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 Óbuda Gate, Árpád 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.	
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).	
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 will be recruited to the cohort. 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.	
Safety Assessment: Safety will be assessed by the collection of data in the patient medical records as part of routine clinical practice.	

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

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.

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.

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