**CELLTRION, Inc**
**CT-P13 4.2**

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

**19th Jun 2020**

Statistical Analysis Plan
**Final version 6.0**

Prepared by:

[redacted]

Prepared by: [redacted] Date: ___/___/___

Approved by: [redacted] Date: ___/___/___

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.

**Table of Contents**

## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ADA | Anti-Drug Antibody |
| AE | Adverse Event |
| BMI | Body Mass Index |
| CRP | C-reactive Protein |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMARD | Disease-Modifying Anti-Rheumatic Drug |
| DAS28 | Disease Activity Score in 28 Joints |
| eCRF | Electronic Case Report Form |
| EOS | End-of-Study visit |
| ESI | Events of Special Interest |
| ESR | Erythrocyte Sedimentation Rate |
| EU | European Union |
| EULAR | European League Against Rheumatism |
| HAQ | Health Assessment Questionnaire |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IGRA | Interferon-gamma Release Assay |
| IRR | Infusion-Related Reaction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| RA | Rheumatoid Arthritis |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SJC | Swollen Joint Count |
| TB | Tuberculosis |
| TEAE | Treatment Emergent Adverse Event |
| TESAE | Treatment Emergent Serious Adverse Event |
| TJC | Tender Joint Count |
| 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 Clinical Statistics team in the analysis and presentation of data for annual report of CELLTRION study number CT-P13 4.2, entitled as "An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Remsima™ in Patients with Rheumatoid Arthritis".

This SAP is based on the following documents:

- Final study protocol Version 4.0 (Korea) – 03 June 2015
- Final Protocol Version 2.1 (EU) – 03 June 2015
- CRF Final Version 4.0 (Korea) – 03 August 2015
- MSL Final Version 3.1 (EU) – 07 September 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
- Immunogenicity Testing
- Descriptive statistic of DAS28
- Proportion of patients in each disease activity categories based on DAS28
- Proportion of patients in each categories based on EULAR criteria
- Descriptive statistic of health assessment questionnaire (HAQ)
- Health-economic data evaluation

# 3 Objectives

The primary objective of this study is to assess the long-term safety of Remsima™ (any other brand names of Remsima™) in rheumatoid arthritis (RA) patients by evaluation of Events of Special Interest (ESI) up to 5 years (2 years initially, followed by an additional 3 years for patients who consent to participate in an extension study) and to compare patients receiving Remsima™ (any other brand names of Remsima™) with patients receiving other anti-TNF drugs.

The secondary objectives of this study are to evaluate efficacy and additional safety of Remsima™ (any other brand names 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.

# 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 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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) – Good Clinical Practice. Informed consent from all patients will be obtained prior to enrollment. This observational study allows drug switching between anti-TNF drugs or switching to anti-TNF drugs from synthetic DMARDs, if required, without intervention from the investigator or sponsor. After switching, data for newly treated drug will be collected to assess the aspect of changes. 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. If switched to synthetic DMARDs, further assessment will not be required after the switch. Patients will undergo safety and efficacy assessments in accordance with routine medical practice. The decision to treat with Remsima™ will be independent from 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 (at least 450 patients treated with Remsima™, at least 450 patients treated

with other anti-TNFs within 6 months prior to enrollment 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 patients 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 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 enrollment (3mg/kg intravenously at weeks 0, 2 and 6, 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 an anti-TNF such as infliximab (Remicade®), Etanercept and Adalimumab prior to enrollment, dosing schedule of the patient 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.

## 4.2 Sample size

EMA guideline 'Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis' [EMA guideline, 2003] is referred to decide a sample size for the Remsima™ cohort. The guideline suggests that at least 300 to 600 patients receiving a drug during more than 6 months and 100 patients who received during more than 12 months are required for safety assessment. In addition, 'ICH-E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions' [ICH-E1A, 1995] also indicates the number of 100 patients is required for safety analysis. According to the study by Wietske Kievit, this long-term follow up study (5-year) recruited 1560 RA patients (606 for Adalimumab group, 700 for Etanercept and 254 for infliximab group) [Wietske Kievit et al. 2011].
On basis of the guidelines and references aforementioned, this study aims to recruit at least 450 patients taking Remsima™ from participating study centers. For comparison, at least 50 RA patients receiving treatment other than biologics and at least 450 patients treated with other anti-TNF drugs will be recruited. Biologic naïve cohort will be recruited in Korea only. Fifty percent or more of the target number of patients will be enrolled from EU or relevant European region for Remsima™ and other anti-TNFs drugs.
The number of patients in the Remsima™ cohort is sufficient to detect adverse events which occur at 1 % of frequency. These 450 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 equal to or more than two switching after enrollment: period between first and second switching

For patients 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 Remsima™ 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 related tables regardless of analysis period.

### 5.2 Analysis Sets

Two analysis sets and four subsets will be analyzed: 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 the study treatment 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 eCRF.

#### 5.2.2 Efficacy Analysis Set

The efficacy analysis set will consist of all patients who receive at least one infliximab (Remsima™ 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 Subsets

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 Subsets

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

Prior biologics for RA will also be considered for determining the analysis group. 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 and biologic treatment other than anti-TNF after enrollment will not be used in determination of analysis group. Definition of analysis groups are like below.

