

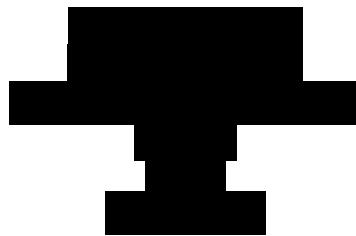
CELLTRION, Inc
CT-P13 4.4

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

13th July 2020

**Statistical Analysis Plan
Final version 2.0**

Prepared by:

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Prepared by: _____ Date: _____

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Approved by: _____ Date: _____

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Upon review of this document, including table and listing shells, the undersigned approves the final statistical analysis plan. The analysis methods and data presentation are acceptable, and the table and listing production can begin.

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List of Abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AS	Ankylosing Spondylitis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BMI	Body Mass Index
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report Form
EOS	End-of-Study
ESI	Events of Special Interest
EU	European Union
HSTCL	Hepatosplenic T-cell lymphoma
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGRA	Interferon-gamma Release Assay
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-inflammatory Drug
PT	Preferred Term
PY	Patient Year
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SD	Standard Deviation
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
VAS	Visual Analogue Scale
WHO	World Health Organization

1 Study Administration Structure

- Study conduct, project manager, data management, clinical monitoring
 - CELLTRION Inc, Incheon, South Korea
 - [REDACTED]
 - [REDACTED]
- Routine blood analysis, urinalysis, urine pregnancy test
 - Local laboratory
- Bioanalytical laboratory (Immunogenicity, IGRA analyses)
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- Preparation of Statistical Analysis Plan (SAP), statistical analysis
 - CELLTRION Inc, Incheon, South Korea
- Medical writing
 - CELLTRION Inc, Incheon, South Korea
 - [REDACTED]

1.1 Data Quality Assurance

CELLTRION will work to ensure that the data collected, analyzed and reported for this study are of the highest quality possible. This will be accomplished in part by having thorough edit checks written, programmed, and updated as needed to guarantee high quality data.

All analyses will be conducted using [REDACTED]

2 Introduction

This Statistical Analysis Plan (SAP) defines the statistical methods and data presentations to be used by the CELLTRION Biostatistics in the analysis and presentation of data for the analyses from CELLTRION study number CT-P13 4.4 entitled An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima™ in Patients with Ankylosing Spondylitis.

This SAP is based on the following documents:

- Final study protocol Version 4.0 (Korea) – 27 May 2015
- Final Protocol Version 2.1 (EU) – 03 June 2015
- CRF Final Version 4.0 (Korea) – 09 July 2015
- MSL Final Version 4.0 (EU) – 27 August 2015

This SAP covers following analyses in aforementioned documents:

- Incidence of Treatment-emergent Adverse Events (TEAEs) in the categories of Event of special interest
- Incidence of Treatment-emergent Serious Adverse Events (TESAEs)
- Incidence of patients discontinuing the study drug due to an TEAE

- Deaths
- Result of interferon-gamma release assay
- Result of chest X-ray
- Result of tuberculosis clinical monitoring
- Pregnancy test
- Immunogenicity testing
- Descriptive statistics of BASDAI scores
- Descriptive statistics of BASFI scores
- Descriptive statistics of Physician and Patient Global Assessment of Disease Status
- Descriptive statistics of Patient Assessment of Spinal Pain
- Health-economics evaluation

3 Objectives

The primary objective of this longitudinal, observational, prospective cohort study is to assess the safety of Remsima™ in Ankylosing Spondylitis (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 secondary objectives of this study are to evaluate additional safety, efficacy and biomarkers of Remsima™ in AS patients, in comparison with patients receiving other TNF blockers. Health-economics parameters will also be assessed.

4 Study Design

4.1 Overall 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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – Good Clinical Practice. Informed consent from all patients and/or legal guardian according to the regulatory and legal requirements will be obtained prior to 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 reaction/hypersensitivity/anaphylactic reaction (IRR), especially if IRRs 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 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.

These 500 patients in Remsima™ cohort are a part of amalgamated registry data of 3100 patients. The sample size of 3100 achieves 80% power with 5% one-sided significance level to detect the difference of incidence rates of tuberculosis (TB) between patients treated with Remsima™ and patients treated with Remicade®, as small as 0.247%. The incidence rate of TB in patients group with Remicade® is estimated as 0.223% from TREAT [Lichtenstein et al, 2012] and BSRBR [Dixon et al, 2010] studies and the power calculation is based on the post-marketing surveillance sample size calculation procedure of [REDACTED].

5 Analysis Periods, Sets and Groups

The patients treated with Inflectra™ or any other brand names of Remsima™ (CT-P13) will be considered as Remsima™.

5.1 Analysis Periods

For some analyses, analysis period will be defined by the number of switching as follows:

- Patient with no switching after enrollment: whole period beginning on the earlier date of screening or first infusion of study drug
- Patient with one switching after enrollment: whole period beginning on the date of first switching
- Patient with more than two switching after enrollment: period between first and second switching

For patients who switched to biologic treatment other than anti-TNF, the period after the switching will be excluded from analysis period. Switching between anti-TNF biologic agents other than RemsimaTM or Remicade[®] will not be considered as switching.

