STUDY PROTOCOL

An observational, prospective cohort study to evaluate the safety and efficacy of Remsima™ in patients with Crohn's disease (CD) or Ulcerative Colitis (UC)

PROTOCOL NUMBER CT-P13 4.3

CONFIDENTIAL

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Protocol Approval

Study Title	An Observational, Prospective Cohort study to Evaluate the Safety and Efficacy of Remsima™ in Patients with Crohn's disease (CD), or Ulcerative Colitis (UC)
Protocol Number	CT-P13 4.3
Protocol Version and Date	Protocol Version 2.1 (EU specific) – 03 June 2015

Protocol accepted and approved by:

[redacted]

Qualified Person Responsible for Pharmacovigilance

[redacted]

Signature Date

Declaration of Investigator

I have reviewed and understand the purpose of the study and all sections of the protocol with the sponsor and its representatives. I will not disclose information regarding this observational study or publish results of the investigation without authorization from CELLTRION, Inc.

I agree to supervise all aspects of the protocol and to conduct this observational study in accordance with the protocol, the International Conference on Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc., or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients.

Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

Protocol Synopsis

Protocol Number: CT-P13 4.3	
Title of Study: An observational, prospective cohort study to evaluate the safety and efficacy of Remsima™ in patients with Crohn's disease (CD), or Ulcerative Colitis (UC)	
Sponsor: CELLTRION, Inc.	
[redacted]	
Study Center(s): Approximately 50 centers in South Korea and EU	
Length of Study: A 5-year continuous period from initiation of treatment for each patient	**Phase of Development:** IV
Objectives: The primary objective of this study is to assess the safety of Remsima™ by evaluation of Events of Special Interest (ESI) in IBD patients, who have active Crohn's disease (CD), fistulizing Crohn's disease (CD), or Ulcerative Colitis (UC) for up to 5 years for each patient. The secondary objectives of this study are to evaluate additional safety and efficacy of Remsima™ in IBD patients, who have active CD, fistulizing CD or UC. Health-economic parameters will also be assessed.	
Study Design: This is a longitudinal, observational, prospective cohort study to assess the safety and efficacy of Remsima™ in patients with IBD, who have active Crohn's disease (CD), fistulizing Crohn's disease (CD), or Ulcerative Colitis (UC). Patients will be included in this registry who are receiving treatment with 5 mg/kg of Remsima™ by IV infusion at weeks 0, 2, 6, and every 8 weeks thereafter in accordance with the product label. A dose visit window of ±3 days is recommended up to and including Dose 3; a dose visit window of ±14 days is recommended thereafter, including the End-of-Study (EOS) Visit. If a patient has been treated with infliximab prior to enrollment, his or her dosing schedule will be continued appropriately. The End-of-Study (EOS) visit only needs to be completed if the patient withdraws prior to study completion. An EOS visit will be made 8 weeks after the last dose is received. If the patient has completed the full 5-year study period, a separate EOS visit is not required. In this case, last visit will be considered the EOS visit. Patients will undergo safety and efficacy assessments in accordance with routine medical practice. The decision to treat with Remsima™ will be independent of the decision to enroll the patient in this registry.	
Sample Size: At least 500 male and female patients with confirmed diagnosis of CD or UC. At least 50 percentage of target number of patients will be enrolled in European regions; recruitment in selected Eastern European and Western European countries will continue for 5 years after respective launches.	
Study Drug, Dose and Regimen: Remsima™ (5 mg/kg) will be administered intravenously at weeks 0, 2, 6, and every 8 weeks thereafter. Dose escalation is permitted in accordance with the local guidelines of the institution in which the patient is receiving treatment. Dose and treatment schedule are recommended to comply with the approved posology in each regulatory authority or investigator's clinical decision.	
Main Selection Criteria: Male or female patients with either moderate to severe active CD, fistulizing active CD, or moderate to severe active UC will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.	
Inclusion Criteria: 1. Patients who can be treated with Remsima™ according to the following criteria: a. Adult patients with moderate to severe active CD who have not responded despite a full and adequate course of therapy with corticosteroids and/or immunosuppressive agents, or who are intolerant to or have medical contraindications to such therapies.	

b. Children and adolescent patients, aged 6 to 17 years old with severe active CD who have not responded to conventional treatment with corticosteroids, immunomodulator and primary nutrition therapy, or who are intolerant to or have contraindications to such therapies.
c. Adult patients with fistulizing active CD who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
d. Adult patients with moderate to severe active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant or have medical contraindications to such therapies.
e. Children and adolescent patients aged 6 to 17 years with severe active UC, who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant or have medical contraindications to such therapies.

2. Female patients of childbearing potential who agree to use of adequate contraception to prevent pregnancy and continuation of contraceptive use for at least 6 months after their final dose of Remsima™. According to EU SmPC, the use of infliximab during pregnancy is not recommended. However should the severity of the condition and treatment benefits outweigh potential risk to the mother and the baby and provided that there is no other available treatment options and provided that pregnant patient is fully informed and aware of the risks and upon careful judgement of the investigator, the treatment may continue throughout the pregnancy. Alternatively, the treatment of Remsima™ should not be done for pregnant patient.
3. Patients (or legal guardian, if applicable) who are willing to give informed consent for long term follow-up including access to all medical records.

Exclusion Criteria:

1. Patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients (Sucrose, Polysorbate 80, Monobasic sodium phosphate and/or Dibasic sodium phosphate).
2. Patients with a current or past history of chronic infection with Hepatitis B, Hepatitis C or infection with human immunodeficiency virus (HIV), or testing positive to those infections at Screening.
3. Patients with current diagnosis of Tuberculosis (TB) or severe or chronic infections (e.g. sepsis, abscesses, opportunistic infections, invasive fungal infections), or previously diagnosed with TB or severe or chronic infection, without sufficient documentation of complete resolution following treatment.
4. Recent exposure to persons with active TB, or a positive test result for latent TB (determined by a positive interferon-γ release assay [IGRA] test, with a negative chest X-ray) at Screening. If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the repeated IGRA result is again indeterminate, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient may be included in the study. A patient who has received at least the first 30 days or recommended period of country-specific TB prophylaxis and intends to complete the entire course of prophylaxis may be enrolled. Patients with sufficient documentation of prophylaxis or complete resolution following TB treatment based on local guidelines can be treated before confirming the IGRA results.
5. Patients with moderate or severe heart failure (NYHA class III/IV).
6. Patients for whom there are investigator's concerns about treatment with TNF-α blockers, such as a history of any malignancy within the previous five years prior to enrollment or a history of herpes zoster within one month prior to enrollment, may be excluded at the investigator's discretion.

Safety Assessment: Safety will be assessed by collection of data in the patient medical records as part of routine clinical practice. Data collection will include ESIs, adverse events (AEs) including serious AEs, other than those classified as ESIs. Safety analysis will also include immunogenicity testing (optional), tuberculosis assessment (IGRA), vital sign and height, weight, hypersensitivity monitoring, concomitant medications, pregnancy test and clinical laboratory analyses including Hepatitis B, and C and HIV tests.

Efficacy Assessments: Efficacy will be assessed by collection of data recorded in the patient medical records as part of routine clinical practice.

- Adult patients with moderate to severe active CD
  - For clinical response, Crohn's Disease Activity Index- 70 (CDAI-70) and CDAI-100
  - Clinical remission (CDAI score<150)
- Pediatric patients with severe active CD
  - For clinical response, decrease from base line in the Pediatric Crohn's Disease Activity Index (PCDAI) ≥15 points; total score ≤30
  - Clinical remission (PCDAI score ≤10)
- Adult patients with fistulizing, active CD
  - number of fistulas in patients
- Adult patients with moderate to severe active UC
  - Mayo scores System (achieving a decrease in Mayo scores from baseline of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1)
  - Clinical remission (a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point)
- Pediatric patients with severe active UC
  - For clinical response, decrease from baseline in the Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥20 score
  - Clinical remission (PUCAI <10 points)

Data Analysis: *Statistical analysis*: The statistical analysis will be performed using [redacted] The data documented in this study including exposure to Remsima™ (e.g. number of patients exposed, number of infusion, duration of exposure and etc.) and the clinical parameters measured will be described using descriptive statistics (n, mean, median, SD, minimum, and maximum) for quantitative variables and frequencies for qualitative variables. The AEs will be coded using the latest version of the MedDRA and summarized by the number of patients reporting an event, and the percentage of patients with that event. The severity, start and stop date, and relationship to treatment will be listed. Severity of adverse events will be graded according to the CTCAE v4.0. Previous and concomitant treatments will be coded using the World Health Organization Drug Dictionary and medical history will be coded using MedDRA. In addition, the results will be compared against relevant historical infliximab data from published reports and articles representing studies conducted with anti-TNF drug (infliximab, adalimumab and etc.). Periodic interim analyses are planned for regulatory reporting purposes. An annual regulatory report will be generated and reported to the regulatory authority. This will contain safety and efficacy data observed since the start of the study until December of each year. The first annual regulatory report is planned to be submitted in May 2015.

