be analyzed by Central Laboratory.

[2] Stool sample to be collected and sent for Central Laboratory

[3] Patients in maintenance with Remsima at study inclusion will be followed every 8 weeks (or every 6 weeks, if required) until completing the 24-month follow up period;

[4] Basal data to be collected, regardless of the patient's treatment status at study inclusion.

W = week.