STUDY PROTOCOL

An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima™ in Patients with Ankylosing Spondylitis

PROTOCOL NUMBER CT-P13 4.4

CONFIDENTIAL

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Protocol Approval

Study Title	An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima™ in Patients with Ankylosing Spondylitis
Protocol Number	CT-P13 4.4
Protocol Version and Date	Protocol Version 2.1 (EU specific) – 01 June 2015

Protocol accepted and approved by:

Clinical Planning Department Leader

[redacted]

CELLTRION, Inc.,
23, Academy-ro, Yeonsu-gu, Incheon,
406-840, Republic of Korea

Signature Date

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 4.4	
Title of Study: An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima™ in Patients with Ankylosing Spondylitis	
Marketing Authorization Holder: Celltrion Healthcare Hungary Kft, 1023 Budapest, Regus Ó buda Gate, Á rpád fejedelem útja 26-28 Hungary	
Study Center(s): Approximately 50 centers in Europe and South Korea	
Length of Study: A 5-year period (2 years initially, followed by an additional 3 years for patients who consent to participate in an extension study)	**Phase of Development:** IV
Objectives: The primary objective of this study is to assess the safety of Remsima™ in ankylosing spondylitis (AS) patients, in comparison with patients receiving other anti-TNF drugs, by evaluation of events of special interest (ESI) for up to 5 years from the first visit of each patient. The secondary objectives of this study are to evaluate efficacy and additional safety of Remsima™ in AS patients, in comparison with patients receiving other TNF blockers. Health-economics 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 AS in comparison with patients receiving other TNF blockers. For the Remsima™ cohort data will be collected for patients who commence treatment with Remsima™ in accordance with the product label at the time of enrolment. Patients who have been treated with Remicade® prior to enrolment, their dosing schedule will be continued appropriately. 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. 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. This observational study allows drug switching between anti-TNF drugs. If switched to Remsima™, data will be collected until the end of study for each patient. If switched to other anti-TNF drugs (infliximab (Remicade®), etanercept, adalimumab and etc.), data will be collected until 1 year from the day of switch or until the end of study for each patient, whichever reaches earlier. For switched patients, their assessment schedule will be re-started from the day of switch. 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: Approximately 1000 male or female patients with confirmed diagnosis of AS (approximately 500 patients treated with Remsima™, 500 patients treated with other anti-TNF drugs). 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 during this study. Dose and treatment schedule are recommended to comply with the approved posology in each regulatory authority or investigator's clinical decision and time intervals between doses are controlled flexibly upon the investigator's clinical decision according to the product label of Remsima™.	
Comparator, Dose and Regimen: The first comparator cohort will be patients recruited with AS who are being treated with other anti-TNFs such as (infliximab (Remicade®), etanercept, adalimumab and etc.). Dose and regimen are recommended to comply with the approved posology in each regulatory authority. The second comparator cohort will be the historical AS cohort of patients who have been exposed to anti-TNF drug (infliximab(Remicade®), etanercept, adalimumab and etc.) from published reports and articles presenting studies conducted with anti-TNF drug (infliximab(Remicade®), etanercept, adalimumab and etc.). The historical AS cohort will be compared with Remsima™ and other TNF blockers cohorts in this study.	
Main selection criteria: Male or female patients with active AS will be considered for enrolment in the	

study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

Inclusion criteria will be applied to all cohorts, if not otherwise specified.

1. Adult patients (aged ≥18 years old).
2. Patients with active AS diagnosed according to the 1984 modified New York classification criteria [van der Linden et al 1984].
3. Patients who meet the following conditions can be enrolled:
   i) The Remsima™ cohort will include all patients who will start Remsima™ at the time of enrolment in accordance to the approved product label
   ii) The other anti-TNF drug cohort will include patients who meet the following conditions at the time of enrolment:
   - Patients who have started to be treated with an established anti –TNF such as Infliximab (Remicade®), Etanercept, Adalimumab and etc. within 6 months
4. 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. For the comparators (other anti-TNF drug), duration for contraceptive use is recommended to comply with the product labels.
5. Patients (or legal guardian, if applicable) have been informed of the full nature and purpose of the study, including possible risks and side effects and provide signed and dated written informed consent for long term follow-up including access to all medical records.

Exclusion criteria:

Exclusion criteria will be applied to all cohorts, if not otherwise specified.

1. Patients with a history of hypersensitivity to murine, chimeric, human, or humanized proteins.
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. Current diagnosis of TB or severe or chronic infections (e.g. sepsis, abscess or opportunistic infections or invasive fungal infections), or a past diagnosis of 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 (defined as a positive interferon-γ release assay [IGRA] with a negative examination of 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 of TB following 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 enrolment or a history of herpes zoster within one month prior to enrolment, 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 and adverse events (AEs) including serious AEs other than those classified as ESI. Safety analysis will also include immunogenicity test (optional), interferon-γ release assay test, pregnancy test, Hepatitis B and C and HIV tests, physical examination, vital sign measurement, chest X-ray, clinical laboratory analyses, hypersensitivity monitoring, concomitant medications (name, dose and duration) and signs and symptoms of TB.