In tables, the analysis period will be considered for safety and efficacy analysis. In listings, the analysis period will not be considered, but instead whole study period will be considered for display.

Baseline will be defined as the last non-missing result on or before first infusion date of analysis period. The baseline will be included in related tables regardless of analysis period.

5.2 Analysis Sets

Two analysis sets and four subsets will be defined: Safety Analysis Set, Efficacy Analysis Set, Safety – ADA Positive Subset, Safety – ADA Negative Subset, Efficacy - ADA Positive Subset and Efficacy - ADA Negative Subset.

5.2.1 Safety Analysis Set

The Safety Analysis Set will consist of all patients who receive at least one dose of either of the study treatments during any dosing period. A patient will be considered to have received study medication if the patient is recorded as having study drug administered on the electronic Case Report Form (eCRF).

5.2.2 Efficacy Analysis Set

The Efficacy Analysis Set will consist of all patients who receive at least one infliximab (RemsimaTM or Remicade[®]) and providing at least one post treatment efficacy result during analysis period. A patient will be considered to have received study medication if the patient is recorded as having study drug administered on the eCRF.

5.2.3 ADA Positive Subset

The Safety – ADA Positive Subset and Efficacy – ADA Positive Subset will consist of all patients who have at least one “Positive” result from immunogenicity tests (Anti-Drug Antibody [ADA]) after first infusion of analysis period in Safety and Efficacy Analysis Set, respectively.

5.2.4 ADA Negative Subset

The Safety – ADA Negative Subset and Efficacy – ADA Negative Subset will consist of all patients who have only “Negative” results from immunogenicity tests (ADA) after first infusion of analysis period in Safety and Efficacy Analysis Set, respectively.

5.3 Analysis Groups

The analysis group will be determined based on treatments that patients have received from before enrollment. Up to one drug switching after enrollment will be considered for determining analysis group. For patients switched after enrollment, their past drug information before enrollment will not be used for determining the analysis group. However, if switching does not occur during study period then their latest treatment before enrollment will be considered. The treatment after 2nd switching will not be used in determination of analysis group. Definition of analysis groups are like below.

- Remsima:
Patients who have received only RemsimaTM will be included in this analysis group.
- Switch to Remsima I:
Patients who switched from Remicade[®] to RemsimaTM will be included in this analysis group.
- Switch to Remsima II:
Patients who switched to RemsimaTM from biologic treatment other than Remicade[®] will be included in this analysis group.
- Remicade:
Patients who have received only Remicade[®] will be included in this analysis group.
- Switch to Remicade I:
Patients who switched from RemsimaTM to Remicade[®] will be included in this analysis group.
- Switch to Remicade II:
Patients who switched to Remicade[®] from biologic treatment other than RemsimaTM will be included in this analysis group.
- Other Anti-TNF:
Following patients will be included in Other Anti-TNF group.
 - Patients who have received only anti-TNF other than RemsimaTM or Remicade[®]
 - Patients who switched from biologic treatment other than anti-TNF before study enrollment to anti-TNF other than RemsimaTM or Remicade[®]
- Switch to Other Anti-TNF:
Patients who switched from RemsimaTM or Remicade[®] to other anti-TNF other than Remicade[®] will be included in this analysis group.

Patient disposition will be summarized by all analysis group. Tables for efficacy analysis and immunogenicity testing will be generated by following 4 analysis groups: Remsima, Switch to Remsima I, Remicade and Switch to Remicade I. The other tables will be generated by following 5 analysis groups: Remsima, Switch to Remsima I, Remicade, Switch to Remicade I and Other Anti-TNF. Additionally, Total Remsima (including Remsima and Switch to Remsima I) and Total Remicade (including Remicade and Switch to Remicade I) groups will be presented in all tables excluding tables for patient disposition and drug exposure.

All listings will be generated by all analysis groups.

6 General Statistical Considerations

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), minimum, median and maximum, unless otherwise indicated. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data, and SD will be presented to two more decimal places than the raw data. In summary tables, all available decimal places will be used although rounded value is listed.

Categorical data will be summarized using counts and percentages. Percentages will be suppressed when the count is zero. The denominator for all percentages will be the number of patients within the analysis group for the analysis set of interest, unless otherwise indicated. Percentages will be presented to one decimal place.

Data will be displayed in all listings sorted by the analysis group and followed by patient number and visit, if applicable. In cases where more ordering is required, other variables will be included in the sorting order as applicable.

7 Patient Disposition

The total number of screened patients will be tabulated. The number and percentages of patients in each analysis sets such as Safety Analysis Set, Safety - ADA Positive Subset, Safety - ADA Negative Subset, Efficacy Analysis Set, Efficacy - ADA Positive Subset and Efficacy – ADA Negative Subset will be tabulated for Safety Analysis Set.

Among the patients in Safety Analysis Set, the number and percentage of patients who completed or discontinued the study will also be displayed along with the primary reason for discontinuation.

The number of patients in Safety Analysis Set will be used as the denominator for percentages and patients will be summarized by analysis group.

The primary reasons for discontinuation will be displayed using the following categories and ordering:

- Patient withdraws consent or refuses to continue treatment or procedures/observation
- Development of signs of disease progression
- Loss of efficacy
- Adverse event
- Protocol violation
- Lost to follow-up
- Death
- Other: study close
- Other: except for study close

“Inclusion/Exclusion criteria not met” in Korea will be collected and considered as Protocol violation.