Subgroup analysis might be conducted for handling risk factors. Subgroup analysis for each risk factor level will be considered. Additionally, propensity score might be considered if it is necessary and relevant. The main risk factor to be considered is geographical region by the level of incidence rates or prevalence rates of events such as TB or pneumonia. Other risk factors such as demographics, prior or concomitant medication and comorbid condition can be also considered in the analysis. An adjusted relative risk by relevant risk factors may be adapted if suitable.

For descriptive purpose, incidence rates per 100 patient-years or 10,000 patient-years will be calculated and analysis items will be specified on statistical analysis plan. For missing data, appropriate imputation

methods will be used, if required. The statistical considerations summarized in this section outline the plan for data analysis of this study. A final and complete statistical analysis plan will be prepared prior to data analysis.

Milestones:

Milestones	**Planned Date**
Start of data collection	・Korea: April 2014 ・European region: 4Q 2014
End of data collection	・Korea: 2026 ・European region: 2026
Study progress report(s)	・Included in Periodic Safety Update Report and/or; ・Upon request from the national competent authorities
Interim report(s) of study results	・Annual report: every May from 2015
Final report of study results	・2026

List of Abbreviations

Abbreviation	Definition
6-MP	6-mercaptopurine
ACR20	20% response, as defined by the American College of Rheumatology
AEs	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-dsDNA	Anti-double stranded DNA
AS	Ankylosing Spondylitis
ASAS20	Assessment of SpondyloArthritis International Society 20% improvement scale
ASAS40	Assessment of SpondyloArthritis International Society 40% improvement scale
AUC_{τ}	Area under the concentration-time curve
AZA	Azathioprine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval
$C_{max,ss}$	Maximum steady state serum concentration
CMV	Cytomegalovirus
CRP	C-reactive protein
CTCAE	Common Terminology Criteria of Adverse Event
EBV	Epstein-Barr virus
EC	Ethics committee
ECG	Electrocardiography
EOS	End of Study

ESI	Events of Special Interest
ESR	Erythrocyte sedimentation rate
EU	European Union
γ-GT	γ-glutamyltransferase
HIV	Human immunodeficiency virus
IBD	Inflammatory Bowel Disease
IGRA	interferon-γ release assay
IRB	Institutional review board
mAb	Monoclonal antibody
MCV	Mean corpuscular volume
MFDS	Ministry of Food and Drug Safety
N/A	Not applicable
PCDAI	Pediatric Crohn's Disease Activity Index
PUCAI	Pediatric Ulcerative Colitis Activity Index
PK	Pharmacokinetics
PsA	Psoriatic arthritis
RA	Rheumatoid Arthritis
SAEs	Serious adverse events
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
TNF-α	Tumor necrosis factor-α
UC	Ulcerative colitis
WBC	White Blood Cell

1. Presentation

1.1. Title

An Observational, Prospective Cohort Study to Evaluate the Safety and Efficacy of Remsima™ in Patients with Crohn's disease (CD), or Ulcerative Colitis (UC)

1.2. Marketing Authorization Holder

[redacted]

1.3. Sponsor

[redacted]

1.4. Lead Investigator

[redacted]

1.5. Research Centers

This study will be conducted in research centers which are located in South Korea and the European region.

1.6. Milestones

Milestones	Planned Date
Start of data collection	・Korea: April 2014 ・European region: 4Q 2014
End of data collection	・Korea: 2026 ・European region: 2026
Study progress report(s)	・Included in Periodic Safety Update Report and/or; ・Upon request from the national competent authorities
Interim report(s) of study results	・Annual report: every May from 2015
Final report of study results	・2026

2. Background and justifications

Remsima™ is an IgG_1 chimeric human-murine monoclonal antibody (mAb) biosimilar to Remicade® (infliximab, Janssen Biologics B.B.) developed by CELLTRION, Inc. Remsima™ is produced in the same type of cell-line as Remicade®, and it has an identical primary sequence. Both Remsima™ and Remicade® are mAbs to tumor necrosis factor-α (TNF-α), and are thought to exert their biological effects by binding, and thus neutralizing TNF-α, preventing it from binding to its endogenous receptors (Van den Brande et al. 2003). Infliximab has also been shown to cause programmed cell death of activated T-lymphocytes expressing TNF-α (Van den Brande et al. 2003).

Indications for Remsima™ are rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis, UC, CD, pediatric UC and pediatric CD. The approval of Remsima™ was based on the results of two large, randomized, double-blinded, phase I and III studies, called the PLANETAS and PLANETRA studies, respectively (Park et al. 2013; Yoo et al. 2013).

The PLANETAS study was a Phase I study conducted in patients with AS that aimed to compare the pharmacokinetics (PKs), safety and efficacy of Remsima™ and Remicade®. A total of 250 patients (Remsima™=125; Remicade®=125) took part in the study (Park et al. 2013). The primary endpoints were area under the concentration-time curve (AUC_{τ}) at steady state and observed maximum steady state serum concentration ($C_{max,ss}$) between weeks 22 and 30 (Park et al. 2013). Additional PK, efficacy endpoints, including 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40), and safety outcomes were also assessed (Park et al. 2013). The PK profiles of Remsima™ and Remicade® were equivalent in patients with active AS ($AUC_{\tau, ss}$: Remsima™- 32,765.8 µgh/mL; Remicade®- 31,359.3 µgh/mL; $C_{max,ss}$: Remsima™- 147.0 µg/mL; Remicade®- 144.8 µg/mL) and the efficacy of the two treatments was also comparable at week 30 (ASAS20 - 70.5% vs. 72.4%; ASAS40 - 51.8% vs. 47.4%, respectively). In the PLANETAS study Remsima™ was well tolerated, with an efficacy and safety profile which was comparable to that of Remicade® up to week 30 (Park et al. 2013).
The PLANETRA study was a phase III study conducted in patients with RA who had inadequate response to methotrexate (MTX) (Yoo et al. 2013). A total of 606 patients (Remsima™=302; Remicade®=304) took part in the study. The primary endpoint was to demonstrate equivalence in

efficacy of Remsima™ and Remicade® at week 30, as determined by ACR20 response criteria (Yoo et al. 2013). Additional secondary efficacy, PK and safety endpoints were assessed up to week 30. At week 30, ACR20 responses were 60.9% for Remsima™ and 58.6% for Remicade® (2% difference; 95% CI: -6% to 10%), demonstrating equivalent efficacy. A comparable PK and safety profile, including immunogenicity, were also observed at week 30 (Yoo et al. 2013).

These two studies demonstrated that the clinical efficacy and PK of Remsima™ are equivalent to that of Remicade®, and that the two treatments are well tolerated with comparable immunogenicity and safety profiles in patients with AS and RA. The evidence from these two studies was deemed appropriate and sufficient by the EMA and the MFDS in Korea to grant a license for Remsima™ equivalent to the license for Remicade®. This license included indications for patients that were not included in the clinical study program, namely patients with PsA, psoriasis, CD and UC.

There is therefore a need to investigate the *a priori* hypothesis that, "Remsima™ is a safe and efficacious treatment in patients with CD and UC, in line with previous observations and comparisons with Remicade® in RA and AS patients". While it is reasonable to assume, based on the results of the PLANETAS/PLANETRA studies, that the two treatments can be used in patients with CD or UC, with comparable efficacy and safety, there remains a need to investigate the safety and efficacy profile of Remsima™ in these patients.

Inflammatory bowel disease is a collective term referring to a group of chronic inflammatory conditions of the colon and small intestine, of which CD and UC are the main types (Baumgart & Carding 2007). CD is characterized by relapsing and remitting episodes, with complications of stricture, fistulas, or abscesses over time (Colombel et al. 2010; Peyrin-Biroulet et al. 2010; Cosnes et al. 2011). UC is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain (Rutgeerts et al. 2005). Whereas the presentation of CD in children is similar to that in adults (Hyams et al. 2007), UC in children appears to manifest more aggressively than the disease in adults, and with a greater disease distribution (Bradley & Oliva-Hemker 2012; Sawczenko 2003).

The efficacy and safety of Remicade®, the reference drug, has been investigated in patients with CD and UC in a number of studies. The ACCENT I, ACCENT II, and SONIC trials have all evaluated the efficacy and safety of Remicade® in CD (Hanauer et al. 2002; Colombel et al. 2010; Sands et al.

2004), while the ACT1 and ACT2 trials evaluated the efficacy and safety of Remicade® in patients with UC (Rutgeerts et al. 2005). There have been two studies investigating the safety and efficacy of Remicade® in pediatric IBD; the REACH study (Hyams et al. 2007) and study C0168T72 (Hyams et al. 2012).