Efficacy Assessments: Efficacy will be assessed by collection of data recorded in the patient medical records as part of routine clinical practice. Data collected will be used for explorative comparison of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Physician and Patient Global Assessment of Disease Status, Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Patient Assessment of Spinal Pain.

Data analysis: *Statistical analysis*: The statistical analysis will be performed using SAS software Version 9.1.3 or later (SAS Institute, Inc, Cary, North Carolina).

Interim analysis and an annual regulatory report will be generated if it is required from a regulatory perspective.

Descriptive analysis will be performed for safety data including drug exposure (e.g. number of patients exposed, number of infusion, duration of exposure and etc.) and data will be presented for Remsima™ cohort, and other anti-TNF drug cohort. Additionally, meta-analysis will be performed with historical data for anti-TNF drug.

The data documented in this study 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.

AEs will be coded using the most recent version of the MedDRA and summarized by the number and percentage of patients reporting an event. The grade, duration, and relationship to treatment of each AE will be recorded. 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.

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, co-morbid condition and prior or concomitant medication 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: 3Q 2014 ・European region: 2Q 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
Final report of study results	・2026

1 Presentation

1.1 Title

An observational, prospective cohort study to evaluate the safety and efficacy of Remsima™ in patients with ankylosing spondylitis (AS)

1.2 Marketing Authorization Holder

Celltrion Healthcare Hungary Kft, 1023 Budapest, Regus Ó buda Gate, Á rpád fejedelem útja 26-28 Hungary

Contact person: [redacted]

1.3 Sponsor

CELLTRION, Inc., 23, Academy-ro, Yeonsu-gu, Incheon, 406-840, Republic of Korea

[redacted]

1.4 Lead Investigator

[redacted]

1.5 Research Centers

This study will be conducted at approximately 50 research centers in European region and South Korea.

1.6 Milestones

Milestones	Planned Date
Start of data collection	・Korea: 3Q 2014 ・European region: 2Q 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
Final report of study results	・2026

2 Background and Justifications

Remsima™ is an IgG1 chimeric human-murine mAb biosimilar to Remicade® (infliximab, Janssen Biologics B.V.) developed by CELLTRION, Inc. Remsima™ is produced in the same type of cell-line and has an identical amino acid sequence to Remicade®.

Remsima™ has been approved by the European Medicines Agency (EMA) and Ministry of Food and Drug Safety (MFDS) in Korea for the treatment of AS, rheumatoid arthritis (RA), psoriatic arthritis, psoriasis, ulcerative colitis and Crohn's disease. The approval of Remsima™ was based on the results of two large, randomized, double-blind, 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 and aimed to compare the pharmacokinetics (PKs), safety and efficacy of Remsima™ to 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, and safety outcomes were also assessed. Additional efficacy endpoints included 20% and 40% improvement response according to Assessment in Ankylosing Spondylitis International Working Group criteria (ASAS20 and ASAS40). [Park *et al*. 2013] The PK profiles of Remsima™ and Remicade® were equivalent in patients with active AS (AUC_{τ}: Remsima™, 32,765.8µgh/mL; Remicade®, 31,359.3µgh/mL; $C_{max,ss}$: Remsima™, 147.0µg/mL; Remicade®, 144.8µg/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 efficacy and safety profile comparable to that of Remicade® up to week 30. [Park *et al*. 2013; Yoo *et al*. 2013]

The PLANETRA study was a phase III study conducted in RA patients with inadequate response to methotrexate (MTX). [Yoo *et al*. 2013] A total of 606 patients (Remsima™ =302; Remicade®=304) took part in the study and 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® (95% Confidence interval: −6%, 10%), demonstrating equivalent efficacy. Comparable PKs and safety profile including immunogenicity were also observed at week 30. [Park *et al*. 2013; 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 both well tolerated with comparable immunogenicity and safety, in patients with AS and RA. The evidence from these two studies was deemed appropriate by the EMA and MFDS in Korea to grant a license for Remsima™ equivalent to the license for Remicade®.

Although randomized controlled trials (RCTs) provide a powerful means of evaluating therapies, they are limited by relatively short study durations and highly selected patient groups that may not represent the wide range of patient characteristics found in a real-world setting. Since the licensing of the first biologic treatment for RA, national rheumatology societies in a number of European countries have established independent registries with the aim of evaluating the long-term safety and real-life effectiveness of these drugs. [Zink *et al*. 2009]. Registry studies involve the monitoring of a larger cohort of patients than would be possible in a RCT and also provide an opportunity to observe patients with a much longer follow-up period. Patient registers recruit unselected patients treated in routine care, overcoming the drawbacks of either spontaneous reporting systems or open label extensions of clinical trials. [Zink *et al*. 2009]. Patient registries are highly valuable for monitoring the long-term efficacy and safety profiles of rheumatology therapies in real-world clinical practice. To date, the European biologicals registers have greatly contributed to our understanding of biologic therapies in rheumatology beyond the patient groups and study durations that are typical of RCTs. [Zink *et al*. 2009]

As well as the demonstration of comparable immunogenicity and safety and equivalent clinical efficacy and PK with Remicade® in patients with AS, there is a need to establish the

safety and efficacy profile of Remsima™ in long-term, real-world clinical practice. This may be effectively accomplished through a registry study.