Time on study drug prior to discontinuation will be calculated as (Date of last visit [For Korea, date of discontinuation] – Date of Visit 1 + 1) and summarized for patients who initiate study treatment and discontinue study treatment prematurely.

It will be listed by patients whether a patient is screening failures, completed the study and included in Safety, Safety – ADA Positive/Negative, Efficacy and Efficacy – ADA Positive/Negative analysis set. The dates of Visit 1, last visit and, if applicable, the reason for discontinuation will also be listed.

8 Demographics and Baseline Characteristics

8.1 Demographics

The following demographic measures will be tabulated by analysis group for the Safety Analysis Set: Age (years); Sex (male, female); Height (cm); Weight (kg); Body Mass Index (BMI) (kg/m²); Race (White, Black, Asian, Other); Region (European, Non-European). Percentages will be calculated using Safety Analysis Set as the denominator.

The BMI will be derived as follows using weight and height at screening:

- BMI: Weight (kg) / [Height (m)]²

A listing of demographics for each patient will also be provided by analysis group for the Safety Analysis Set.

8.2 Smoking Status

At screening and EOS visit, smoking status will be collected. The following measures will be tabulated for Safety Analysis Set by status; smoking status (Never Smoking, Current Smoking, Former Smoking); average cigarettes per day; duration of smoking (years). The duration of smoking will be collected in the eCRF for only Korean patients and this will be derived for European patients as follows:

- Current smoking: (date of collection - date when started smoking+1)/365.25
- Former smoking: (date when stopped smoking - date when started smoking+1)/365.25

If an incomplete smoking start or end date is recorded for European patients, this will be imputed using the latest possible date for calculating duration of smoking (years). For instance, if the day is missing (i.e. XXMAR2017) the date will be the last day of the month (i.e. 31MAR2017). If the day and month are missing (i.e. XXXXX2017) the date will be set to the 31st December (i.e. 31DEC2017). If the imputed date is later than the collection date or date when stopped smoking, this will be imputed using the collection date or date when stopped smoking respectively. If the whole date is missing, the date will not be imputed and duration of smoking will not be calculated.

Percentages will be calculated using the number of patients in the Safety Analysis Set by analysis group.

A listing of smoking status for each patient will also be provided by analysis group for the Safety Analysis Set.

8.3 Ankylosing Spondylitis Surgery

Patients' AS related surgeries during the study will be collected in eCRF only for European patients. All AS related surgeries will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. Surgical details will also be listed by analysis group.

8.4 Ankylosing Spondylitis History

AS history is captured at screening. The descriptive statistics of time since AS diagnosis will be tabulated for the Safety Analysis Set. Time since AS diagnosis will be calculated as [date of screening visit – date of diagnosis + 1]/365.25]. If an incomplete date is recorded for a patient, this will be imputed using the latest possible date. That is, if the day is missing (i.e. XXMAR2017) the date will be the last day of the month (i.e. 31MAR2017). If the day and month are missing (i.e. XXXXX2017) the date will be set to the 31st December (i.e. 31DEC2017). If the imputed date is later than screening date, then it will be imputed using the screening date. If the whole date is missing, the date will not be imputed and time since AS diagnosis will not be calculated.

AS history will also be listed by analysis group for the Safety Analysis Set. Time since AS diagnosis will be presented to two decimal places.

8.5 Medical History

Medical history is captured at screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher. Medical history will be summarized by analysis group, system organ class (SOC) and preferred term (PT) for the Safety Analysis Set. The total number of medical history and the number and percentage of patients with at least one medical history will also be presented in the table by analysis group. Medical history will also be listed by analysis group for the Safety Analysis Set.

8.6 Hepatitis B and C, and Human Immunodeficiency Virus Testing

At screening, viral serology test will be performed at the investigator's discretion based on results of previously performed test or patient's status.

Viral serology test results will be listed by analysis group for the Safety Analysis Set.

9 Treatments and Medications

9.1 Prior Biologics for Ankylosing Spondylitis

Biologic therapy details will be coded using World Health Organization (WHO) Drug Global B3 Version September 1, 2019 or later. Biologic therapy will be tabulated by drug class, Preferred Term (PT) and also be listed by analysis group for the Safety Analysis Set.

9.2 Prior and Concomitant Medication

Prior and concomitant medications will be coded using WHODrug Global B3 Version September 1, 2019 or later. Medications will be classed as either prior or concomitant. For the purpose of inclusion in prior or concomitant medication listings, incomplete medication start and stop dates will be imputed as follows:

If the stop date is incomplete the following rules will be applied:

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as missing.

In the case of the death of a patient, and the imputed end date is after the date of death, the end date will be imputed as the date of death.

If the start date is incomplete the following rules will be applied. If the stop date is incomplete, imputed end date will be used instead of reported end date:

- Missing day: Assume the first day of the month.
However, if the partial date and the date of first administration (defined as the earliest date recorded on the study drug administration page of eCRF) lie within the same month and year and the date of first administration is not after the stop date of the medication, set to the date of first administration. Otherwise, set to stop date of the medication.
- Missing day and month: Assume January 1st.
However, if the partial date and the date of first administration lie within the same year and the date of first administration is not after the stop date of the medication, set to the date of first administration. Otherwise, set to stop date of the medication.
- Missing day, month and year: Assume date of first administration, if not after the stop date for the medication. Otherwise, set to stop date for the medication.

