STUDY PROTOCOL

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

PROTOCOL NUMBER CT-P13 4.2

CONFIDENTIAL

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Protocol Approval

Study Title	An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima™ in Patients with Rheumatoid Arthritis
Protocol Number	CT-P13 4.2
Protocol Version and Date	Protocol Version 2.1 (EU specific) – 03 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 4.2	
Title of Study: An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima™ in Patients with Rheumatoid Arthritis	
Sponsor: CELLTRION, Inc.	
Marketing Authorization Holder: Celltrion Healthcare Hungary Kft, 1023 Budapest, Regus Ó buda Gate, Á rpád fejedelem útja 26-28 Hungary	
Study Center(s): Approximately 61 centers in South Korea and EU.	
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 long-term safety of Remsima™ in Rheumatoid Arthritis (RA) patients by evaluation of events of special interest (ESI) up to 5 years and to exploratory compare patients receiving Remsima™ with patients receiving non-biologic treatments or other anti-TNF drugs. The secondary objectives of this study are to evaluate efficacy. Further, additional safety of Remsima™ in RA patients, in comparison with patients receiving non-biologic treatments or other anti-TNF drugs. 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 RA in comparison with patients receiving non-biologic treatments or other anti-TNF drugs. 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 (3 mg/kg of Remsima™ by IV infusion at weeks 0, 2, 6 (±3 days) and every 8 weeks (±14 days) thereafter). For patients who have been treated with Remicade® prior to enrolment, their 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. 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: Planned 950 male and female patients with confirmed diagnosis of RA (planned: 450 patients treated with Remsima™, 50 biologic naïve patients [in Korea only] and 450 patients treated with other anti-TNFs drugs); recruitment in selected European countries will continue for 5 years after respective launches. Fifty percent or more of the target number of patients will be enrolled from the EU or relevant European region for Remsima™ and other anti-TNFs drugs.	
Study Drug, Dose and Regimen: Remsima™ (3 mg/kg) will be administered intravenously at weeks 0, 2, 6 (±3 days) and every 8 weeks (±14 days) thereafter and co-administered with methotrexate (MTX) in accordance to the approved posology in the respective country. Dose and treatment schedule are recommended to comply with the approved posology in each regulatory authority or investigator's clinical decision.	
Comparator, Dose and Regimen: The first comparator cohort will be patients who have been treated with non-biologic treatments. Fifty patients will be enrolled for this control group. The second comparator cohort will include RA patients receiving other anti-TNF drug than Remsima™. Patients with RA who have been registered within 6 months of first exposure to an established anti-TNF drug such as infliximab (Remicade®), etanercept, adalimumab and etc. will be recruited to the cohort.	

The third comparator cohort will be historical RA cohort of patients who have been exposed to anti-TNF drug (infliximab, etanercept, adalimumab and etc.) from published reports and articles presenting studies conducted with anti-TNF drug (infliximab (Remicade®), etanercept, adalimumab and etc.).

For the comparators, dose and regimen are recommended to comply with the approved posology in each regulatory authority.

Main Selection Criteria: Patients, with active RA diagnosed according to the revised 1987 ACR or 2010 ACR/EULAR classification criteria, for the Remsima™ and other anti-TNF drug cohort and patients who require treatment with DMARDs and have never been exposed to biologic therapeutics for treatment of RA, for the biologic-naïve cohort will be considered for enrollment 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 RA diagnosed according to the revised 1987 ACR [Arnett et al.1988] or 2010 ACR/EULAR classification criteria [Aletaha et al. 2010].
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 condition at the time of enrolment:
      - Patients who have started to treat with an established anti-TNF such as infliximab (Remicade®), etanercept, adalimumab and etc. within 6 months
   iii) Patients who require treatment with disease-modifying anti-rheumatic drugs (DMARDs), including MTX, and have never been exposed to biologic therapeutics for treatment of RA, may be allocated to the biologic-naïve cohort.
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, 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 tuberculosis (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, 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 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.

Safety Assessment: Safety will be assessed by the 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 ESI. Safety analysis will also include hypersensitivity monitoring, signs and symptoms of TB, interferon-γ release assay test and chest X-ray, immunogenicity test (optional), pregnancy test, Hepatitis B and C and HIV tests, physical examination, vital sign measurement, clinical laboratory analyses, and concomitant medications.