The proposed study is a prospective registry cohort study to compare safety and efficacy over 5 years (2 years initially, followed by an additional 3 years for patients who consent to participate in an extension study), between patients with AS who are recipients of Remsima™ and patients receiving other TNF blockers.

3 Study Objectives

3.1 Primary Objective

The primary objective of this longitudinal, observational, prospective cohort study is to assess the safety of Remsima™ in AS patients receiving infusions of Remsima™ over a 5-year period (2 years initially, followed by an additional 3 years for patients who consent to participate in an extension study), in comparison with patients receiving other TNF blockers, by evaluation of events of special interest (ESI).

The risk associated with the following endpoints (ESI) will be evaluated:

Identified risks:

- Hepatitis B virus reactivation
- Congestive heart failure
- Opportunistic infections (excluding tuberculosis)
- Serious infections including sepsis (excluding opportunistic infection and tuberculosis)
- Tuberculosis
- Serum sickness (delayed hypersensitivity reactions)
- Haematologic reactions
- Systemic lupus erythematosus/lupus-like syndrome
- Demyelinating disorders
- Lymphoma (not HSTCL)
- Hepatobiliary events
- Hepatisplenic T-cell Lymphoma (HSTCL)
- Serious infusion reaction during a re-induction following disease flare
- Sarcoidosis/sarcoid-like reactions
- Leukaemia

Potential risks:

- Malignancy (excluding lymphoma)
- Skin cancer
- Pregnancy exposure[†]

[†]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 in the statistical analysis plan.

3.2 Secondary Objectives

3.2.1 Secondary safety objective

- Adverse events (AEs) including serious AEs (SAEs), other than those classified as ESI
- TB monitoring
- Interferon-γ release assay (IGRA) test
- Immunogenicity (anti-infliximab antibody, optional)
- Other safety assessments (hypersensitivity monitoring, pregnancy test, Hepatitis B/C, human immunodeficiency virus [HIV] test, physical examination, vital sign, clinical laboratory tests, chest X-ray and concomitant medication)

3.2.2 Secondary efficacy objective

The secondary efficacy objective of this study is to evaluate the efficacy of Remsima™ in AS patients, in comparison with patients receiving other TNF blockers, in relation to the following endpoints (Specific schedule of measurement is provided in section 8. Appendix.):

a. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
b. Bath Ankylosing Spondylitis Functional Index (BASFI)
c. Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Physician and Patient Global Assessment of Disease Status
d. Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Patient Assessment of Spinal Pain

3.2.3 Health-economics objective

Cost-effectiveness will be evaluated in AS patients treated with anti-TNF drug.

- 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 is a longitudinal, observational, prospective cohort study to assess the safety and efficacy of Remsima™ in patients with AS in comparison with patients receiving other TNF blockers. The study will be conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice. Informed consent from all patients and/or legal guardian according to the regulatory and legal requirements will be obtained prior to enrolment. This observational study allows drug switching between anti-TNF drugs. If switched to Remsima™, data will be collected until the end of study for each patient. If switched to other anti-TNF drugs (infliximab (Remicade®), etanercept, adalimumab and etc.), data will be collected until 1 year from the day of switch or until the end of study for each patient, whichever reaches earlier. For switched patients, their assessment schedule will be re-started from the day of switch. 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 enrol the patient in this registry.

The study will be carried out at approximately 50 centers in European region and South Korea with a sample size of approximately 1000 male and female patients with confirmed diagnosis of AS (approximately 500 patients treated with Remsima™ and 500 patients treated with other anti-TNF drugs). Study participants will be followed for a 5-year period (2 years initially, followed by an additional 3 years for patients who consent to participate in an extension study). For patients who have started to be treated with other anti-TNFs within the last 6 months prior to enrolment, medical records will also be collected from the date of first exposure prior to enrolment and the date of first exposure is considered as a baseline. For the historical AS cohort, data will be collected for patients who treated with anti-TNF from published studies conducted with Remicade® or other anti-TNF products. The historical AS cohort will be compared with Remsima™ and other TNF blockers cohorts in this study.

For the Remsima™ cohort, data will be collected for patients who commence treatment with Remsima™ in accordance with the product label at the time of enrolment. Dose and treatment schedule are recommended to comply with the approved posology in each regulatory authority or investigator's clinical decision and the time intervals between doses are controlled flexibly upon the investigator's clinical decision according to the product label of Remsima™. If a patient has been treated with Remicade® prior to enrolment, their dosing schedule will be continued appropriately. For the other anti-TNFs cohort, data will be collected for patients who are receiving treatment with other anti-TNF drug (infliximab(Remicade®), etanercept, adalimumab and etc.) according to the approved dose and regimen of the drug. If a patient has been treated with other anti-TNFs prior to enrolment, their dosing schedule will be continued appropriately.