For the missing day imputation, the following examples should be used for reference:

- Example 1:
Medication start: UNJUN2017
Medication end: 20OCT2017
Date of first administration: 16OCT2017
Medication start imputed: 01JUN2017
- Example 2:
Medication start: UNOCT2017
Medication end: 20OCT2017
Date of first administration: 16OCT2017
Medication start imputed: 16OCT2017
- Example 3:
Medication start: UNOCT2017
Medication end: 20OCT2017
Date of first administration: 24OCT2017
Medication start imputed: 20OCT2017

A prior medication is defined as any medication where the start and stop dates or imputed start and stop dates are before the date of first administration. A concomitant medication is defined as any medication that has an actual or imputed stop date on or after the date of first administration, marked as ongoing or missing. The actual or imputed start date of a concomitant medication can be before or after the date of first administration.

The Non-steroidal anti-inflammatory drug (NSAID) is collected separately in the NSAID page of eCRF for Korean patients. These medications will also be considered as prior or concomitant medication in the same manner.

Prior and concomitant medications will be listed by analysis group for the Safety Analysis Set.

9.3 Drug Exposure

A summary table for the duration of drug exposure and the maximum dose of infliximab (mg/kg) during analysis period will be presented for the Safety Analysis Set. For the summary of duration of drug exposure, frequency table for the categorized dose duration will be

displayed along with mean duration of drug exposure. For the summary of maximum dose of infliximab, administered dose will be divided by weight at the same visit. If the weight is missing, the last available weight will be used.

The drug exposure for each patient will be listed by analysis group for the Safety Analysis Set.

10 Safety Analysis

All analysis of safety will be conducted using the Safety Analysis Set.

10.1 Adverse Events and Treatment-emergent Adverse Events

An Adverse Event (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 Adverse Event (TEAE) is defined as any event not present before first exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher will be used to code all AEs. AEs will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) V4.0.

Listings for AEs will include the following information from the eCRF: System Organ Class (SOC), PT and reported term; start and stop date; whether the event is a TEAE throughout study and during analysis period; frequency (intermittent, continuous); outcome (recovered, recovering, not recovered, recovered with sequelae, fatal, unknown); any treatment required (no, yes with specified treatment); intensity (CTCAE Grade 1: Mild, Grade 2: Moderate, Grade 3: Severe, Grade 4: Life-threatening and Grade 5: Death); action taken by investigator (unknown, dose increased, dose decreased, dose not changed, permanently discontinued, stopped temporarily, dose interruption (or dose prolonged)); relationship to study drug (unrelated, possible, probable, definite); whether the event was serious (no, yes); ESI to which the AE corresponds; and batch number for RemsimaTM treated patients after enrollment. Listings will be generated by analysis group for the Safety Analysis Set. Patients in the Safety – ADA Positive Subset and Safety – ADA Negative Subset will be flagged in the listing.

AEs will be considered to be related if relationship is possible, probable or definite. TEAEs with no relationship recorded will be summarized separately under a missing category.

If the end date of an AE is partial or missing the following rules will be applied.

- Missing day (e.g. XXFEB2017): Assume the last day of the month. (e.g. 28FEB2017)
- Missing day and month (e.g. XXXXX2017): Assume December 31st. (e.g. 31DEC2017)
- Missing day, month and year (e.g. XXXXXXXXX): Leave it as missing.

If the start date of an AE is partial or missing the following rules will be applied. If the end date of the AE is partial, imputed end date will be used instead of reported end date.

If the day of an AE is missing (e.g. XXFEB2017), the month and year of the partial date will be compared to the Visit 1 date of this study.

- If month and year are equal for both dates,
 - If whole AE end date is missing, the AE start date will be imputed as the Visit 1 date of this study.

- If whole AE end date is not missing, the AE start date will be imputed as the earlier date of: (i) the Visit 1 date of this study, or (ii) the recorded end date of the AE.
- If the month or year is not equal, the AE start date will be imputed as the first day of the month (e.g. 01FEB2017).

If the day and month are missing (e.g. XXXXX2017), the year of the partial date will be compared to the Visit 1 date of this study.

- If the year of both dates is equal,
 - If whole AE end date is missing, the AE start date will be imputed as the Visit 1 date of this study.
 - If whole AE end date is not missing, the AE start date will be imputed as the earlier date of: (i) the Visit 1 date of this study, or (ii) the recorded end date of the AE.
- If the year is not equal, start date will be imputed as the 1st of January the partial date year (e.g. 01JAN2017).

If the AE start date is missing (e.g. XXXXXXXXX), start date will be imputed as the earlier date of: (i) the Visit 1 date of this study and (ii) the recorded end date of the AE.

In summary tables, only TEAEs during analysis period ([Section 5.1](#)) will be included.

10.1.1 Incidence of Treatment-emergent Adverse Events

TEAEs will be summarized by SOC, PT, relationship and severity displaying the number and percentage of patients with at least one TEAE using only the worst severity recorded at each level of summarization. The total number of events and number of patients with at least one TEAE will also be displayed. The summarization of TEAEs for the patients in Safety – ADA Positive/Negative Subset will be provided additionally.