In the ACCENT I and ACCENT II clinical trials, where patients received either a single infusion of Remicade® or maintenance therapy, the most commonly reported adverse events (AEs) were headache, abdominal pain, and upper respiratory tract infection (URTI) in ACCENT I (Hanauer et al. 2002), and abdominal pain, nausea, fatigue, abscess, arthralgia, URTI, and headache in ACCENT II (Sands et al. 2004). The proportion of patients with serious adverse events (SAEs) was similar in both groups of patients receiving either a single Remicade® infusion or Remicade® maintenance therapy in ACCENT I; in ACCENT II SAEs were only reported in the Remicade® maintenance therapy group (Sands et al. 2004). However it should be noted that ACCENT II was a much smaller study, in a limited cohort of patients and so such data should be interpreted with caution. In ACCENT I serious infections occurred in 4% (22/573) of all patients, with no difference in the incidence of infections requiring treatment between patients receiving a single infusion and those receiving multiple Remicade® infusions. In ACCENT II serious infection was reported in 3.6% of all patients (1/28), occurring in the maintenance therapy group only. Infusion reactions occurred in 4-6% of patients on maintenance therapy compared to 3% of patients receiving a single infusion of Remicade® in ACCENT I, and 26.7% of patients on Remicade® maintenance therapy compared to 23.1% of patients on placebo maintenance therapy in ACCENT II. In ACCENT I more patients developed anti-dsDNA and anti-nuclear antibodies (ANA) in the Remicade® maintenance therapy group (34% and 56% respectively) compared to those receiving a single infusion (11% and 35% respectively). This endpoint was not assessed in ACCENT II (Hanauer et al. 2002; Sands et al. 2004).

The SONIC trial compared the efficacy of Remicade® monotherapy, azathioprine (AZA) monotherapy, and combination therapy. Patients received study medication through week 30 and could continue in a blinded study extension through week 50 (Colombel et al. 2010). Through week 50, the incidence of AEs was similar among the three groups. The most commonly reported AEs were nausea, abdominal pain, worsening of CD, vomiting, diarrhea, fatigue, pyrexia, arthralgia, headache, and nasopharyngitis. In this study the overall proportion of SAEs was significantly higher in the monotherapy groups (26.7% AZA monotherapy, 23.9% Remicade® monotherapy) than in the

combination therapy group (15.1%, $p<0.05$ for both comparisons), while the incidence of serious infections was similar across all groups (3.9% - 4.9%). The number of infusion reactions was significantly higher in the Remicade® monotherapy than in either the AZA monotherapy group or the combination therapy group (16.6% vs. 5.6% and 5.0% respectively, $p=0.002$ and $p<0.001$, respectively). Antibodies to Remicade® were detected at week 30 in 0.9% of patients receiving combination therapy and 14.6% of patients receiving Remicade® monotherapy (Colombel et al. 2010).

In the REACH study, the safety and efficacy of Remicade® was investigated in pediatric patients with moderately to severely active Crohn's disease. Patients were treated with 5 mg/kg Remicade® at weeks 0, 2, and 6. Those responding to treatment at week 10 were subsequently randomized to receive maintenance Remicade® every 8 or 12 weeks through to week 46. In this study the proportion of patients reporting AEs or SAEs was similar for both maintenance regiments, although the proportion of patients with infections was higher in the group receiving maintenance therapy every 8 weeks compared with those receiving maintenance therapy every 12 weeks (73.6% vs. 38.0%, respectively). However the respective incidence of serious infections was comparable for both maintenance groups (5.7% vs. 8.0%, respectively). The incidence of infusion reactions was also comparable for the two maintenance therapy regimens. 17.0% of patients receiving maintenance therapy every 8 weeks experienced an infusion reaction, while 18.0% of patients receiving maintenance therapy every 12 weeks experienced an infusion reaction. No cases of serum sickness-like reactions or delayed hypersensitivity reactions were reported. Newly positive antinuclear antibodies were detected in 22.9% of patients receiving maintenance therapy every 8 weeks, and in 27.9% of patients receiving maintenance therapy every 12 weeks. Newly positive antidouble-stranded DNA antibodies were detected in 5.9% of patients receiving maintenance therapy every 8 weeks, and in 8.3% of patients receiving maintenance therapy every 12 weeks (Hyams et al. 2007).

In the ACT1 and ACT2 trials, patients with moderate-to-severe UC despite treatment with concurrent medications, received placebo or Remicade® (5 mg/kg or 10 mg/kg) intravenously at weeks 0, 2, and 6, and then every 8 weeks through week 46 (ACT1) or week 22 (ACT2). Patients were followed for 54 weeks in ACT1, and 30 weeks in ACT2 (Rutgeerts et al. 2005). In both ACT1 and ACT2 the proportion of patients with AEs was similar in the placebo group and the two Remicade® treatment groups. The most commonly reported AEs were worsening UC, abdominal pain, nausea, URTI, pharyngitis, sinusitis, pain, rash, arthralgia, headache, fever, anemia, and fatigue. In ACT1 the

incidence of SAEs in the placebo-treated group (25.6%), 5 mg/kg Remicade® group (21.5%), and 10 mg/kg Remicade® group (23.8%) were similar, while in ACT2 trial, the respective rates of SAEs were 19.5%, 10.7%, and 9.2%. The incidence of infections was similar among the groups in both studies, occurring in 2.5% to 6.6% of patients in ACT1 and 0.8% to 2.5% of patients in ACT2. In both ACT1 and ACT2 the incidence of acute and possible delayed infusion reactions was also similar (9.9% to 12.3%, and 0% to 1.7%, respectively, for ACT1; 8.1% to 11.7%, and 0% to 0.8%, respectively, for ACT2) (Rutgeerts et al. 2005). In ACT1, of the 229 patient serum samples that were available for the assessment of antibodies against Remicade®, 6.1% tested positive for anti-drug antibodies(ADAs) at some point after the first infusion of Remicade®, 15.7% tested negative for ADAs, and 78.2% had inconclusive test results. In ACT2, out of 188 patient serum samples that were available for the assessment of antibodies against Remicade®, 6.4% were positive for ADAs, 18.1% had negative test results, and 75.5% were inconclusive. The data from these key trials demonstrates that the reference drug Remicade® , is a relatively safe and generally well-tolerated therapy.

In the C0168T72 trial the safety and efficacy of Remicade® was assessed in a small cohort of pediatric patients with moderately to severely active UC (60 patients). Patients received 5 mg/kg Remicade® at weeks 0, 2, and 6. The primary endpoint of this study was clinical response at week 8. Those patients responding to therapy at week 8 were randomized to receive maintenance therapy every 8 or every 12 weeks through to week 54. Among the patients who were not randomized at week 8, 80% (12 of 15 patients) experienced at least one AE. The overall safety profile was similar between the two maintenance therapy groups. The number of patients experiencing ≥1 SAE in the group receiving maintenance therapy every 8 weeks was 18.2% (4 of 22 patients), compared to 21.7% of patients (5 of 23) receiving maintenance therapy every 12 weeks. The incidence of infections was similar between the two maintenance group - 59.1% (13 of 22) among patients receiving maintenance therapy every 8 weeks developed ≥1 infection; 60.9% (14 of 23) among patients receiving maintenance therapy every 12 weeks developed ≥1 infection. Infusion reactions were reported in 6.7% (1 of 15) of patients not responding to therapy after 8 weeks, 18.2% (4 of 22) of patients receiving maintenance therapy every 8 weeks, and 13.0% (3 of 23) of patients receiving maintenance therapy every 12 weeks. Newly positive anti-nuclear antibodies were detected in 33.3% (6 of 18) of patients receiving maintenance therapy every 8 weeks, and 15.0% (3 of 20) of patients receiving maintenance therapy every 12 weeks. Anti-double stranded DNA (anti-dsDNA) antibodies were detected in 10.5% (2 of 19) of patients receiving maintenance therapy every 8 weeks, and 0.0% (0 of 20) of patients receiving maintenance

therapy every 12 weeks. Four of the 52 evaluable patients (7.7%) were positive for antibodies to Remicade®.

In all of the aforementioned studies, Remicade® was found to be efficacious for the treatment of IBD. In the ACCENT I trial it was concluded that patients with CD responding to an initial dose of Remicade® were more likely to be in remission at weeks 30 and 54, to discontinue corticosteroids, and maintain their response for a longer period of time with maintenance therapy (Hanauer et al. 2002). In the ACCENT II trial it was concluded that Remicade® was effective in short-term closure of rectovaginal fistulas, with maintenance treatment being more effective than placebo in prolonging the duration of fistula closure (Sands et al. 2004). In the SONIC study, where efficacy of Infliximab monotherapy, AZA monotherapy and the combination was compared, patients on Remicade® monotherapy or the Remicade® - AZA combination therapy, were more likely to have a corticosteroids-free clinical remission than those receiving AZA alone (Colombel et al. 2010). In pediatric patients with moderately to severely active CD, 88.4% of patients overall had a clinical response to Remicade® treatment, and 58.9% of patients achieved clinical remission. It was found that patients responding to an induction regimen of Remicade® were more likely to be in remission at week 54 when maintenance therapy was administered every 8 weeks, rather than every 12 weeks (Hyams et al. 2007). Finally, data generated from patients with moderate-to-severe UC in ACT1 and ACT2 demonstrated that patients treated with Remicade® were more likely to have clinical response at weeks 8, 30, and 54 than those receiving placebo (Rutgeerts et al. 2005). In the C0168T72 study which involved pediatric patients with moderately to severely active UC, 73.3% of patients experienced a clinical response to Remicade® (Hyams et al. 2012). Similar to the REACH study, a regimen of maintenance therapy every 8 weeks was found to be more efficacious than a regimen of maintenance therapy every 12 weeks; 38.1% (8 of 21) of patients were in clinical remission in the 8 week maintenance therapy group compared with 18.2% (4 of 22) of patients in the 12 week maintenance therapy group (p=0.146) (Hyams et al. 2012).