Patients may be pre-treated with antihistamines, hydrocortisone and/or paracetamol, and infusion rate may be slowed in order to decrease the risk of infusion-related reactions, especially if infusion-related reactions have occurred previously. 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.

4.2 Study Population

The study group will consist of adult patients (≥18 years old) diagnosed with AS to be treated with Remsima™ or other TNF blockers.

4.2.1 Inclusion criteria

Inclusion criteria will be applied to all cohorts, if not otherwise specified.

1. Adult patients (aged ≥18 years old).
2. Patients with active AS diagnosed according to the 1984 modified New York classification criteria [van der Linden et al 1984].
3. Patients who meet the following conditions can be enrolled:

i) The Remsima™ cohort will include all patients who will start Remsima™ at the time of enrolment in accordance to the approved product label

ii) The other anti-TNF drug cohort will include patients who meet the following conditions at the time of enrolment:

- Patients who have started to be treated with an established anti-TNF such as infliximab (Remicade®), etanercept, adalimumab and etc. within 6 months

4. 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. For the comparators (other anti-TNF drug), duration for contraceptive use is recommended to comply with the product labels.
5. Patients (or legal guardian, if applicable) have been informed of the full nature and purpose of the study, including possible risks and side effects, and provide signed and dated written informed consent for long term follow-up including access to all medical records.

4.2.2 Exclusion Criteria

Exclusion criteria will be applied to all cohorts, if not otherwise specified.

1. Patients with a history of hypersensitivity to murine, chimeric, human, or humanized proteins.
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. Current diagnosis of TB or severe or chronic infections (e.g. sepsis, abscess or opportunistic infections or invasive fungal infections), or a past diagnosis of 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 (defined as a positive interferon-γ release assay [IGRA] with a negative examination of 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 of TB following treatment based on local guidelines can be treated before confirming the 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 enrolment or a history of herpes zoster within one month prior to enrolment, may be excluded at the investigator's discretion.

4.3 Patient Withdrawal

Patients will be recruited at participating study centers and allocated to the Remsima™ or other TNF blockers cohorts. Patients may withdraw their consent at any time during the study. 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
- no efficacy from study drug
- withdrawal of consent or refusal to continue treatment or procedures/observations
- development of any malignancy

- any AE that would compromise the safety of the patient if they continue their participation 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. If the patient stopped treatment due to safety reason, it should be recorded in (S)AE page. Study result from the discontinued patient may be reviewed and evaluated by sponsor at the final assessment stage. If a patient in the Remsima™ cohort is discontinued, collection of available safety data should be continued until 6 months from the day of withdrawal and the data will be included in the analyses.

4.4 Sample Size

This study aims to recruit approximately 1,000 male and female patients with confirmed diagnosis of AS (approximately 500 patients treated with Remsima™ and approximately 500 patients treated with other anti-TNFs drugs) from participating test centers. 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. 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. The number of patients is sufficient enough to detect adverse events which occur at 1 % of frequency.

4.5 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 in section 8 Appendix, where available.

4.5.1 Collection of core baseline data

Patients 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
- Date of birth, ethnicity, gender
- Previous drug history of non-biologic DMARDs and biologics, including duration of therapy
- Any significant co-morbidity and medical history
- All current therapy/medications
- Height, weight, blood pressure
- BASDAI
- BASFI
- Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Physician and Patient Global Assessment of Disease Activity
- Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Patient Assessment of Spinal Pain

In addition, personal and medical information will be obtained directly from each patient recruited (e.g. smoking history). Smoking status will also be collected at the EOS visit.

4.5.2 Safety assessments

4.5.2.1 Events of special interest

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

Identified risks:

- Hepatitis B virus reactivation
- Congestive heart failure
- Opportunistic infections (excluding tuberculosis)
- Serious infections including sepsis (excluding opportunistic infection 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)
- Serious infusion reaction during a re-induction following disease flare
- Sarcoidosis/sarcoid-like reactions
- Leukaemia

Potential risks:

- Malignancy (excluding lymphoma)
- Skin cancer
- Pregnancy exposure[†]

[†]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 in the statistical analysis plan.

4.5.2.2 Other adverse events

Assessment of AEs including infections, and serious AEs, other than those classified as ESI will be assessed during the study. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and severity will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 as shown below.

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

4.5.2.2.1 Assessment of causality

The relationship or association of the test article in causing or contributing to the AE will be characterised 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, i.e., 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.

4.5.2.2.2 Reporting of Adverse Events and Pregnancy

All adverse events, including SAE, 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 fax or email to ensure Sponsor or CRO can take necessary actions. In addition, SAE will be reported to Ethics Committee (EC) or Institutional Review Board (IRB) according to the site policy/local regulation. The Sponsor or CRO, within 15 days from the day of being informed of the SAE, must report the occurrence of such event in Remsima™ cohort to regulatory authorities along with the results of actions taken and relevant basic data, through website, phone, fax, mail, or otherwise electronically.