All AEs will be listed including the variables detailed in [Section 10.1](#).

10.1.2 Deaths

A listing will be provided showing any deaths during the course of the trial in the Safety Analysis Set including the variables detailed in [Section 10.1](#).

10.1.3 Serious Adverse Events

A Serious Adverse Event (SAE) is defined using the following serious criteria:

- Death
- 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)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Important medical event based on appropriate medical judgment

Treatment-Emergent Serious Adverse Events (TESAEs) will be summarized by SOC, PT, relationship and severity displaying the number and percentage of patients with at least one TESAE using only the worst severity recorded at each level of summarization. The total number of events and number of patients with at least one TESAE will also be displayed.

All serious AEs will be listed including the variables detailed in [Section 10.1](#).

10.1.4 Treatment-emergent Adverse Events leading to Permanent Study Drug Discontinuation

TEAEs which lead to permanent discontinuation of the study drug will be summarized by SOC, PT, relationship and severity displaying the number and percentage of patients with at least one TEAE which led to permanent discontinuation of the study drug using only the worst severity recorded at each level of summarization. The total number of events and number of patients with at least one TEAE which led to permanent discontinuation of the study drug will also be displayed.

All AEs leading to permanent discontinuation of study drug will be listed including the variables detailed in [Section 10.1](#).

10.1.5 Incidence of Events of Special Interest

In order to assess the safety of RemsimaTM, the following ESI will be evaluated:

- Hepatitis B virus reactivation
- Congestive heart failure
- Opportunistic infections (excluding tuberculosis)
- Serious infections including sepsis (excluding opportunistic infections and tuberculosis)
- Tuberculosis
- Serum sickness (delayed hypersensitivity reactions)
- Haematological reactions
- Systemic lupus erythematosus/lupus-like syndrome
- Demyelinating disorders
- Lymphoma (excluding 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-related reaction/hypersensitivity/anaphylactic reaction(IRR)

AEs will be determined as ESI using the detailed algorithm in [Appendix 2](#) and [Appendix 3](#). TEAEs of special interest will be summarized by SOC, PT, relationship and severity displaying the number and percentage of patients with at least one TEAE of special interest using only the worst severity recorded at each level of summarization. The summary table will include the total number of events, the number and percentage of patients with at least one TEAE of special interest, and the number of patients per 100 patient-years (PY). The number of patients with TEAE of special interest per 100PY is calculated as 100 X (the number of patients with TEAE of special interest) / (the sum of treatment duration [years] for each patients). Treatment

duration (years) are calculated as [Date of last visit (For Korea, date of discontinuation) – Date of first infusion during analysis period + 1]/365.25. In case patients are switched to biologic treatment other than anti-TNF, switching date will be used for calculation of treatment duration instead of date of last visit (for Korea, date of discontinuation).

Signs and symptoms of IRR will be presented in separate listings including categories of sign and symptoms, intensity and blood pressure (systolic blood pressure, diastolic blood pressure).

10.2 Tuberculosis Assessment

Tuberculosis (TB) will be assessed using IGRA, Chest X-ray and clinically monitored throughout the study.

- Interferon-gamma Release Assay (IGRA): Results will be classified as “Positive”, “Indeterminate” or “Negative”.
- Chest X-ray: Results will be classified as either “Normal”, “Abnormal, Not Clinically Significant” or “Abnormal, Clinically Significant”.

The number and percentage of patients who have missing baseline IGRA ([Section 5.1](#)) will be displayed. IGRA conversion occurs when positive result of central IGRA follows baseline IGRA of negative. However, IGRA conversion will not be considered for patients who have at least one positive result on or before baseline. Number and percentage of patients with IGRA conversion will be displayed. TEAEs for patients with IGRA conversion will be summarized in a manner similar to that described in [Section 10.1.1](#).

Separate listings for central IGRA, chest X-ray assessments and TB clinical monitoring results will be provided by analysis group. In addition, flags for whether IGRA results were converted or not for each visit will be presented in the listing for IGRA assessments.

10.3 Pregnancy Test

A serum or urine pregnancy test will be conducted for female patients of childbearing potential who have not been surgically sterilized. Tests will be performed by a local laboratory. All pregnancy test results will be listed by analysis group.

10.4 Immunogenicity Testing

Blood samples for immunogenicity assessments (anti-infliximab antibodies) will be obtained at Baseline, at every 12 months (or 6 months for Korea) and EOS visit. Assessments (anti-infliximab antibodies) will be performed prior to dose infusion for patients who are treated with infliximab (RemsimaTM and Remicade[®]). Anti-infliximab antibodies will be assessed in an ADA assay. The assay will involve both screening and specificity/confirmatory assay to confirm positive results. The test outcome for the screening assay will be: {‘Potential Positive’ or ‘Negative’ or NRR: No Result Reported}. Samples that are ‘Potential Positive’ in the screening assay will be spiked with excess RemsimaTM/ Remicade[®] to determine if patients are a true positive. The test outcome for the specificity/confirmatory assay will be: {‘Positive’, ‘Negative’, ‘N/A’ and ‘NRR’}. ‘Positive’ indicates a true positive test outcome and will be labelled as ‘Positive’ in outputs, ‘Negative’ is considered negative, and ‘N/A’ means the result of screening phase was either ‘Negative’ or ‘NRR’. If screening result is ‘Potential positive’ and confirmation result is ‘NRR’ then final result is considered as ‘NRR’. Patients with a ‘Negative’ test outcome for either the screening or specificity/confirmatory assay will be considered negative for the overall ADA assessment.