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 evaluation of Disease Activity Score 28 (DAS28) and Health Assessment Questionnaire (HAQ).

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 will be performed after 2 years prior to 3 year- period follow up. 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.

Descriptive analysis will be performed for safety data including drug exposure and data will be presented for Remsima™ cohort, other anti-TNF drug cohort and biologic-naïve 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, standard deviation(SD), minimum, and maximum) for quantitative variables and frequencies and proportions 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 will be specified on Statistical Analysis Plan (SAP). For missing data, appropriate imputation methods will be used, if required.

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

Milestones:

Milestones	Planned Date
Start of data collection	・Korea: December 2013 ・European region: 2Q 2015
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 ・2 years result: 2023
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 rheumatoid arthritis (RA)

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]

[redacted]

1.3 Sponsor

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

[redacted]

1.4 Lead Investigator

[redacted]

[redacted]

1.5 Research Centers

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

1.6 Milestones

Milestones	Planned Date
Start of data collection	・Korea: December 2013 ・European region: 2Q 2015
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 ・2 years result: 2023
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 RA, ankylosing spondylitis, 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]

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. [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 the 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 RA, 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 RA who are recipients of Remsima™ and reference cohorts of other anti-TNF drugs and biologic naïve patients.

3 Study Objectives

3.1 Primary Objective

The primary objective of this study is to assess the long-term safety of Remsima™ in RA patients by evaluation of events of special interest (ESI) up to 5 years and to exploratory compare patients receiving Remsima™ with patients receiving non-biologic treatments or other anti-TNF drugs.

The risk associated with the following endpoints (events of special interest – ESI) will be evaluated:

- Hepatitis B virus reactivation
- Congestive heart failure
- Opportunistic infection (excluding tuberculosis)
- Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
- Tuberculosis (TB)
- 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 reactions during a re-induction regimen following disease flare
- Sarcoidosis/sarcoid-like reactions
- Leukaemia
- Malignancy (excluding lymphoma)
- Skin cancer
- Pregnancy exposure
- Infusion reaction associated with shortened infusion duration

- Others

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

3.2 Secondary Objectives

3.2.1 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 test)
- Other safety assessments (hypersensitivity monitoring, pregnancy test, Hepatitis B/C, human immunodeficiency virus [HIV] test, physical examination, vital sign, laboratory tests, chest X-ray and concomitant medication)

3.2.2 Efficacy objective

The secondary efficacy objective of this study is to evaluate efficacy in patients with RA.

- Disease Activity Score using 28 joint count (DAS28) at every six months during study period
- Health Assessment Questionnaire (HAQ) at every six months during study period

3.2.3 Health-economics objective

Cost-effectiveness will be evaluated in RA 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 Subject Randomization

As this is a longitudinal, observational, prospective cohort study, randomization will not be carried out.

4.2 Study Design

This is a longitudinal, observational, prospective cohort study to assess the safety and efficacy of Remsima™ in patients with RA in comparison with patients receiving non-biologic treatments or other anti-TNF drugs. 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 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 enroll the patient in this registry.

The study will be carried out with a sample size of approximately 950 patients with confirmed diagnosis of RA (planned: 450 patients treated with Remsima™, 450 patients treated with other anti-TNFs within 6 months prior to enrolment and 50 biologic naïve patients). 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 patient who have started to be treated with other anti-TNFs within the last 6 months prior to enrollment, medical records will also be collected from the date of first exposure prior to enrollment, and the date of first exposure is considered as a baseline.

For the historical RA cohort, data will be collected for patients who treated with anti-TNF from published studies conducted with Remicade® or other anti-TNF products.

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 (3 mg/kg intravenously at weeks 0, 2, 6 (±3 days) and every 8 weeks (±14 days) thereafter and co-administered with methotrexate (MTX). Dose and treatment schedule are recommended to comply with the approved posology in each regulatory authority or investigator's clinical decision. 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 Remicade® prior to enrolment, their dosing schedule will be continued appropriately. MTX will be co-administered for the duration of the study, unless it is contraindicated. Patients may be pre-treated with antihistamines, hydrocortisone and/or paracetamol, or 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.