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 an SAE. If a patient is hospitalized solely due to disease progression, the hospitalization does not qualify as a 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.

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 mother and new born baby. Specific guideline and form for reporting will be provided to the study centers.

[Contact Information]
CELLTRION, Inc. Pharmacovigilance Team
Address: 19, Academy-ro 51beon-gil, Yeonsu-gu, Incheon, Korea

4.5.2.3 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) will be performed as per local guidelines and documented. Any clinically significant abnormal findings, upon judgement of the investigator, will be reported.

4.5.2.4 Tuberculosis assessment

At Screening, a current diagnosis of TB or a past diagnosis without sufficient documentation of complete resolution following treatment 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 IGRA 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 can 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.

At scheduled visits during the study, if a patient has a positive result at the initial test or at the repeated test for IGRA and a negative examination of chest x-ray at any other visits, the patient will be treated according to country specific TB prophylaxis and complete the entire course of the prophylaxis.

A chest X-ray (both posterior–anterior and/or lateral views) will be taken at Screening and read by a qualified radiologist or pulmonary physician to specifically look for evidence of active or prior TB. If a chest X-ray taken four weeks prior to Screening is available, the results of this will be recorded in the patient's electronic CRF (eCRF) at Screening. A chest X-ray will also be taken at every year and EOS visit.

IGRA will be performed at Screening, every year and EOS visit to identify positive conversion of previously negative results according to the schedule of events in section 8 Appendix. Additional IGRA will be performed if symptoms raise a suspicion of TB upon judgement of the investigator during study period. 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 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].

4.5.2.5 Immunogenicity testing (optional)

Blood samples for immunogenicity testing (anti-infliximab antibodies) will be collected from patients who will be treated with infliximab (Remsima™ and Remicade®), given patient's written informed consent. Immunogenicity testing will be performed at the central laboratory. To see a detailed test schedule, please refer section 8 Appendix.

4.5.2.6 Clinical laboratory parameters

Blood and urine samples for clinical laboratory assessments can be collected, schedules for each referring a test schedule in section 8 Appendix. The following laboratory analyses can be performed at local laboratory and any clinically significant abnormal findings, upon judgement of the investigator, will be reported:

Clinical Chemistry	Total protein, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, creatine kinase, lactate dehydrogenase, and C-reactive protein (CRP)
Hematology	Red blood cell count, Erythrocyte sedimentation rate (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 and Protein

4.5.2.7 Pregnancy test

Pregnancy tests will be performed in accordance with the investigator's medical judgement. If available, a serum pregnancy test results will be documented at Screening and EOS. All urine pregnancy test results, for women of childbearing potential who have not been surgically sterilized, will be documented during the observation period to confirm the

absence of pregnancy. Tests will be conducted at the local laboratory. To see a test schedule, please refer section 8 Appendix.

4.5.2.8 Physical examination

Investigators will carefully evaluate patients for any indication of infection or infusion-related reaction and pursue further investigation and treatment, according to the investigator's clinical judgement. Any clinically significant abnormal findings and illnesses reported after the start of the study that meets the definition of an AE will be recorded. Physical examination results will be documented at the time points specified in section 8 Appendix, where available.

4.5.2.9 Vital signs and weight

Vital signs (including blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minute rest (sitting). Any clinically significant abnormal findings, upon judgement of the investigator, will be reported. Results will be documented at the time points specified in section 8 Appendix, where available.

4.5.2.10 Hepatitis B and C, and human immunodeficiency virus testing

Hepatitis B and C and HIV tests will be performed referring to a test schedule in section 8 Appendix. At screening, hepatitis B and C and HIV test will be performed at the investigator's discretion based on results of previously performed test or patient's status. Tests will be conducted at the local laboratory.

4.5.2.11 Prior and concomitant medication

Use of all concomitant medications from within six months prior to Screening and during the study will be recorded in the patient's eCRF. Any biologic therapy for treatment of AS will be recorded, regardless of the time when these were administered, including duration of therapy and reason for stopping. Any changes in concomitant medications will also be recorded in the patient's eCRF. 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 the principal investigator to ensure that details regarding the medication are recorded in full in the eCRF.

4.5.3 Efficacy assessments

All efficacy assessments will be performed in accordance with routine clinical practice and results will be collected only from patients who will be treated with infliximab (Remsima™ and Remicade®). Efficacy outcomes will be assessed by collection of available results from patient medical records.

4.5.3.1 BASDAI

Patient disease activity will be assessed using the BASDAI at baseline and every six months thereafter during maintenance therapy (Section 8.3).

4.5.3.2 BASFI

Functional ability will be assessed using the BASFI at baseline and every six months thereafter during maintenance therapy (Section 8.4).