The number and percentage of patients for the overall ADA assessment will be displayed by analysis group and every six months during analysis period. Time point will be assigned to 'Month XX' by every six months when the date of sample is in every six months visit window (± 6 weeks) from the first infusion date of analysis period (Day 0). Additionally, the number and percentage of patients who achieved at least one positive ADA result, and all negative results respectively after the first infusion of analysis period will be displayed by analysis group. In summary of patients who achieved at least one positive ADA result after first infusion of analysis period, results on subcategory for "Baseline Positive" and "Newly Positive" will be presented together. "Baseline Positive" is defined as patients who have ADA Positive result at Baseline and "Newly Positive" is defined as patients who have ADA Negative or NRR or missing result at Baseline.

Listing for ADA assessments will be provided by analysis group.

11 Efficacy Analysis

Efficacy will be assessed by the evaluation of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Global Assessment Score and Spinal Pain Score.

All efficacy tables will be summarized by analysis group and every six months during analysis period for the Efficacy Analysis Set, Efficacy – ADA Positive Subset and Efficacy – ADA Negative Subset. For summary, time point will be assigned to 'Month XX' by every six months when the date of visit is in every six months visit window (± 6 weeks) from the first infusion date of analysis period (Day 0). All efficacy listings will be generated by analysis group for the Efficacy Analysis Set including flags for patients in Efficacy – ADA Positive Subset and Efficacy – ADA Negative Subset.

11.1 BASDAI

The BASDAI questionnaire consists of the following 6 components about the disease activity.

1. How would you describe the overall level of fatigue/tiredness you have experienced?
2. How would you describe the overall level of AS neck, back, or hip pain you have had?
3. How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of morning stiffness you have had from the time you wake up?
6. How long does your morning stiffness last from the time you wake up?

For each question the possible answer from the patient is a whole number from 0 to 10 inclusive where 0 = None and 10 = Very severe. The BASDAI score is generated from the set of 6 questions and calculated using the following formula:

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

Descriptive statistics for actual value of BASDAI score will be summarized by analysis group and every six months including Day 0. In a separate table, the number and percentage of patients achieving BASDAI 50 will be displayed. BASDAI 50 is defined as a 50% decrease of

the baseline BASDAI score. Percentages will be calculated using the number of patients who perform the assessment at each time point.

A listing of BASDAI will be generated by analysis group.

11.2 BASFI

The BASFI questionnaire consists of the following 10 components measuring functionality:

1. Putting on your socks or tights without help or aids (e.g. sock aid).
2. Bending forward from the waist to pick up a pen from the floor without an aid.
3. Reaching up to high shelf without help or aids (e.g. helping hand).
4. Getting up out of an armless dining room chair without using your hands or any other help.
5. Getting up off the floor without help from lying on your back.
6. Standing unsupported for 10 minutes without discomfort.
7. Climbing 12-15 steps without using a handrail or walking aid, with one foot at each step.
8. Looking over your shoulder without turning your body.
9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).
10. Doing a full day's activities, whether it be at home or at work.

Each item is given a rating by the patient which is a whole number from 0 to 10 inclusive where 0 = Easy and 10 = Impossible. The BASFI score is generated from the mean of the scores for the 10 items.

Descriptive statistics for actual value of BASFI score will be summarized by analysis group and every six months including Day 0.

A listing of BASFI will be generated by analysis group.

11.3 Global Assessment Score

Physician and Patient Global Assessment of disease status will be measured by Visual Analogue Scale (VAS) (0-100 mm) for EU patients and Numerical Rating Scale (NRS) (0-10) for Korea patients where higher scores indicates poorer status.

Descriptive statistics for actual value of Global Assessment Score will be summarized by analysis group and every six months including Day 0. For the summary table, each score of Korea patients in NRS will be transformed by multiplying 10.

A listing of Global Assessment Score will be generated by analysis group.

11.4 Spinal Pain Score

Patient Assessment of Spinal Pain will be measured by VAS (0-100 mm) for EU patients and NRS (0-10) for Korea patients where higher scores indicates more severe pain.

Descriptive statistics for actual value of Spinal Pain Score will be summarized by analysis group and every six months including Day 0. For the summary table, each score of Korea patients in NRS will be transformed by multiplying 10.

A listing of Spinal Pain Score will be generated by analysis group.

12 Health-economics Analysis

For cost-effectiveness, the following information will be collected throughout the study in eCRF only for European patients.

- Days of Hospitalizations Related to Disease
- Medication and Surgery Interventions Related to Disease
- Days off Work in Employed Patients
- Retirement and Return to Work (Working Days Gained)

The number and percentage of patients with above information at each category will be summarized by analysis group at each visit during analysis period. The percentage will be calculated using the number of patients who performed assessment at each visit as denominator. For patients who have duration information, a separate table will be provided displaying descriptive statistics (of number of hospitalization days, number of days off and number of working days gained) by analysis group. Listing for health-economics evaluation will be provided by analysis group and visit for the Safety Analysis Set.