The availability of targeted biologic therapies has revolutionized the treatment of several disease areas, including IBD. However, the significant cost of these medications creates a major barrier that limits universal access to these effective therapeutic agents. This has led to interest in developing biosimilar products, which are highly similar, but not identical, to the approved ‘reference’ agents (Dörner et al. 2013). Because of the complex three-dimensional structure, heterogeneity, and dependence of

biologic therapies on production in living cells, it is unlikely that a biosimilar will be identical. As such safety is a key consideration in the introduction of biosimilars to the market, more so than for conventional generics, particularly with regard to immunogenicity (Schellekens 2009). AEs previously reported to be encountered with mAb therapy include immune reactions following infusion, infectious diseases (with reactivation of tuberculosis being a particular concern for anti-TNF therapies), thrombocytopaenia, and auto-immune conditions such as lupus-like syndromes and cancer (Hansel et al. 2010).

This study will be initiated to evaluate and further characterize the long-term safety and efficacy of Remsima™ treatment in patients with CD or UC. Data generated in this study will build upon safety data already generated in the PLANETAS and PLANETRA studies in patients with AS and RA.

3. Study Objectives

3.1. Primary Objective

The primary objective of this longitudinal, observational, prospective cohort, phase IV registry study is to assess the safety of Remsima™ in IBD patients, who have either moderate to severe active CD, fistulizing active CD, or moderate to severe active UC by evaluation of events of special interest (ESI) up to 5 years and to exploratory compare patients receiving Remsima™.

3.1.1. Events of special interest

In order to assess the primary study outcomes, the following ESI will be evaluated:

- Hepatitis B virus reactivation
- Congestive heart failure
- Opportunistic infections (excluding tuberculosis)
- Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
- Tuberculosis
- Serum sickness (delayed hypersensitivity reactions)
- Haematologic reactions
- Systemic lupus erythematosus/lupus like syndrome
- Demyelinating disorders
- Lymphoma (not HSTCL)
- Hepatobiliary events
- Hepatosplenic T cell lymphoma (HSTCL)
- Intestinal or perianal abscess (in Crohn's disease)
- Serious infusion reactions during a re-induction regimen following disease flare
- Sarcoidosis/sarcoid-like reactions
- Paediatric malignancy
- Leukaemia
- Malignancy (excluding lymphoma)
- Colon carcinoma/dysplasia (in ulcerative colitis)
- Skin cancer
- Pregnancy exposure[†]

- Bowel stenosis, stricture, obstruction (in Crohn's disease)
- Others

†According to EU SmPC, the use of Infliximab during pregnancy is not recommended. However should the severity of the condition and treatment benefits outweigh potential risk to the mother and the baby and provided that there is no other available treatment options and provided that pregnant patient is fully informed and aware of the risks and upon careful judgement of the investigator, the treatment may continue throughout the pregnancy. Alternatively, the treatment should be discontinued. All pregnancy cases will be followed-up for the outcome.

Other items may be added or specified on the statistical analysis plan.

3.2. Secondary Objectives

3.2.1. Safety objectives

Safety of Remsima ™ over the study period will be assessed through the following outcomes:

- Adverse events (AEs), including serious AEs and AEs of special interest (such as infection and infusion-related reaction)
- Vital sign measurements (including blood pressure, heart and respiratory rates, and temperature), height, weight
- Physical examination findings
- Hypersensitivity monitoring
- Immunogenicity (optional)
- IGRA(interferon-γ release assay) test
- Clinical laboratory analyses
- Pregnancy test
- TB monitoring
- Concomitant medications
- Hepatitis B/C, human immunodeficiency virus (HIV) test

Safety assessments will be collected at the time points specified in the Table 7: Study Schedule of Events.

3.2.2. Efficacy objectives

Key efficacy endpoints will be as follows:

- Adult patients with moderate to severe active CD
  - Proportion of patients achieving a decrease of ≥70 points from baseline scores in CDAI (CDAI-70) (Colombel et al. 2010).
  - Proportion of patients achieving a decrease of ≥100 points from baseline scores in CDAI (CDAI-100)
  - Proportion of patients achieving clinical remission defined by CDAI score of less than 150 points (CDAI-150) (Hanauer et al. 2002; Colombel et al. 2010).
- Pediatric Patients with severe active CD
  - Proportion of patients achieving a decrease of ≥15 points from baseline scores in PCDAI and total score is 30 or less (Hyams et al. 2007)
  - Proportion of patients achieving clinical remission defined by PCDAI score 10 or less (Hyams et al. 2007)
- Adult patients with fistulizing, active CD
  - Proportion of patients achieving a ≥50% reduction from baseline in the number of draining fistulas over a period of ≥4 weeks compared to baseline (Sands et al. 2004).
  - Proportion of patients achieving complete response defined as the absence of draining fistulas (Sands et al. 2004).
- Adult patients with moderate to severe active UC
  - Proportion of patients achieving a decrease in Mayo scores from baseline of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1 (Rutgeerts et al. 2005) .
  - Proportion of patients achieving clinical remission, which is defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point (Rutgeerts et al. 2005)
- Pediatric patients with severe active UC
  - Proportion of patients achieving decrease from baseline in the PUCAI 20 or more (Turner et al. 2007)
  - Proportion of patients achieving clinical remission, which defined as a less than 10 points in the PUCAI score (Turner et al. 2007)

Efficacy assessments will be collected at the time points specified on the Table 7: Study Schedule of Events.

3.2.3. Health-economics objective

Cost-effectiveness will be evaluated in IBD patients with treated with Remsima™.

- Days of hospitalizations
- Medication and surgery interventions related to disease
- Days off work in employed patients
- Early retirement and return to work (working days gained)

4. Methods

4.1. Study Design

This study is a longitudinal, observational, prospective cohort, phase IV study to assess the safety and efficacy of Remsima™ in patients with CD, UC for up to 5 years from initiation of treatment for each patient. The study will be conducted according to the Declaration of Helsinki and the International Conference on Harmonisation of technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) – Good Clinical Practice. Informed consent from all patients and/or legal guardian according to the regulatory and legal requirements will be obtained prior to enrollment. Patients will undergo safety and efficacy assessments in accordance with routine medical practice. The decision to treat with Remsima™ will be independent of the decision to enroll the patient in this registry.

Patients will be included in this registry who are receiving treatment with 5mg/kg of Remsima™ by IV infusion at weeks 0, 2 and 6, and every 8 weeks thereafter in accordance with the product label. Dose and treatment schedule are recommended to comply with the approved posology in each regulatory authority or investigator's clinical decision. A dose visit window of ± 3 days is recommended up to and including Dose 3; a visit window of ± 14 days at maximum is recommended after Dose 3. Practicing physician will choose an assessment time point among visits near every 6 months or 1 year. If a patient has been treated with infliximab prior to enrollment, their dosing schedule will be continued appropriately. Participating patients will be followed for a period of up to 5 years after the first dose of Remsima™. The End-of-Study (EOS) visit only needs to be completed if the patient withdraws prior to study completion. An EOS visit will be made 8 weeks after the last dose is received. If the patient has completed the full 5-year study period, a separate EOS visit is not required. In this case, last visit will be considered the EOS visit. For those patients who initially respond to 5 mg/kg Remsima™ but who subsequently loose response, dose escalation is permitted in accordance with the local guidelines of the institution in which the patient is receiving treatment. Pre-treatment with antihistamines, hydrocortisone and/or paracetamol is permitted and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously.

4.2. Study Population

The study population will consist of at least 500 male and female patients with active CD, fistulizing active CD, and UC.

4.3. Inclusion Criteria

1. Patients who can be treated with Remsima™ according to the following criteria:
    a. Adult patients with moderate to severe active CD who have not responded despite a full and adequate course of therapy with corticosteroids and/or immunosuppressive agents, or who are intolerant to or have medical contraindications to such therapies
    b. Children and adolescent patients aged 6 to 17 years old with severe active CD who have not responded to conventional treatment with corticosteroids, immunomodulator and primary nutrition therapy, or who are intolerant to, or have contraindications to, such therapies
    c. Adult patients with fistulizing active CD who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy)
    d. Adult patients with moderate to severe active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or AZA, or who are intolerant or have medical contraindications to such therapies
    e. Children and adolescent patients aged 6 to 17 years old with severe active UC who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant or have medical contraindications to such therapies
2. Female patients of childbearing potential who agree to use adequate contraception to prevent pregnancy and continue contraceptive use for at least 6 months after their final dose of Remsima™. According to EU SmPC, the use of infliximab during pregnancy is not recommended. However should the severity of the condition and treatment benefits outweigh potential risk to the mother and the baby and provided that there is no other available treatment options and provided that pregnant patient is fully informed and aware of the risks and upon careful judgement of the investigator, the treatment may continue throughout the pregnancy. Alternatively, the treatment of Remsima™ should not be done for pregnant patient.