4.5.3.3 Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Physician and Patient global assessment of disease status

Physician and Patient global assessment of disease status will be assessed at baseline and every six months thereafter during maintenance therapy (Section 8.5).

4.5.3.4 Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Patient Assessment of Spinal Pain

Patient assessment of pain is measured will be assessed at baseline and every six months thereafter during maintenance therapy (Section 8.6).

4.5.4 Health-economic data eveluation

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)

4.6 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 either freezing or refrigerating. 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 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.

4.7 Data Collection

The study monitor will check the recording of data during monitoring visits to the site. The investigator will ensure that the data collected are accurate, complete and legible.

All data obtained during the study will be promptly recorded on 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.

4.8 Data Handling

All clinical trial findings and documents will be regarded as confidential. The investigator and members of their research team must not disclose any 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.

4.9 Data Analysis

The statistical analysis will be performed using SAS software Version 9.1.3 or later (SAS Institute, Inc, Cary, North Carolina).

Interim analysis and an annual regulatory report will be generated if it is required from a regulatory perspective.

For analyses, patients who switch to a second biologic (either Remsima™ or Remicade® only) will have their follow-up censored at the time of switching treatments and the data before switching will be analyzed under the prior drug cohort and data after switching will be analyzed under the new drug cohort.

Descriptive analysis will be performed for safety data including drug exposure and data will be presented for Remsima™ cohort, and other anti-TNF drug cohort. Additionally, meta-analysis will be performed with historical data for anti-TNF drug.

The data documented in this study 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.

AEs will be coded using the most recent version of the MedDRA and summarized by the number and percentage of patients reporting an event. The grade, duration, and relationship to treatment of each AE will be recorded. 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.

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, co-morbid condition and prior or concomitant medication 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.

For an assessment out of window, methods of analysis will be provided in the statistical analysis plan.

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.

4.10 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.

4.11 Limitations of the Research Methods

Because subjects are not randomized to treatments, bias in the allocation of treatments to subjects and 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, types of patients participating in the comparison groups (potential for bias), 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 registry 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 (WMA 2013). The clinical trial will also 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, including the IRB/IEC compliance with Good Clinical Practice, will be obtained prior to beginning the study.

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 of approval and/or a when favourable opinion was granted.

The principal investigator or investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The principal investigator or investigator 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 and 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

Prior to enrolment, written informed consent will be obtained from each subject 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.

7 References

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8 Appendices

8.1 Schedule of Events

Assessment \ Visit		Screening (-56D~-D0)	Study Period[1, 2]													End of Study visit[4]
			Baseline (Dose 1, D0)[3]	Every Dose	1 year			2 year		3 year		4 year		5 year		
					3 M	6 M	12 M	18 M	24 M	30 M	36 M	42 M	48 M	54 M	60 M	
Drug Infusion			●	●	●	●	●	●	●	●	●	●	●	●	●	
Informed Consent[5]		●							●							
Demography[6]		●														
Smoking status		●													●	●
Medical History[7]		●														
Prior Medication History		●														
Hepatitis B&C, HIV[8,9]		●														
Inclusion and Exclusion Criteria[11]		●	●													
Safety	Pregnancy Test[10,11]	(●)		(●)	(●)	(●)	(●)	(●)	(●)	(●)	(●)	(●)	(●)	(●)	(●)	(●)
	Physical Examination[11,12]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Vital Sign and Weight[11,12,13]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Clinical Laboratory[11,12,14]	●			●	●	●	●	●	●	●	●	●	●	●	●
	Chest X-ray[11]	●					●		●		●		●		●	●
	Interferon-γ release assay[11,15,16]	●					●		●		●		●		●	●
	TB monitoring[11,12]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Immunogenicity Test[11,15,17]		(●)				(●)		(●)		(●)		(●)		(●)	(●)
	Hypersensitivity monitoring[12,18]		●	●	●	●	●	●	●	●	●	●	●	●	●	●

	Adverse events (ESI)[19]	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
	Concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Efficacy	BASDAI[11]		●			●	●	●	●	●	●	●	●	●	●	●
	BASFI[11]		●			●	●	●	●	●	●	●	●	●	●	●
	Global Assessment Score (VAS or NRS)[11]		●			●	●	●	●	●	●	●	●	●	●	●
	Spinal Pain Score (VAS or NRS)[11]		●			●	●	●	●	●	●	●	●	●	●	●
Health-economics			●	●	●	●	●	●	●	●	●	●	●	●	●	●

eCRF, electronic case report form; HIV, human immunodeficiency virus; M, Month; NRS, Numerical Rating Scale; TB, tuberculosis; VAS, visual analogue scale
Assessment of which names in brackets is subject to the investigator's decision on its test method or schedule. See details aforementioned details in the protocol.