13 References

- [1] Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol.* 2012;107(9):1409–1422. doi:10.1038/ajg.2012.218
- [2] W G Dixon, Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR), *Ann Rheum Dis* 2010;69:522-528. 2010.

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APPENDIX 2: Infusion-related Reaction/ hypersensitivity/anaphylactic reaction AEs

ESI related to infusion-related reaction/hypersensitivity/anaphylactic reaction will be identified using the following three algorithms. An AE can be identified as being ESI related to infusion-related reaction/hypersensitivity/anaphylactic reaction only if it satisfies any of the three algorithms, and classed as 'possible', 'probable' or 'definite' for relationship to study drug.

1. Preferred Term (PT) Selection: Hypersensitivity, Drug hypersensitivity, Anaphylactic shock, Anaphylactic reaction, or Infusion related reaction
2. AE Term selection: The event should be defined by any word in Term 1, as well as one word in the Term 2 - 8 groups.

AE Term 1 (Reported term, Mandatory)	Infusion, study drug, drug reaction, hypersensitivity, hipersenstivity, hypersensitiviti, postinfusion
PT Term 2	Pyrexia, body temperature increased, chills
PT Term 3	Pruritus, pruritus allergic, rash pruritic, rash, rash macular, rash maculo-papular, urticaria, eye irritation, burning sensation, erythema, dermatitis allergic, angioedema, lip oedema
PT Term 4	Dyspnoea, non-cardiac chest pain, chest pain, chest discomfort, upper respiratory tract congestion, bronchospasm
PT Term 5	Hypotension, procedural hypotension, hypertension, procedural hypertension, blood pressure increased, supraventricular extrasystoles
PT Term 6	Bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, palpitations, atrial fibrillation
PT Term 7	Vomiting, nausea, oropharyngeal pain, abdominal pain upper, abdominal pain
PT Term 8	Back pain, myalgia, arthralgia, headache, migraine

3. The event should be defined by any PT term listed below for which the AE start date matches an Infliximab infusion date.
 - Pyrexia, body temperature increased, chills, pruritus, pruritus allergic, rash pruritic, rash, rash macular, rash maculo-papular, urticaria, injection site urticaria, eye irritation, burning sensation, erythema, dermatitis allergic, angioedema, lip oedema, dyspnoea, non-cardiac chest pain, chest pain, chest discomfort, upper respiratory tract congestion, bronchospasm, hypotension, procedural hypotension, hypertension, procedural hypertension, blood pressure increased, supraventricular extrasystoles, bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, palpitations, atrial fibrillation, vomiting, nausea, oropharyngeal pain, abdominal pain upper, abdominal pain, myalgia, arthralgia, headache, migraine, dizziness, wheezing, stridor, hypoxia, throat irritation, hypotonia, syncope, incontinence, flushing, lip swelling, swollen tongue, enlarged uvula.

APPENDIX 3: Capture rule of Event of Special Interest

Hepatitis B virus reactivation	<ol style="list-style-type: none"> 1. Hepatitis B virus infection in medical history (PT term): <ul style="list-style-type: none"> • Hepatitis B, Hepatitis viral, Hepatitis acute, Hepatitis toxic 2. Diagnosis possibly related to HBV reactivation (PT term): <ul style="list-style-type: none"> • Hepatitis B, hepatitis, hepatitis toxic, hepatitis acute, hepatotoxicity, hepatomegaly, hepatic steatosis, liver disorder 3. Possible relevant abnormal lab results (PT term): <ul style="list-style-type: none"> • Alanine aminotransferase increased • Aspartate aminotransferase increased • Gamma-glutamyltransferase increased • Blood alkaline phosphatase increased • Hypertransaminasaemia • Transaminases increased • Hyperbilirubinaemia • Hepatic enzyme increased • Liver function test abnormal • Liver function test increased • Blood bilirubin increased <p>In case of satisfying the 1. Hepatitis B virus infection in medical history and one of 2. Diagnosis possibly related to HBV reactivation (PT term) simultaneously, and also in case when there are at least three elevations among 3 Possible relevant abnormal lab results.</p>
Congestive heart failure	PT: Cardiac failure congestive
Opportunistic infections (excluding TB)	<ol style="list-style-type: none"> 1. SOC: Infections and infestations, and 2. Reported SAE, and 3. Exclude Tuberculosis, and 4. Systemic and invasive fungal infections (PTs: blastomycosis, Pneumocystis jirovecii pneumonia, mucocutaneous candidiasis, aspergillus infection, histoplasmosis, coccidioidomycosis, cryptococcosis, herpes simplex, oral herpes, vulvovaginal candidiasis, Herpes zoster, Ophthalmic herpes zoster, Herpes zoster oticus and etc.) 5. It would be also determined by medical review, separately.
Serious infections including sepsis (excluding opportunistic infections and TB)	<ol style="list-style-type: none"> 1. SOC: Infections and infestations, and 2. Reported SAE, and 3. Exclude opportunistic infections and tuberculosis
Tuberculosis	Any PTs with tuberculosis
Serum sickness (delayed hypersensitivity reactions)	<ol style="list-style-type: none"> 1. IRRs captured by capture rule in Appendix 2, and, 2. IRR case which occurs 5 to 14 days after the latest Infliximab infusion. 3. It would be also determined by medical review, separately.