4.3 Study Population

The study group will consist of adult patients (≥18 years old) diagnosed with RA.

4.3.1 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 RA diagnosed according to the revised 1987 ACR [Arnett *et al.*1988] or 2010 ACR/EULAR classification criteria [Aletaha *et al.* 2010].
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 condition at the time of enrolment:

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

iii) Patients who require treatment with disease-modifying anti-rheumatic drugs (DMARDs), including MTX, and have never been exposed to biologic therapeutics for treatment of RA, may be allocated to the biologic-naïve cohort.

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, 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.

4.3.2 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, 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 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.

4.4 Withdrawal of Patients from the Study

Patients will be recruited at participating study centers and allocated to the Remsima™, biologic naïve cohorts , or other anti-TNF drug cohort. 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
- 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.

4.5 Sample Size

This study aims to be planned to recruit 450 patients taking Remsima™ from participating study centers. For comparison, 50 RA patients receiving treatment other than biologics and 450 patients treated with other anti-TNF drugs are planned to recruit. A sample size is determined not on the basis of formal statistical hypotheses but using an exploratory descriptive approach.

The number of patients in the Remsima™ cohort is sufficient enough to detect adverse events which occur at 1 % of frequency and the number of patient in the biologic naïve cohort is to determine 50 patients which is 10% of that of Remsima™ cohort. Biologic naïve cohort will be recruited in Korea only. Fifty percent or more of the target number of patients will be enrolled from the EU or relevant European region for Remsima™ and other anti-TNFs drugs.

4.6 Data Required

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.

4.6.1 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 of rheumatoid arthritis
- Date of birth, 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
- DAS28
- HAQ scores

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

4.6.2 Safety assessments

4.6.2.1 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 infection (excluding tuberculosis)
- Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
- Tuberculosis (TB)
- 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 reactions during a re-induction regimen following disease flare
- Sarcoidosis/sarcoid-like reactions
- Leukaemia
- Malignancy (excluding lymphoma)
- Skin cancer
- Pregnancy exposure[†]
- Infusion reaction associated with shortened infusion duration
- 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.

4.6.2.2 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 AE (minor; no specific medical intervention; asymptomatic laboratory findings only; radiographic findings only; marginal clinical relevance)

Grade 2: Moderate AE (minimal intervention; local intervention; non-invasive intervention [packing, cautery])

Grade 3: Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)

Grade 4: Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life-threatening physiological consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy, or operation)

Grade 5: Death related to AE

4.6.2.3 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.

4.6.2.4 Immunogenicity testing (optional)

Blood samples for immunogenicity testing (anti-infliximab antibodies) will be collected from patients who are treated with infliximab (Remsima™ and Remicade®), given patient's written informed consent at baseline, at 6 months (Week 30), at every year and EOS visit . Test will be performed at central laboratory.

4.6.2.5 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, Protein

4.6.2.6 Pregnancy test

A serum or urine pregnancy test will be conducted at Screening for women of childbearing potential who have not been surgically sterilized, in order to confirm that these patients are not pregnant. Test will be performed at local laboratory.

4.6.2.7 Physical examination

Physical examinations results 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, 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.

4.6.2.8 Vital signs and weight measurement

Vital signs (including blood pressure, heart and respiratory rates, and body temperature) and weight will be measured at every visit when patient is stable (sitting position). 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.

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

4.6.2.10 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 4 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 also will be taken at every year and EOS visit.

IGRA will be performed at Screening, at every year (± 6 weeks) and EOS visit to identify positive conversion of previously negative results. 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 in patients with RA. Assay will be performed at 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].

4.6.2.11 Hepatitis B and C, and human immunodeficiency virus testing

At screening, hepatitis B and C and HIV tests will be performed at the investigator's discretion based on results of previously performed test or patient's status. Test will be performed at local laboratory.

4.6.2.12 Prior and concomitant medication

Use of all concomitant medications from within 6 months prior to Screening and during the study will be recorded in the patient's eCRF. Any biologic therapy for treatment of RA will be recorded, regardless of the time when these were administered, including

duration of therapy and reason for stopping. Any changes in concomitant medications or co-administration drug (MTX) treatment 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 investigator to ensure that details regarding the medication are recorded in full in the eCRF.