1. For Remsima™ and Remicade® treatments, 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. Administration of other anti-TNFs should follow the drug's own dosing schedule and regimen as approved.
2. Time points will be calculated from the first dose of either Remsima™ or other anti-TNFs. For Assessments at Month 3 and every 6 month and 1 year, a visit window of ± 6 weeks at maximum is recommended. Investigator will choose an assessment time point among visits near Month 3 and every 6 months or 1 year.
3. For all switched patients, their assessment schedule will be re-started from the day of switch. IGRA test will be required for those who switched to Remsima™ with no positive IGRA result in previous testing. If IGRA test is performed within 8 weeks prior to switching, no additional test is required.
4. 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.
5. Patients who have been followed-up for 2 year are asked to sign a new informed consent before being observed in the extension period
6. Demography: date of birth, age, gender, height, weight and race will be collected.
7. Medical records should include whether patients have been BCG-vaccinated or not.
8. At screening, hepatitis B and C and HIV test will be performed at the investigator's discretion based on results of previously performed test or patient's status.
9. Assessment is not required at Screening if a result from within 3 months prior to Screening is available. The results of that assessment should be entered in an eCRF at Screening.
10. Pregnancy Test (local laboratory): using serum or urine chosen by the investigator. A serum pregnancy test will be documented at Screening and EOS, if available. All urine pregnancy test results will be documented on each dosing day.
11. Assessment will be performed prior to dose infusion.
12. Any clinically significant abnormal findings, upon judgement of the investigator, will be reported.
13. Vital signs (including blood pressure, heart and respiratory rates, temperature) and weight will be measured after 5 minutes of rest (sitting).
14. Recommended parameters for clinical laboratory (local laboratory)

Clinical Chemistry	Total protein, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, creatine kinase, lactate dehydrogenase, and C-reactive protein (CRP)

Hematology	Red blood cell count, Erythrocyte sedimentation rate (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 and Protein

15. Test will be performed at the central laboratory (PPD Global Central labs).
16. Additional IGRA will be performed if symptoms raise a suspicion of TB upon judgement of the investigator during study period. 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.
17. Anti-infliximab antibody will be measured in patients who are treated with infliximab (Remsima™ and Remicade®).
18. Patients will be monitored from the start of infusion, and until 1-2 hours after the end of infusion.
19. The risk associated with the following endpoints (events of special interest – ESI) will be evaluated.

8.2 Informed consent form

The ICF will be provided as a separate document

8.3 BASDAI

The BASDAI is one of the measures used to assess the signs and symptoms of AS (pain, spinal stiffness), spinal mobility, and physical function [Sieper et al 2009]. The BASDAI score is generated from a set of 6 questions and calculated using the following formula:

$$\text{BASDAI} = \frac{Q1 + Q2 + Q3 + Q4 + ([Q5 + Q6]/2)}{5}$$

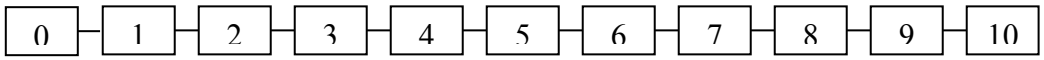
An example of the questionnaire is included in 8.3.1.

8.3.1 BASDAI Questionnaire

Please cross the box which represents your answer, ie, 

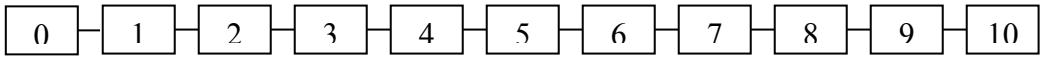
All questions refer to last week.

1. How would you describe the overall level of fatigue/tiredness you have experienced?



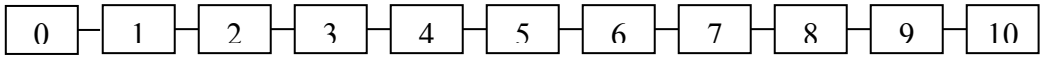
none very severe

2. How would you describe the overall level of AS **neck, back or hip** pain you have had?



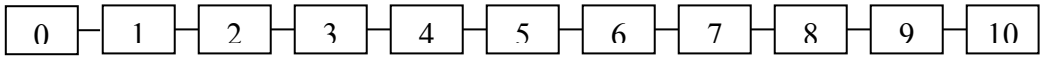
none very severe

3. How would you describe the overall level of pain/swelling in joints **other than** neck, back or hips you have had?



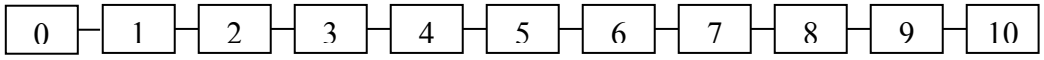
none very severe

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?



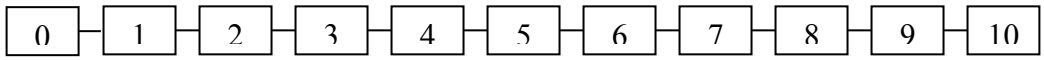
none very severe

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?



none very severe

6. How long does your morning stiffness last from the time you wake up?



0 hour 1 hour 2 or more hours

8.4 BASFI

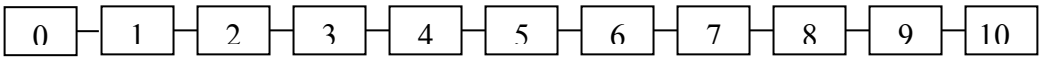
The BASFI is one of the measures used to assess the signs and symptoms of AS (pain, spinal stiffness), spinal mobility, and physical function [Sieper et al 2009]. The BASFI is the mean of scores for the 10 items completed on a numerical rating scale. An example of the 10-item questionnaire is in 8.4.1.