3. Patients (or legal guardian, if applicable) who are willing to give informed consent for long term follow-up including access to all medical records.

4.4. Exclusion Criteria

1. Patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients (Sucrose, Polysorbate 80, Monobasic sodium phosphate and/or Dibasic sodium phosphate).
2. Patients with a current or past history of chronic infection with Hepatitis B, Hepatitis C or infection with human immunodeficiency virus (HIV), or testing positive to those infections at Screening.
3. Patients with current diagnosis of Tuberculosis (TB) or severe or chronic infections (e.g. sepsis, abscesses, opportunistic infections, invasive fungal infections), or previously diagnosed with TB or severe or chronic infection, without sufficient documentation of complete resolution following treatment.
4. Recent exposure to persons with active TB, or a positive test result for latent TB (determined by a positive interferon-γ release assay [IGRA] with a negative chest X-ray) at Screening. If the result of the IGRA is indeterminate at Screening, one retest will be possible during the Screening period. If the repeated IGRA result is again indeterminate, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient may be included in the study. A patient who has received at least the first 30 days or recommended period of country-specific TB prophylaxis and intends to complete the entire course of prophylaxis may be enrolled. Patients with sufficient documentation of prophylaxis or complete resolution following TB treatment based on local guidelines can be treated before confirming IGRA result.
5. Patients with moderate or severe heart failure (NYHA class III/IV).
6. Patients for whom there are investigator's concerns about treatment with TNF-α blockers, such as a history of any malignancy within the previous five years prior to enrollment or a history of herpes zoster within one month prior to enrollment, may be excluded at the investigator's discretion.

4.5. Withdrawal of patients from the study

During the study, patients will be able to withdraw their consent at any time. Patients may also withdraw from the study if any of the following occur:

- development of a life-threatening infusion-related anaphylactic reaction
- development of signs of disease progression
- withdrawal of consent or refusal to continue treatment or procedures/observations
- development of any malignancy
- any AEs that would compromise the safety of the patient if they continue to participate in the study
- a significant or major protocol violation
- patient is lost to follow-up
- death of the patient

In case of early discontinuation from the observation, an investigator should record all the data collected until the time of discontinuation in the patient's case report form including the date of discontinuation, reason for discontinuation, treatment and follow-up result. Also, collection of available safety data should continue until 6 months from the day of discontinuation and data will be included in the analyses. If the patient stopped treatment due to safety reason, it should be recorded in (S)AE pages.

4.6. Sample Size

This study aims to recruit at least 500 patients taking Remsima™ from participating test centers. A sample size is determined not on the basis of formal statistical hypotheses but using an exploratory descriptive approach. The proposed number of subjects is considered to be sufficient to achieve the objectives of the study. At least 50 percentage of target number of patients will be enrolled in European regions; recruitment in selected Eastern European and Western European countries will continue for 5 years after respective launches.

4.7. Assessments

The following data will be collected in order to assess the primary and secondary study outcomes. Data will be obtained from assessments performed as part of routine clinical practice. Data will be

collected for the time points specified in the Schedule of Events table (Table 7: Study Schedule of Events), where available.

4.7.1. Collection of core baseline data

Patient will be informed of the full nature and purpose of the study, and provide signed and dated written informed consent before entering this study. The following information will be collected from the patient medical records by the recruiting clinician, using a standardized form:

- Diagnosis of IBD
- Date of birth, race, gender
- Previous drug history of therapy with corticosteroids, immunosuppressive agents and biologic agents including duration of therapy
- Any significant co-morbidity and medical history
- All current therapy/medications
- Height, weight, blood pressure
- Efficacy assessment

In addition, personal and medical information will be obtained directly from each patient recruited (e.g. smoking status).

4.7.2. Safety Assessments

4.7.2.1. Events of special interest (ESI)

In order to assess the primary study outcomes, the following ESI will be evaluated:

- Hepatitis B virus reactivation
- Congestive heart failure
- Opportunistic infections (excluding tuberculosis)
- Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
- Tuberculosis
- Serum sickness (delayed hypersensitivity reactions)
- Haematologic reactions
- Systemic lupus erythematosus/lupus like syndrome
- Demyelinating disorders
- Lymphoma (not HSTCL)

- Hepatobiliary events
- Hepatosplenic T cell lymphoma (HSTCL)
- Intestinal or perianal abscess (in Crohn's disease)
- Serious infusion reactions during a re-induction regimen following disease flare
- Sarcoidosis/sarcoid-like reactions
- Pediatric malignancy
- Leukaemia
- Malignancy (excluding lymphoma)
- Colon carcinoma/dysplasia (in ulcerative colitis)
- Skin cancer
- Pregnancy exposure[†]
- Bowel stenosis, stricture, obstruction (in Crohn's disease)
- Others

[†]According to EU SmPC, the use of Infliximab during pregnancy is not recommended. However should the severity of the condition and treatment benefits outweigh potential risk to the mother and the baby and provided that there is no other available treatment options and provided that pregnant patient is fully informed and aware of the risks and upon careful judgement of the investigator, the treatment may continue throughout the pregnancy. Alternatively, the treatment should be discontinued. All pregnancy cases will be followed-up for the outcome.

Other items may be added or specified on the statistical analysis plan.

4.7.2.2. Other Adverse Events

Assessment of AEs including serious AEs, and AEs of special interest (such as infections, and infusion-related reactions) will be assessed throughout the study. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and intensity will be graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Table 1: Common Terminology Criteria for Adverse Events (CTCAE) v4.0

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE

4.7.2.3. Assessment of causality

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgement based on the investigator's clinical experience, the association of the event with the study drug seems likely.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

4.7.2.4. Reporting of Adverse Events

All adverse events, including SAEs, reported or observed during the study must be recorded on the relevant pages of the case report form, regardless of their causality with study drug treatment, with regard to the time of onset and resolution of adverse events, severity/intensity, and causality with study drug, and related action and outcomes.

An AE is defined as any untoward medical occurrence, including a clinically significant laboratory finding, symptom, or disease in a patient enrolled into this study regardless of its causal relationship to study drug. A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An adverse drug reaction defined as any untoward medical occurrence in patient and its causal relationship to study drug cannot be ruled out.

If any serious adverse event (as defined herein) occurs, the investigator must inform this event to the study Sponsor or CRO within 24 hours by completing the eCRF or by phone or by fax or email to ensure Sponsor or CRO can take necessary actions. The Sponsor or CRO, within 15 days from the day of being informed of the SAE, must report the occurrence of such event to regulatory authorities along with the results of actions taken and relevant basic data, through website, phone, fax or mail, or otherwise electronically. In addition, SAE will be reported to Ethics Committee (EC) or Institutional Review Board (IRB) according to the site policy/local regulation.

An SAE is defined as any event that

- results in death
- is immediately life threatening (includes events which put patients at risk of death at the time of the event but not events which may have caused patient death if more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. If a patient is hospitalized purely for convenience (eg, for easier performance of study assessments), the

hospitalization does not qualify as a SAE. If a patient is hospitalized solely due to disease progression, the hospitalization does not qualify as an SAE but that event should be reported as an AE.

The reporting of serious expected AEs in an expedited manner varies among countries. Time frames for other types of serious reports vary among countries, depending on source, expectedness and outcome.

[Contact Information]

[redacted]

[redacted]

4.7.2.5. Reporting of Pregnancy

All pregnancy cases from female patients and partner of male patients should be reported to the Sponsor or CRO within 24 hours after awareness and the outcome of all pregnancy will be followed-up for the outcome for mother and new born baby. Sepcific guideline and form for reporting will be provided to the study centers.

4.7.2.6. Immunogenicity testing (Optional)

Immunogenicity testing will be carried out in accordance with investigator's medical judgement. Blood samples for immunogenicity testing (anti-drug antibodies) will be collected from patients given patient's written informed consent at the time points specified on the Table 7: Study Schedule of Events.

4.7.2.7. Tuberculosis Assessment

At Screening, a current or past diagnosis of TB, recent exposure to person with active TB, or examination findings indicating the presence of TB will result in patient exclusion from the study. Patients with latent TB, or who have had recent exposure to persons with active TB at Screening will not be enrolled. Latent TB is defined as the presence of a positive interferon-γ release assay (IGRA) test, with a negative chest X-ray. Throughout the study, including Screening and the End-of-Study Visit, if the result of the IGRA is indeterminate, 1 retest will be performed at the visit. If the repeat IGRA result is again indeterminate at Screening, the patient will be excluded from the study. If the repeat IGRA result is negative, the patient may be included in the study. A patient who has received at least the first 30 days or recommended period of country-specific TB prophylaxis and intends to complete the entire course of prophylaxis may be enrolled. Patients with sufficient documentation of prophylaxis or complete resolution following TB treatment based on local guidelines can be treated before confirming the IGRA result.