4.6.3 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.

4.6.3.1 DAS28

DAS28 will be collected at baseline at every 6 months thereafter (± 6 weeks) and EOS visit and calculated in two ways at the efficacy visits using the following equations:

i)

$$DAS28(ESR) = (0.56 \times \sqrt{TJC28}) + (0.28 \times \sqrt{SJC28}) + (0.70 \times \ln(ESR)) + (0.014 \times GH)$$

ii)

$$DAS28(CRP) = (0.56 \times \sqrt{TJC28}) + (0.28 \times \sqrt{SJC28}) + (0.36 \times \ln(CRP + 1)) + (0.014 \times GH) + 0.96$$

Where:

TJC28 = number of tender joints (0-28)

SJC28 = number of swollen joints (0-28)

ESR = ESR measurement (mm/h)

CRP = CRP measurement (mg/L)

GH = patient's general assessment of disease activity measured on the Visual Analog Scale (VAS) (0-100 mm) (Section 8.3)

4.6.3.2 HAQ

HAQ will be assessed at baseline, at every 6 months thereafter (± 6 weeks) and EOS visit to evaluate treatment effectiveness (Section 8.4).

4.6.4 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)

4.7 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. The samples will be shipped from the study center to the central laboratory (PPD Global Central Labs). Details in storage and shipment will be followed according to the lab manual. Additionally, blood samples for immunogenicity should be retained at the central laboratory 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.

4.8 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.

4.9 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.

4.10 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 will be performed at 2 years prior to 3 years period follow up. 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.

Descriptive analysis will be performed for safety data including drug exposure and data will be presented for Remsima™ cohort, other anti-TNF drug cohort and biologic-naïve 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, standard deviation (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. Adjusted relative risk by relevant risk factors may be adapted if suitable.

For descriptive purpose, incidence rate per 100 patient-years or 10,000 patient-years will be calculated and analysis items will be specified on Statistical Analysis Plan (SAP). For missing data, appropriate imputation methods will be used, it required.

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

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 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.

4.13 Adverse Events and Pregnancy Reporting

4.13.1 Adverse Event

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.

4.13.2 Adverse Drug Reaction

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

4.13.3 Serious Adverse Event

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.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or 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 a SAE but that event should be reported as an AE..

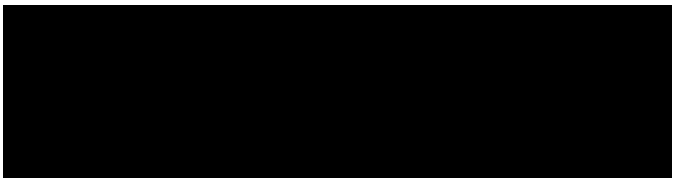
4.13.4 Collection and Reporting of Serious Adverse Events

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 e-mail 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 it is 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.

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.

CELLTRION, Inc. Pharmacovigilance team

Address: 23, Academy-ro, Yeonsu-gu, Incheon, Korea



4.13.5 Pregnancy

All pregnancy cases from female patients and partner of male patient's 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.

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 subinvestigator 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 subinvestigator 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