Haematological reactions	PTs: Anaemia, Anaemia megaloblastic, Eosinophilia, Granulocytopenia, Hypochromic anaemia, Iron deficiency anaemia, Leukocytosis, Leukopenia, Lymphocytosis, Macrocytosis, Microcytic anaemia, Monocytosis, Neutropenia, Neutrophilia, Polycythaemia, Thrombocytopenia, Thrombocytosis, Haemoglobin decreased, Lymphocyte count increased, Lymphopenia, Mean cell volume increased, Neutrophil count decreased, Platelet count decreased, Platelet count increased, White blood cell count increased, White blood cell count decreased, Pancytopenia, Red blood cell count decreased
Systemic lupus erythematosus/lupus-like syndrome	PTs: Acute cutaneous lupus erythematosus, Chronic cutaneous lupus erythematosus, Cutaneous lupus erythematosus, Systemic lupus erythematosus, Lupus-like syndrome, Subacute cutaneous lupus erythematosus, Systemic lupus erythematosus disease activity index abnormal, Systemic lupus erythematosus disease activity index decreased, Systemic lupus erythematosus disease activity index increased, Systemic lupus erythematosus rash, Antinuclear antibody increased, Antinuclear antibody positive, Central nervous system lupus, Neuropsychiatric lupus, Pericarditis lupus, Peritonitis lupus, SLE arthritis
Demyelinating disorders	PTs (under SMQ “Demyelination”): Demyelination, Acute disseminated encephalomyelitis, Acute haemorrhagic leukoencephalitis, Chronic inflammatory demyelinating polyradiculoneuropathy, Clinically isolated syndrome, Concentric sclerosis, Demyelinating polyneuropathy, Encephalitis periaxialis diffusa, Encephalomyelitis, Expanded disability status scale score decreased, Expanded disability status scale score increased, Guillain-Barre syndrome, Hypergammaglobulinaemia benign monoclonal, Leukoencephalomyelitis, Leukoencephalopathy, Lewis-Sumner syndrome, MELAS syndrome, Marburg's variant multiple sclerosis, Marchiafava-Bignami disease, Multiple sclerosis, Multiple sclerosis relapse, Multiple sclerosis relapse prophylaxis, Myelitis transverse, Myoclonic epilepsy and ragged-red fibres, Neuromyelitis optica spectrum disorder, “Neuropathy, ataxia, retinitis pigmentosa syndrome”, Noninfectious myelitis, Noninfective encephalomyelitis, Optic neuritis, Osmotic demyelination syndrome, Primary progressive multiple sclerosis, Progressive multifocal leukoencephalopathy, Progressive multiple sclerosis, Progressive relapsing multiple sclerosis, Relapsing-remitting multiple sclerosis, Secondary progressive multiple sclerosis, Anti-interferon antibody negative, Anti-interferon antibody positive, Band sensation, Lhermitte's sign, Myokymia, Saccadic eye movement, Trigeminal neuralgia, Uhthoff's phenomenon, Anti-myelin-associated glycoprotein associated polyneuropathy, Anti-myelin-associated glycoprotein antibodies positive, Autoimmune demyelinating disease, Toxic leukoencephalopathy, Tumefactive multiple sclerosis
Lymphoma (excluding HSTCL)	Any PTs with Lymphoma except Hepatosplenic T-cell lymphoma
Hepatobiliary events	PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Cholecystitis acute, Cholecystitis chronic, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Hepatic steatosis, Hepatitis, Hepatitis acute, Hepatitis toxic, Hepatomegaly, Hepatotoxicity, Hyperbilirubinaemia, Hypertransaminasaemia, Liver disorder,

	Liver function test abnormal, Transaminases increased, Liver function test increased, Hepatic cyst, Autoimmune hepatitis, Cholestasis, Cholelithiasis
Hepatosplenic T-cell lymphoma (HSTCL)	PT: Hepatosplenic T-cell lymphoma
Serious infusion reactions during a re-induction regimen following disease flare	1. IRRs captured by capture rule in Appendix 2 , and, 2. Reported as SAE, and 3. IRRs which occurred after infliximab-free intervals of more than 16 weeks during a re-induction regimen (Week 0 – Week 6), and 4. It would be also determined by medical review, separately.
Sarcoidosis/sarcoid-like reactions	1. PTs: Heerfordt's syndrome, erythema nodosum, or 2. Any PTs with sarcoidosis, or granuloma
Leukaemia	Any PTs with Leukaemia
Malignancies (excluding lymphoma)	1. Any terms under the HLTs with malignancy and malignant, and 2. Exclude lymphoma, HSTCL and skin cancer, and 3. It would be also determined by medical review, separately.
Skin cancer	1. SOC term: 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)', and, 2. It would be also determined by medical review, separately.
Pregnancy Exposure	Any PTs with pregnancy except pregnancy test
Infusion-related reaction/hyper sensitivity/anaphylactic reaction	IRRs captured by capture rule in Appendix 2 .