Title:	A study in the real-world practice to evaluate the impact of bio**sim**ilar infliximab (Remsima) in clinical outcomes in patients with inflammatory bowel diseases: a 2-year longitudinal analysis from the GEDII **Reg**istry
Study Code:	**REMREGISTER**
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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 Remsima 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 analyzed at start of Remsima and then weeks 2, 6, 14, 22, 38, 54, 70, 86 and 102. . 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 2 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. • To assess the change in PDAI score at weeks 2, 14, 22, 54 and 102 comparing to baseline score. **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 28 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 Clinical response was defined as a decrease in the partial Mayo score of ≥2 points and ≥30% from baseline, with a decrease in the rectal bleeding subscore of ≥1 or absolute rectal bleeding subscore of 1 or 0. at week 8, 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 8, after induction therapy with Remsima. • To determine the proportion of patients with mucosal healing (defined as Mayo endoscopy subscore ≤ 1) at week 16, 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 16, 24, 32, 40, 48, 72 and 96). • To determine the rate of mucosal healing (defined as Mayo endoscopy subscore ≤ 1) during maintenance therapy with Remsima at weeks 56 and 96. • To determine the proportion of patients with biomarker remission, defined by calprotectine < 100 µg/g at weeks 2, 8, 16, 24, 40, 56, 72, 88 and 96. **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 16, 56 and 96. 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, 14, 22, 54 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 3230 (CD) or week 32 (UC), week 52 54 (CD) or week 56 (UC) and week 102 (CD) or 96 (UC) - 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. • To determine serum infliximab levels at each data collection time points. • 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 4th Quarter of 2014. Study closure is expected to occur 1st Quarter of 2018.