The Remsima™ cohort/ Other TNFs drug cohort												
Visit / **Assessment**		Screening (-56D~ D0)	Baseline (Dose 1, D0)[2]	Study Period								End of Study visit[5]
				2W	6W[3]	14W[4]	22W[4]	30W[4]	Every 8Weeks[4]	Every 6Months[4]	Every year[4]	
Drug Infusion			●	●	●	●	●	●	●	●	●	
Informed Consent[1]		●										
Demography[6]		●										
Medical History[7]		●										
Smoking status		●										●
Prior Medication History		●										
Hepatitis B&C, HIV[8]		●										
Inclusion and Exclusion Criteria		●	●									
Safety	Pregnancy Test[9]	●										
	Physical Examination[17]	●	●[10]	●[16]	●[16]	●[16]	●[16]	●[16]	●[16]	●[16]	●[16]	●
	Vital Sign and weight[11,17]	●	●[16]	●[16]	●[16]	●[16]	●[16]	●[16]	●[16]	●[16]	●[16]	●
	Clinical Laboratory[12,17]	●	●[10]			●[16]		●[16]		●[16]	●[16]	●
	Chest X-ray	●									●[16]	●
	Interferon-γ release assay (IGRA)[13]	●	●[2]								●[16]	●
	TB symptoms and signs monitoring[17]	●	●	●	●	●	●	●	●	●	●	●
	Immunogenicity Test (Optional)[13, 14]		●[16]					●[16]			●[16]	●
	Hypersensitivity monitoring[17]		●	●	●	●	●	●	●	●	●	
	Adverse events (ESI)[15]	●	●	●	●	●	●	●	●	●	●	●
	Concomitant medication		●	●	●	●	●	●	●	●	●	●
Efficacy	DAS28		●[16]					●[16]		●[16]	●[16]	●
	HAQ		●[16]					●[16]		●[16]	●[16]	●
Health-economics			●	●	●	●	●	●	●	●	●	●

HIV, human immunodeficiency virus; TB, tuberculosis; DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire;

*The schedule is presented with focus on dosing schedule for patients who started with infliximab at the time of enrollment for better understanding. The schedule of events in the other TNFs cohort basically follows that of the Remsima™ cohort. Administration of other TNFs drug should follow the drug's own dosing schedule and regimen.

1. Patients who have been followed-up for 2 years are asked to sign a new informed consent before being observed in the extension period.
2. 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.
3. A visit window of ±3 days is recommended.
4. A visit window of ±14 days is recommended.
5. 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.
6. Demography: date of birth, age, gender, race and height 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. Test will be performed at local laboratory.
9. Pregnancy Test (local laboratory): using serum or urine
10. Test result between the start of screening (-56 days) and prior to 1st dose infusion could be used at the investigator's discretion.
11. Vital signs (including blood pressure, heart and respiratory rates, temperature) and weight will be measured after 5 minutes of rest (sitting).
12. 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, Protein

13. Test will be performed at the central laboratory (PPD Global Central Labs). 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.
14. Anti-infliximab antibody will be measured in patients who are treated with infliximab (Remsima™ and Remicade®).
15. The risk associated with any adverse event (especially events of special interest – ESI) will be evaluated
16. Assessment will be performed prior to dose infusion
17. Any clinically significant abnormal findings, upon judgement of the investigator, will be reported.

8.2 Informed consent form

The ICF will be provided as a separate document

8.3 DAS28 and VAS

DAS28

The DAS28 score uses a calculation that requires the assessment of 28 joints for swelling and tenderness. The 28 joints are: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and the knees.

More information on DAS28 can be found at http: www.das-score.nl

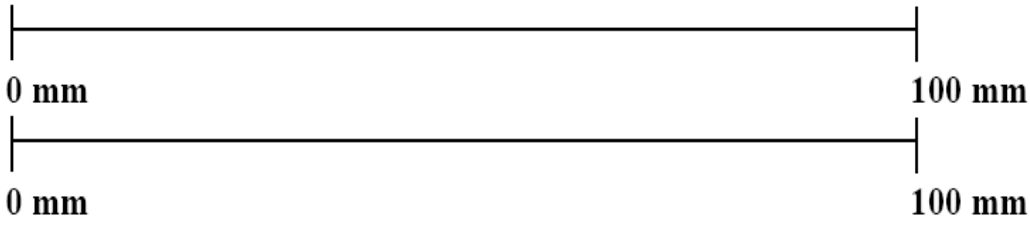
		Left Swollen	tender	Right Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
Total		Swollen		Tender	

MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints

Reference: http://www.reuma-nijmegen.nl/www.das-score.nl/DAS28frm.doc

VAS Patient Global Assessment of Disease Activity

Patient global assessment of disease activity is determined by the patient indicating the patient's current disease status by marking an X through a 100-mm line (0 mm equalling no activity and 100 mm equalling extreme activity). The length of the line is measured from the left (in mm) and the value (in mm) is recorded in the patient's CRF.