8.4.1 BASFI Questionnaire

Please indicate your level of ability with each of the following activities during the last week, ie, 10

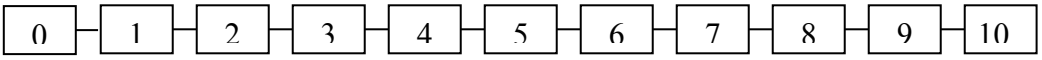
(An aid is a piece of equipment which helps you to perform an action or movement)

1. Putting on your socks or tights without help or aids (eg sock aid).



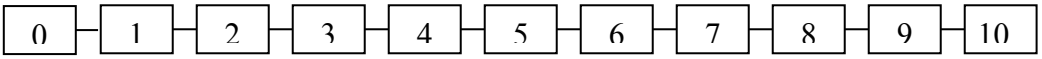
easy impossible

2. Bending forward from the waist to pick up a pen from the floor without an aid.



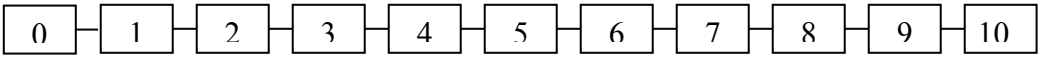
easy impossible

3. Reaching up to a high shelf without help or aids (eg helping hand).



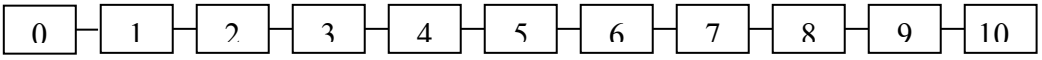
easy impossible

4. Getting up out of an armless dining room chair without using your hands or any other help.



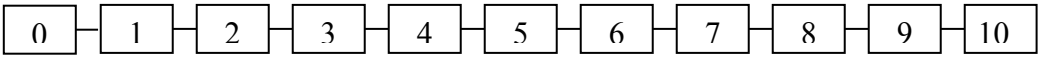
easy impossible

5. Getting up off the floor without help from lying on your back.



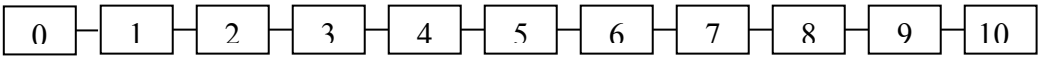
easy impossible

6. Standing unsupported for 10 minutes without discomfort.



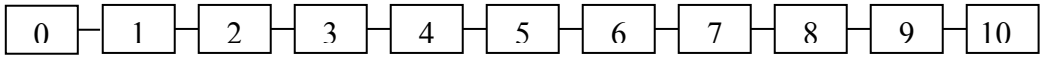
easy impossible

7. Climbing 12-15 steps without using a handrail or walking aid. One foot at each step.



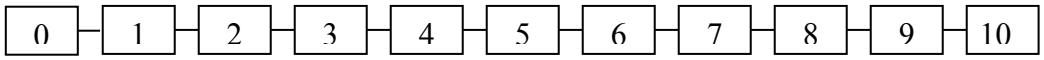
easy impossible

8. Looking over your shoulder without turning your body.



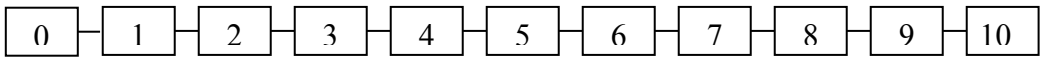
easy impossible

9. Doing physically demanding activities (eg physiotherapy exercises, gardening or sports).



easy impossible

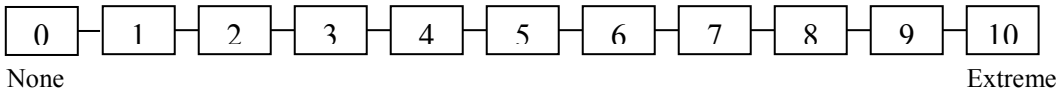
10. Doing a full day's activities, whether it be at home or at work.



easy impossible

8.5 Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Physician and Patient Global Assessment of Disease Status

Patient global assessment of disease status is measured by the patient indicating their current disease status by crossing the box, ie 10 (0 equals no activity and 10 equals extreme activity). The value is recorded in the patient's case report form.



8.6 Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) Patient Assessment of Spinal Pain

Patient assessment of pain is measured by the patient indicating the extent of their pain by crossing the box, ie, 10 (0 equals no pain and 10 equals extreme pain). The value is recorded in the patient's case report form.