A chest x-ray (both posterior–anterior and/or lateral views) will be performed within 4 weeks prior to Screening or at Screening. Samples for IGRA test will be obtained at the time points specified in the Table 7: Study Schedule of Events.

IGRA will be performed at Screening, every year and EOS visit to identify positive conversion of previously negative results according to Table 7: Study Schedule of Events. As described in the literature (Park et al. 2009), IGRA can be used as a method of identifying patients with a false negative response to latent TB infections or new TB infections. IGRA will be carried out at the central laboratory.

Throughout the study, patients will be monitored for the results of chest X-ray and/or the clinical signs and symptoms of TB.

Active TB is more likely to be developed during induction phase. Recurrent TB can occur at any time after the completion of TB treatment but mostly after 3-6 months (Korean Guideline for Tuberculosis 2nd Edition. 2014, Johnson J.L. et al. 2012, Jasmer R.M. et al. 2004). Patients with an abnormal chest radiograph consistent with past TB who have received previous adequate treatment, should be monitored clinically every three months with a chest radiograph and sputum cultures if respiratory symptoms develop (BTS Guideline. 2005).

4.7.2.8. Vital Signs, Height, and Weight Measurements

Vital signs (including blood pressure, heart and respiratory rates, and body temperature) will be measured after 5 minutes rest (sitting) before the beginning of the Remsima™ infusion (on the same day as the Remsima™ infusion) at the time points specified on the Table 7: Study Schedule of Events. Any clinically significant abnormal findings, upon judgement of the investigator, will be reported. Height, and weight will also be documented at the time points specified on the Table 7: Study Schedule of Events, where available.

4.7.2.9. Hypersensitivity Monitoring

Vital signs collected as a result of hypersensitivity monitoring on each dosing day (from the start of infusion, and until 1-2 hours after the end of infusion) will be documented. If required, electrocardiography (ECG) may be performed and documented for hypersensitivity monitoring as per local guidelines. Any clinically significant abnormal findings, upon judgement of the investigator, will be reported.

4.7.2.10.Clinical Laboratory Analyses

Clinical laboratory analyses can be conducted as laid out in Table 2: Clinical Laboratory Analyses. The following laboratory analyses results can be documented at the time points specified on the Table 7: Study Schedule of Events. Tests will be conducted at the local laboratory and any clinically significant abnormal findings, upon judgement of the investigator, will be reported.

Table 2: Clinical Laboratory Analyses

	Tests
Clinical Chemistry	total protein, serum bilirubin, alanine aminotransferase(ALT), aspartate aminotransferase(AST), alkaline phosphatase(ALP), γ-glutamyltransferase(γ-GT), blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, creatine kinase, lactate dehydrogenase, and C-reactive protein (CRP)
Hematology	red blood cells, ESR, total and differential white blood cell count, absolute neutrophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	white blood cell, red blood cell, protein
Optional	Epstein-Barr virus (EBV), cytomegalovirus (CMV), folic acid, ferritin

4.7.2.11. Pregnancy Test

A serum and urine pregnancy test may be carried out in accordance with the investigator's medical judgement. If available, a serum pregnancy test results will be documented at Screening and EOS. A result of urine pregnancy test perfomed before dosing on each dosing day, for women of childbearing potential who have not been surgically sterilized, will be documented during the observational period to confirm the absence of pregnancy. Tests will be conducted at the local laboratory.

4.7.2.12. Hepatitis B and C, and human immunodeficiency virus testing

Hepatitis B and C and HIV tests will be performed at the time points specified on the Table 7: Study Schedule of Events. Hepatitis B and C and HIV tests may be carried out in accordance with the investigator's medical judgement based on results of previously performed test or patient's status and will be conducted at the local laboratory.

4.7.2.13. Physical examination

Physical examinations result will be documented at each visit. Investigators will carefully evaluate patients for any indication of infection or infusion related reaction and pursue further investigation and treatment, indicated in accordance with the investigator's medical judgement. Any clinically significant abnormal findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded.

4.7.2.14. Prior and concomitant medication

Concomitant medications which are considered clinically significant upon the judgement of investigators within 6 months prior to Screening and any use of concomitant medications during the study period will be recorded in the patient's CRF. Any changes in concomitant medications will also be recorded in the patient's CRF. However, prior history of biologic therapy the patient has received for the treatment of IBD at any point in the patients history will be recorded, including duration of therapy, and reason for stopping. Any changes in Remsima™ treatment such as change in dose or stopping, dates and reasons should be recorded with details. Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of all investigators to ensure that details regarding the medication are recorded in full in the CRF.

4.7.3. Efficacy Assessments

All efficacy assessments will be performed in accordance with routine clinical practice. Efficacy outcomes will be assessed by collection of available results from patient medical records. For efficacy assessment at baseline, the efficacy assessment results prior to first exposure to infliximab should be recorded. However, for patients whom have already received 3 or more doses of infliximab prior to the study enrolment, baseline efficacy assessed at Day 0 (prior to dose administration) or at the last dosing visit prior to study enrolment will be used.

4.7.3.1. Crohn's Disease Activity Index (CDAI)

Patients with moderate to severe active CD will have their condition assessed using the CDAI. The CDAI will be documented prior to first dose administration and every 6 months (± 6 weeks) thereafter until the end of the study (EOS). The CDAI is a clinical tool for measuring disease activity in CD patients and is a multifactoral itemized scale used to assess different disease activity measures and symptoms. The scoring of patients on the CDAI will be conducted by investigator or designee-led interview at the study center. Measures of activity are weighted differently and scores are multiplied by the weighting to produce an overall score (refer to Table 3: Crohn's Disease Activity Index*).

Efficacy of Remsima™ in moderate to severe active CD patients will be assessed by the proportion of CD patients achieving a decrease of ≥70 points and the proportion of CD patients achieving a decrease of ≥100 points from baseline scores in CDAI, prior to exposure to Remsima™, and the proportion of moderate to severe CD patients achieving clinical remission defined by CDAI score of less than 150, as previously described (Hanauer et al. 2002).

Table 3: Crohn's Disease Activity Index*

Events	Weighting factor
Total number of diarrhea stools in one week	2X
Sum of abdominal pain ratings in one week (None=0, Mild=1, Moderate=2, Severe=3 per day)	5X
Sum of ratings of general well-being in one week (Well=0, Slightly below par=1, Poor=2, Very poor=3, Terrible=4 per day)	7X
Number of symptoms the patient currently has out of the following six conditions: • Arthritis/arthralgia • Iritis/uveitis • Erythema nodosum, pyodermagangrenosum or apththous stomatitis • Anal fissure, fistula or perirectal abscess • Other fistula • Fever >37.8°C for the last week	20X
Taking a narcotic antidiarrheal drug (0 for no; 1 for yes)	30X

An abdominal mass (0 for none; 2 for suspected; 5 for definite)	10X
Deviation of hematocrit from 47% in men and 42% in women	6X
Percentage deviation from standard weight ((Standard weight – Patient weight)/Standard weight) x 100(%)	1X

*Adapted from Best *et al*.(Best et al. 1976)

4.7.3.2. Pediatric Crohn's Disease Activity Index*

Pediatric patients with severe active CD will have their condition assessed using the PCDAI. The PCDAI will be documented prior to first dose administration and every 6 months (± 6 weeks) thereafter until the end of the study (EOS). The PCDAI is a clinical tool for measuring disease activity in pediatric CD patients and is a multifactoral itemized scale used to assess different disease activity measures and symptoms. The scoring of pediatric patients on the PCDAI will be conducted by investigator or designee-led interview at the study center. The PCDAI score can range from 0-100, with higher scores signifying more active disease. Each items are scored differently ranges from 0 to 10 and the higher score means more severe clinical conditions (refer to Table 4: Pediatric Crohn's Disease Activity Index*).

Efficacy of Remsima™ in pediatric patients with severe active CD will be assessed by the proportion of CD patients achieving a decrease of ≥15 points from baseline scores in PCDAI, prior to exposure to Remsima™, and total score is 30 or less. Also, the proportion of severe CD pediatric patients achieving clinical remission defined by PCDAI score of 10 or less as previously described (Hyams JS et al. 1991), will be assessed.