None Extreme

8.4 HAQ and Scoring of the HAQ

HEALTH ASSESSMENT QUESTIONNAIRE

Name_____ **Date**_____

PATKEY#_____
QUESTDAT_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE_____

PMSVIS_____

RASTUDY_____

QUESTNUM_____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
- Shampoo your hair?	_____	_____	_____	_____
ARISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
- Cut your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

DRESSNEW_____

RISENEW_____

EATNEW_____

WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane

_____ Walker

_____ Crutches

_____ Wheelchair

_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)

_____ Built up or special utensils

_____ Special or built up chair

_____ Other (Specify:_____)

DRSGASST_____

RISEASST_____

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming

_____ Arising

_____ Eating

_____ Walking

EATASST_____

WALKASST_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	_____	_____	_____	_____	
- Take a tub bath?	_____	_____	_____	_____	
- Get on and off the toilet?	_____	_____	_____	_____	HYGNNEW_____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____	
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____	REACHNEW_____
GRIP					
Are you able to:					
- Open car doors?	_____	_____	_____	_____	
- Open jars which have been previously opened?	_____	_____	_____	_____	
- Turn faucets on and off?	_____	_____	_____	_____	GRIPNEW_____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	_____	_____	_____	_____	
- Get in and out of a car?	_____	_____	_____	_____	
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____	ACTIVNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____Raised toilet seat
_____Bathtub seat
_____Jar opener (for jars previously opened)
_____Bathtub bar
_____Long-handled appliances for reach
_____Long-handled appliances in bathroom
_____ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____Hygiene
_____Reach
_____Gripping and opening things
_____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 ——————————— SEVERE PAIN 100

PAINSCAL_____

The HAQ is composed of 9 items investigating 2 domains.

Domains and Clusters

Domains	Number of Items	Cluster of Items	Item reversion	Direction of Domains
* Disability	8	Dressing (DRESSNEW), Arising (RISENEW), Eating (EATNEW), Walking (WALKNEW), Hygiene (HYGNEW), Reach (REACHNEW), Grip (GRIPNEW), Common activities (ACTIVNEW) & the type of assistance needed for each items (DRSGASST, RISEASST, EATASST, WALKASST, HYGASST, RCHASST, GRIPASST & ACTVASST)	No	Higher scores indicate greater dysfunction
* Discomfort and pain	1	VAS scale (PAINSCAL)	-	Higher score indicate more severe pain

**** The first two domains, which comprise the HAQ Disability Index and Pain Scale, can be used independently***

Scoring of Domains

Item scaling	4-point scale for the disability items: DRESSNEW, RISENEW, EATNEW, WALKNEW, HYGNEW, REACHNEW, GRIPNEW, ACTIVNEW 0= Without any difficulty 1= With some difficulty 2= With much difficulty 3= Unable to do 4-point scale for DRSGASST, RISEASST, EATASST, WALKASST, HYGASST, RCHASST, GRIPASST & ACTVASST: 0= No assistance is needed 1= A special device is used by the patient in his/her usual activities 2= The patient usually needs help from another person 3= The patient usually needs both a special device and help from another person Visual Analogue Scale for PAINSCAL from 0 (no pain) to 100 (Severe pain) **** Although the original scale was a 15-cm VAS scale, the usual length is a 10-cm VAS scale. Of note, depending on the printer used, the length of the VAS scale may vary, but this does not make any difference. Whatever the length, the scale should be divided into 100 equal parts***
Weighting of items	No
Range of scores	For Disability dimension: Range 0-3 The VAS Pain Scale ranges from 0 to 100. But it may be converted to a 0-3 scale
Scoring Procedure	<u>Disability Index:</u> 1. The highest score reported for any component question of the eight categories (DRESSNEW, RISENEW, EATNEW, WALKNEW, HYGNEW, REACHNEW, GRIPNEW, ACTIVNEW) determines the score for that category 2. If either devices and/or help from another person are checked for a category (DRSGASST, RISEASST, EATASST, WALKASST, HYGASST, RCHASST, GRIPASST & ACTVASST), then the score is set to "2" , but if the patient's highest score for that sub-category is a two it remains a two, and if a three, it remains a three. 3. A global score is calculated by summing the scores for each of the categories and dividing by the number of categories answered 4. If there are fewer than 6 categories with responses, an index score cannot be calculated <u>Alternative Disability Index:</u> Summing the scores of the eight categories (DRESSNEW, RISENEW, EATNEW, WALKNEW, HYGNEW, REACHNEW, GRIPNEW & ACTIVNEW) and dividing by the number of categories

<table>
<tr><td></td><td>answered. In that case, the aids and devices are not used

<u>Pain scale:</u>
Measure the distance (D in cm) from the left side of the line to the mark.

<u>For a 15-cm VAS scale:</u>
➢ For a 0-100 scale: Score = (100 * D) / 15
➢ For a 0-3 scale: Score = D * 0.2

<u>For a 10-cm VAS scale</u>:
➢ For a 0-100 scale: Score = (100 * D) / 10
➢ For a 0-3 scale: Score = D * 0.3

<u>For a X-cm VAS scale:</u>
➢ For a 0-100 scale: Score = (100 * D) / X
➢ For a 0-3 scale: Score = D * (3 / X)</td></tr>
<tr><td>Interpretation and Analysis of missing data</td><td><u>Disability Dimension:</u>
• If a component question is left blank or the response is too ambiguous to assign a score, then the score for that category is determined by the remaining completed question(s)
• If all component questions are blank or if more than one answer is given, then follow up with the respondent is required
• If the respondent's mark is between the response columns, then move it to the closest one. If it's directly between the two, move it to the higher one

<u>Pain:</u>
• If the patient writes in a number on the pain scale, or writes a number in addition to making a mark, you need only take the number, converting it to the corresponding score. In this case, do not measure the mark. For example, if the patient writes "50" on the line, this should be coded as 1.5.
• If an individual records a percentage, multiply the percentage by 3. Pain severity coding translations follow below: If a patient puts more than one mark, the midpoint is used

PAIN SEVERITY CODING TRANSLATIONS (0-3 scale)
Applicable only for a 15-cm VAS scale

Measurement (Cm) = Score
0 = 0
0.1 - 0 .7 = 0.1
0.8 - 1.2 = 0.2
1.3 - 1.7 = 0.3
1.8 - 2.2 = 0.4
2.3 - 2.7 = 0.5
2.8 - 3.2 = 0.6
3.3 - 3.7 = 0.7
3.8 - 4.2 = 0 .8
4.3 - 4.7 = 0 .9
4.8 - 5.2 = 1.0
5.3 - 5.7 = 1.1
5.8 - 6.2 = 1.2

Measurement (Cm) = Score
7.8 - 8.2 = 1.6
8.3 - 8.7 = 1.7
8.8 - 9.2 = 1.8
9.3 - 9.7 = 1.9
9.8 - 10.2 = 2.0
10.3 - 10.7 = 2.1
10.8 - 11.2 = 2.2
11.3 - 11.7 = 2.3
11.8 - 12.2 = 2.4
12.3 - 12.7 = 2.5
12.8 - 13.2 = 2.6
13.3 - 13.7 = 2.7
13.8 - 14.2 = 2.8</td></tr>
</table>

	6.3 - 6.7 = 1.3 14.3 - 14.7 = 2.9 6.8 - 7.2 = 1.4 14.8 - 15.0 = 3.0 • If a patient makes a horizontal line below the pain scale, instead of a vertical one, the midpoint of that line is taken. If the line starts at the beginning of the scale, measure to the end of the line not the middle Disability Index: • If an item does not apply to an individual, e.g., they don't shampoo their hair, take tub baths, or reach for a heavy object above their heads, then they should leave the item(s) blank since the purpose is to obtain data about what they can do • If a patient uses adapted or modified aids or devices (e.g., clothing, faucets, cars), then they should answer the questions based on their usual equipment. If they have no difficulty using the adapted equipment, then they would mark the "no difficulty" column. The adapted equipment (aids and devices) will be taken into account in the assistance variables (see below) • If an individual can open their own door but not for others, then they should respond in consideration of their own requirements • Relative to inquiries about distance in responding to the item about walking, patients should be advised to make their own decisions

REFERENCE(S):

Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995-status and review. In: Quality of Life and pharmacoeconomics in clinical trials. Second edition. Edited by B Spilker. Lippincott-Raven Publishers, Philadelphia, 1996