Table 4: Pediatric Crohn's Disease Activity Index*

		Score
History (Recall, 1week) †		
Abdominal Pain	None	0
	Mild-brief, does not interfere with activities	5
	Moderate/severe - daily, longer lasting, affects activities, nocturnal	10
Stools per day	0 ~ 1 liquid stools, no blood	0

	Up to 2 semi-formed with small blood, or 2 ~ 5 liquid with or without small blood				5
	Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea				10
Patient functioning, General well-being	No limitations of activities, well‡				0
	Occasional difficulty in maintaining age-appropriate activities, below par				5
	Frequent limitation on activity, very poor				10
Examination					
Weight	Weight gain or voluntary weight stable/loss				0
	Involuntary weight stable, weight loss 1% ~ 9%				5
	Weight loss ≥ 10%				10
Height	< 1 channel decrease (at diagnosis) or Height velocity ≥ -1 SD (at follow-up)				0
	≥ 1, < 2 channel decrease (at diagnosis) or Height velocity < -1 SD, > -2 SD (at follow-up)				5
	≥ 2 channel decrease (at diagnosis) or Height velocity ≤ -2 SD (at follow-up)				10
Abdomen	No tenderness, no mass				0
	Tenderness, or mass without tenderness				5
	Tenderness, involuntary guarding, definite mass				10
Perirectal disease	None, asymptomatic tags				0
	1 ~ 2 indolent fistula, scant drainage, no tenderness				5
	Active fistula, drainage, tenderness, or abscess				10
Extra-intestinal manifestations	fever ≥ 38.5 for 3 days over past week, oral ulcers, definite arthritis, uveitis, erythema nodosum, pyoderma gangrenosum, None = 0, one = 5, more than 2 = 10				
Laboratory (values obtained within the past week)					
ESR, mm/hr	< 20				0
	20 ~ 50				2.5
	> 50				5
Alb, g/dL	≥ 3.5				0
	3.1~3.4				5
	≤ 3.0				10
Hct, %	**Age <10**	**11< Age <19 Female**	**11< Age <14 Male**	**15< Age <19 Male**	
	> 33	≥ 34	≥ 35	≥ 37	0
	28 ~ 32	29 ~ 33	30 ~ 34	32 ~ 36	2.5
	< 28	< 29	< 30	< 32	5

* The total score of Pediatric Crohn's Disease Activity Index ranges from 0 to 100, with higher scores indicating more severe disease (Hyams JS et al. 1991).

†Patients will be scored based on the their history of the last week prior to assessment date.

‡The limitation of activity should be based on the most significant limitation during the past week, even if it is only for 1 day.

4.7.3.3. Assessment of Fistulas

Patients with fistulizing active CD will have their condition assessed by counting fistulas. The fistula count will be documented prior to first dose administration and every 6 months (± 6 weeks) thereafter until the end of the study (EOS). Efficacy will be assessed through the proportion of fistulizing CD patients achieving a ≥50% reduction from baseline in the number of draining fistulas over a period of ≥4 weeks. The proportion of patients achieving complete response defined as the absence of draining fistulas will be assessed as well, as previously described (Sands et al. 2004).

4.7.3.4. Mayo Scores

Patients with moderate to severe UC will have their condition assessed using the Mayo scoring system. The Mayo Score will be documented prior to first dose administration and every 6 months (± 6 weeks) thereafter until the end of the study (EOS). The Mayo scoring system is a clinical tool to measure disease activity in UC patients and is a multifactoral itemized scale used to assess different disease activity measures and symptoms. The scoring of patients on the Mayo scoring system will be conducted by an investigator or designee-led interview at the study center. There are four catagories assessed, each which is scored 0 to 3 (0 being normal function or inactive disease and 3 being severe symptoms and highly active disease). The four categories assessed are: stool frequency, rectal bleeding, findings on endoscopy, and physicians global assessment of disease. The scores for each category are combined to give an overall score which ranges from 0 to 12, with higher scores indicating more severe disease. (refer to Table 5: Mayo Scoring System for Assessment of Ulcerative Colitis Activity*)

Efficacy or clinical response to Remsima™ in this study is defined as the proportion of UC patients achieving a decrease in Mayo scores from baseline of at least 3 points and at least 30%, with an

accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1. Clinical remission will also be assessed which is defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point.

Table 5: Mayo Scoring System for Assessment of Ulcerative Colitis Activity*

Stool frequency[†]	**Score**
Normal no. of stools for this patient	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools more than normal	3
Rectal bleeding[‡]	
No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood with stool most of the time	2
Blood alone passes	3
Endoscopic Findings	
Normal or inactive disease	0
Mild disease (erythema, decreased vascular pattern, mild friability)	1
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
Severe disease (spontaneous bleeding, ulceration)	3
Physician's global assessment[§]	
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3

*The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease (Schroeder et al. 1987).

[†]Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

[‡]The daily bleeding score represents the most severe bleeding of the day.

[§]The physician's global assessment acknowledges the three other criteria; the patient's daily recollection of abdominal discomfort and general sense of well being, and other observations, such as physical findings and the patient's performance status.

4.7.3.5. Pediatric Ulcerative Colitis Activity Index (PUCAI)

Pediatric patients with severe UC will have their condition assessed using the PUCAI at prior to first dose administration and every 6 months (± 6 weeks) thereafter until the end of the study (EOS). The PUCAI is a clinical tool to measure disease activity in pediatric UC patients and is a multifactoral itemized scale used to assess different disease activity measures and symptoms. The scoring of patients on the PUCAI will be conducted by an invetigator or designee-led interview at the study center. There are six catagories assessed, each which is scored ranges from 0 to 30. The four categories assessed are: stool frequency, rectal bleeding, findings on endoscopy, and physician's global assessment of disease. The scores for each category are combined to give an overall score which ranges from 0 to 12, with higher scores indicating more severe disease.

Efficacy or clinical response to Remsima™ in this study is defined as a decrease of 20 or more from baseline in the PUCAI score. Clinical remission will also be assessed which is defined as the proportion of pediatric UC patients achieving less than 10 points in PUCAI score. (refer to Table 6: Pediatric Ulcerative Colitis Activity Index*)

Table 6: Pediatric Ulcerative Colitis Activity Index*

Abdominal pain	**Score**
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
Rectal bleeding[†]	
None	0
Small amount only, in less than 50% of stools	10
Small amount with most stools	20
Large amount (more than 50% of the stool content)	30
Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
Number of stools per 24 hours[§]	

0 ~ 2 times	0
3 ~ 5 times	5
6 ~ 8 times	10
More than 8 times	15
Nocturnal stools (any episode of causing wakening)	
No	0
Yes	10
Activity level‡	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted acivity	10

*Sum of PUCAI ranges from 0 to 85 with higher scores indicating more severe disease (Turner et al. 2007). Answers should reflect a daily average of the last 2 days: If clinical conditions are changing rapidly (i.e., during intense intravenous therapy), the most recent 24 hours should be considered.

† "Large amount" should be selected if large amound of blood is present in most stools.

§Clustered several small stools over a very short period of time that could be related to tenesmus or incomplete evacuation should be considered as 1 stool.

‡ "Occasional limitation of activity" means "could attend school or equivalent but reduced activity" and "Severe restricted activity" means "could not attend school or equivalent activity".

4.7.4. Health-economic data evaluation

For cost-effectiveness evaluation, the following information will be collected throughout the study.

- Days of hospitalizations
- Medication and surgery interventions related to disease
- Days off work in employed patients
- Early retirement and return to work (working days gained)

4.8. Sample Storage and Shipment

During the study, blood samples will be collected for IGRA assessment and immunogenicity analysis (optional). Where appropriate, the serum should be transferred into a sufficient number of transfer vials prior to freezing. Additionally, blood samples for immunogenicity should be retained at the central laboratory (PPD Global Central Labs) up to the End of the Study in case additional analysis is

required. If additional analysis is not required during the study or after the End of the Study, blood samples will be stored in a CELLTRION, Inc. or designated biobank for a further 5 years (from the date the sample is transferred to the CELLTRION, Inc. or biobank) unless a specific authorization is given by CELLTRION, Inc. to destroy the sample. At CELLTRION, Inc. or biobank, additional tests can be conducted if it is required from a regulatory or medical perspective. The samples for IGRA assessment and immunogenicity testing will be shipped from the study center to the central laboratory for testing in weekly or monthly batches.
Details in storage and shipment will be followed according to the lab manual.

4.9. Data Collection

The study monitor will check the recording of data during the monitoring visits to the site and confirm that this study is performed in compliance with protocol and Good Clinical Practice. The investigator will ensure that the data collected are accurate, complete and legible.
All data obtained during the study will be promptly recorded on the eCRFs which allow for on-site data entry and data management. Site users can read from and write to the sponsor's database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. All source documents from which eCRF entries are derived will be placed in the subject's personal records. The original eCRF entries for each subject will be checked against source documents by the monitor.

Following the report of any serious morbidity, either by subject or physician, the referring physician will be contacted and asked to provide further details, where available. For ESI, specific details may be requested.

4.10. Data Handling

All clinical trial findings and documents will be regarded as confidential. The investigator and members of their research team must not disclose such information. The anonymity of participating subjects will, and must be, maintained. Subjects will be specified on CRFs and other documents by their subject number, initial or birth date and not by name. Documents that identify the subject (e.g.,

the signed subject information sheet and informed consent document) will, and must be, maintained as confidential by the investigator.

4.11. Data archiving

Any and all documents and data created from this registry including protocol, CRF, other source documents, database, all computer programs and study report will be kept in proper storage at least for 5 years after final report or first publication of the study results, which comes later. However, these documents should be retained for a longer period if required by the applicable legal or regulatory requirements.

4.12. Data Analysis

The statistical analysis will be performed using [redacted] The data documented in this study including exposure to Remsima™ (e.g. number of patients exposed, number of infusion, duration of exposure and etc.) and the clinical parameters measured will be described using descriptive statistics (n, mean, median, SD, minimum, and maximum) for quantitative variables and frequencies (counts and percentages) for qualitative variables. The AEs will be coded using the latest version of the MedDRA and summarized by the number of patients reporting an event and the percentage of patients with that event. The severity, start and stop date, and relationship to treatment will be listed. Severity of adverse events will be graded according to the CTCAE v4.0. Previous and concomitant treatments will be coded using the World Health Organization Drug Dictionary and medical history will be coded using MedDRA. In addition, the results would be compared against relevant historical infliximab data from published reports and articles presenting studies conducted with anti-TNF drug.

Subgroup analysis might be conducted for handling risk factors. Subgroup analysis for each risk factor level will be considered. Additionally, propensity score might be considered if it is necessary and relevant. The main risk factor to be considered is geographical region by the level of incidence rates or prevalence rates of events such as TB or pneumonia. Other risk factors such as demographics, prior or concomitant medication and comorbid condition can be also considered in the analysis. An adjusted relative risk by relevant risk factors may be adapted if suitable.

For descriptive purpose, incidence rates per 100 patient-years or 10,000 patient-years will be calculated and analysis items will be specified on statistical analysis plan. For missing data, appropriate imputation methods will be used, if required.

The statistical considerations summarized in this section outline the plan for data analysis of this study. A final and complete statistical analysis plan will be prepared prior to data analysis.

4.13. Interim Analysis

Periodic interim analyses are planned for regulatory reporting purposes. An annual regulatory report will be generated and reported to the regulatory authority. This will contain safety and efficacy data observed since the start of the study until December of each year. The first annual regulatory report is planned to be submitted in May 2015.

4.14. Limitations of the Research Methods

Less monitoring compared to interventional trial may compromise study findings. In addition, the inclusion and exclusion criteria, potential of the inclusion of ineligible patients, accuracy and completeness of data, use of historical data (type and quality) and type of data which are collected may influence the study results.

5. Ethical Considerations

5.1. Good Clinical Practice

The procedures set out in this clinical trial protocol are designed to ensure that the investigator abides by the principles of the International Conference on Harmonisation guideline E6 (R1): Good Clinical Practice, and the Declaration of Helsinki (Version 2013). The clinical trial also will be carried out in keeping with national and local legal requirements.

Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with Good Clinical Practice will be maintained by the site.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number and the date approval and/or a favourable opinion was granted.

The investigators are responsible for obtaining continued review of the clinical research at intervals not exceeding one year or otherwise specified by the IRB/IEC. The investigators must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

To alter the protocol, amendments must be written, which must be released by the responsible staff and receive IRB/IEC/competent authority approval prior to implementation (as appropriate).

Administrative changes may be made without the need for a formal amendment, but will also be mentioned in the integrated clinical trial report. All amendments will be distributed to all study protocol recipients, with appropriate instructions.

5.2. Informed Consent

Before each subject is enrolled in the registry, written informed consent will be obtained from the subject and/or legal guardian according to the regulatory and legal requirements. The subject information sheet and informed consent document must be signed and dated; one copy will be handed to the subject and the investigator will retain a copy as part of the clinical trial records. The investigator must ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to withdraw from the study at any time without prejudice to future care. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

If a protocol amendment is required, the subject information sheet and informed consent document may need to be revised to reflect the changes to the protocol. If the subject information sheet and informed consent document is revised, it must be reviewed and approved by the responsible IRB/IEC, and signed by all subjects subsequently enrolled in the clinical trial as well as those currently enrolled in the clinical trial.

5.3. Other Ethical and Regulatory Issues

A safety issue of clinical relevance is one that has a relevant impact on the course of the clinical trial or program (including the potential for suspension of the clinical trial program or amendments to protocols) or warrants immediate update of the subject information sheet and informed consent document.

6. Project Management

6.1. Final Report and Publication Policy

By signing the clinical trial protocol, the investigator agrees that the results of the clinical trial may be used for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the competent authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

An investigator or Clinical Research Organization shall not publish, or present for publication, any articles or papers or make any presentations, nor assist any other person in publishing any articles or papers or making any presentations, or making any public declaration relating or referring to the clinical trial, the results of the clinical trial, in whole or in part, without the prior written consent of the Sponsor.

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8. Appendices

8.1. Study Schedule of Events

Table 7: Study Schedule of Events

	Screening (Day -56 to 0)	Prior to first dose administration (Day 0)	Throughout the study (at every dose)[1]	Every 6 months[2]	Every 1 year[2]	End of Study Visit[3]
Informed Consent	X					
Diagnosis and diagnosis date	X					
Demography (Age, gender, race)	X					
Medical history[4]	X					
Smoking status	X					X
Inclusion and exclusion criteria	X					
Safety assessment						
Hepatitis B[5] and C[5], HIV[5]	X					
Pregnancy test (using serum)[13]	X					X
Pregnancy test (using urine)[8,13]			X			
Latent TB Screening and monitoring[6]	X					
Interferon-γ release assay[7, 8]	X				X	X
Immunogenicity testing [8,10]		X			X	X
Physical examination[8, 15]	X		X			X
Vital sign measurement[8,11, 15] and weight[8], height[12]	X		X			X
Hypersensitivity monitoring[14, 15]			X			
Clinical laboratory analyses[8, 15]	X			X		X
Previous/Concomitant medication	X		X			X
TB monitoring[6, 15]	X		X			X
AEs			X			X
Efficacy assessment[9]						
CDAI[8]		X[9]		X		X
PCDAI[8]		X[9]		X		X
Fistula counting[8]		X[9]		X		X
Mayo score System[8]		X[9]		X		X
PUCAI[8]		X[9]		X		X
Health-economics			X			X

1. For treatment, a dose visit window of ± 3 days is recommended up to and including Dose 3; a visit window of ± 14 days at maximum is recommended after Dose 3.
2. Time points will be calculated from the first dose of Remsima™ in this study. For assessments at every 6 month and 1 year, a window visit of ± 6 weeks is recommended. Practicing physician will choose an assessment time point among visits near every 6 month or 1 year.
3. The End-of-Study (EOS) visit only needs to be completed if the patient withdraws prior to study completion. An EOS visit will be made 8 weeks after the last dose is received. If the patient has completed the full 5-year study period, a separate EOS visit is not required. In this case, the last visit will be considered the EOS visit.
4. Medical records should include whether patients have been BCG-vaccinated or not.
5. Hepatitis B and C and HIV-1 or -2 tests may be carried out at Screening in accordance with the investigator's medical judgement which is based on results of previously performed test or patient's status and will be conducted at local laboratory.
6. At Screening, a chest x-ray and an interferon-γ release assay will be performed. A chest x-ray (both posterior-anterior and/or lateral views) is not required at Screening if a chest x-ray within 4 weeks prior to Screening is available. The results of the chest x-ray should be entered in an eCRF at Screening. Throughout the study, patients will be monitored for the results of chest x-ray and/or the clinical signs and symptoms of TB. Chest x-rays will be evaluated at the local level and the interferon-γ release assay will be performed at the central laboratory.
7. Interferon gamma release assay (IGRA) test will be performed at the central laboratory. Patients who test positive for IGRA during the Study period, including Screening, with sufficient documentation of prophylaxis or complete resolution of TB following treatment based on local guidelines, the IGRA tests are not required at every year at EOS visit.
8. Assessed prior to Remsima™ infusion
9. For efficacy assessment at baseline, the efficacy assessment results prior to first exposure to infliximab should be recorded. However, for whom already exposed to infliximab 3 or more times prior to the study enrolment, baseline efficacy assessed at Day 0 (prior to dose administration) or at the last dosing visit prior to study enrolment will be used.
10. Serum samples for immunogenicity testing (anti-infliximab) will be drawn at the same time as the clinical laboratory tests before dosing, where applicable. Immunogenicity will be carried out in accordance with investigator's medical judgement. Testing will be performed at the central laboratory.
11. Vital signs (including weight, blood pressure, heart and respiratory rates, and temperature) will be measured after 5 minutes of rest (sitting) before the beginning of the Remsima™ infusion.
12. Height will be measured only at Screening.
13. These assessments will be conducted in accordance with the investigator's medical judgement
14. Patients will be monitored for hypersensitivity from the start of infusion, and at least 1-2 hours after the end of infusion, on each dosing day by vital sign monitoring. If required, ECG may be performed for hypersensitivity monitoring as per local guidelines.
15. Any clinically significant abnormal findings, upon judgement of the investigator, will be reported.

8.2. Informed Consent Form

Refer to separate file.