- Remsima:
  Patients who have received only Remsima™ or switched from non-biologic treatment to Remsima™ will be included in this analysis group.
- Switch to Remsima I:
  Patients who switched from Remicade® to Remsima™ will be included in this analysis group.
- Switch to Remsima II:
  Patients who switched to Remsima™ from biologic treatment other than Remicade® will be included in this analysis group.
- Remicade:
  Patients who have received only Remicade® or switched from non-biologic treatment to Remicade® will be included in this analysis group.
- Switch to Remicade I:
  Patients who switched from Remsima™ to Remicade® will be included in this analysis group.
- Switch to Remicade II:
  Patients who switched to Remicade® from biologic treatment other than Remsima™ 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 Remsima™ or Remicade®
  - Patients who switched from non-biologic treatment to anti-TNF other than Remsima™ or Remicade®

    - Patients who switched from biologic treatment other than anti-TNF before study enrollment to anti-TNF other than Remsima™ or Remicade®
- Switch to Other Anti-TNF:
  Patients who switched from Remsima™ or Remicade® to other anti-TNF other than Remicade® will be included in this analysis group.
- Biologic Naïve:
  Patients who received only non-biologic treatment will be included in this analysis group

Patient disposition will be summarized by all analysis groups. 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 group: 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 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), median, minimum 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, 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 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 separately 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 and last visit and, if applicable, the reason for discontinuation will be also 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) ($kg/m^2$); race (white, black, Asian, other, unspecified); Region (European, Non-European). Percentages will be calculated using safety analysis set as the denominator.

The BMI will be collected in eCRF for only Korean patients and will be derived for European patients as follows using weight at Visit 1 and screening height:

- BMI: Weight (kg) / $[\text{Height (m)}]^2$

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 end of study visit, smoking status will be collected. The following measures will be tabulated for Safety analysis set by status; smoking status (Current Smoking, Never Smoking, Former Smoking); average cigarettes per day; duration of smoking (years). The duration of smoking will be collected in eCRF for only Korean patient 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. XXMAR2010) the date will be the last day of the month (i.e. 31MAR2010). If the day and month are missing (i.e. XXXXX2010) the date will be set to the 31st December (i.e. 31DEC2010). 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 Rheumatoid Arthritis Surgeries

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

### 8.4 Rheumatoid Arthritis History

Rheumatoid Arthritis history is captured at screening visit. The descriptive statistics of time since Rheumatoid Arthritis diagnosis will be tabulated for the Safety analysis set. Time since RA diagnosis is 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. XXMAR2010) the date will be the last day of the month (i.e. 31MAR2010). If the day and month are missing (i.e. XXXXX2010) the date will be set to the 31st December (i.e. 31DEC2010). If the imputed data 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 RA diagnosis will not be calculated.
Rheumatoid Arthritis history will also be listed by analysis group for the Safety analysis set. Time since RA 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 the higher version). Medical history will be summarized by analysis group, SOC and 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 Rheumatoid Arthritis

Biologic therapy details will be coded using the World Health Organization (WHO) Drug Dictionary (WHODrug Global B3 Version September 1, 2019 or the later version). 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 the WHO Drug Dictionary (WHODrug Global B3 Version September 1, 2019 or the later version). 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.

Prior and concomitant medications will be listed by analysis group for the safety analysis set. Co-administration of Methotrexate and Folic Acid will be listed separately 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. It will be rounded to the nearest integer. 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.

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or the higher version 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), preferred term (PT), and reported term; start and stop date; whether the event is a TEAE throughout the 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); batch number for Remsima™; and ADA subset information (Positive, Negative). Listings will be generated by analysis group for the safety analysis set.

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. XXFEB2014): Assume the last day of the month. (e.g. 28FEB2014)
- Missing day and month (e.g. XXXXX2014): Assume December 31st. (e.g. 31DEC2014)
- 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 day of an AE is missing (e.g. XXFEB2014), 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. 01FEB2014).

If the day and month are missing (e.g. XXXXX2011), 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. 01JAN2011).

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 relationship, severity, SOC and PT 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
- Important medical event based on appropriate medical judgment
- Congenital anomaly/birth defect

Treatment-emergent serious adverse event (TESAE) will be summarized by relationship, severity, SOC and PT 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 relationship, severity, SOC and PT displaying the number and percentage of patients with at least one TEAE which led to permanent discontinuation of the study drug. 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 Remsima™, the following Events of Special Interest (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 reactions associated with shortened infusion duration
- Infusion related reaction/hypersensitivity/anaphylactic reaction

AEs will be determined as ESI using the detailed algorithm in Appendix 3. ESI related to infusion-related reaction/hypersensitivity/anaphylactic reaction (IRR) will be determined using algorithms in Appendix 2. TEAEs of special interest will be summarized by relationship, severity, system organ class and preferred term 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) is 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 a separate listing including category of sign and symptom, intensity and blood pressure (systolic blood pressure and diastolic blood pressure).

## 10.2 Tuberculosis Assessment

TB will be clinically monitored throughout the study and the followings are conducted for TB assessment.

- 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 the central IGRA result at baseline (Section 5.1) will be displayed. IGRA conversion occurs when positive result of central IGRA follows baseline IGRA of negative. If the central IGRA result at baseline is missing, IGRA conversion occurs when positive IGRA follows first post-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 for safety analysis set. In addition, IGRA conversion flag will also be provided in the listing for IGRA assessments.

## 10.3 Pregnancy Test

A serum or urine pregnancy test will be conducted at Screening 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 for safety analysis set.

## 10.4 Immunogenicity Testing

Blood samples for immunogenicity assessments (anti-infliximab antibodies) will be obtained at Baseline, at 6 months (Week 30), at every year and EOS visit. Assessment will be performed prior to dose infusion for patients who are treated with infliximab (Remsima™ and Remicade®). Anti-infliximab antibodies will be assessed in an Anti-Drug Antibody (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 Remsima™/ Remicade® to determine if patients are a true positive. The test outcome for the specificity/confirmatory assay will be: {'Reactive', 'Negative' and 'N/A'}. 'Reactive' indicates a true positive test outcome and will be labeled as 'Positive' in outputs, 'Negative' is considered negative, and 'N/A' means the result of screening phase was either 'Negative' or '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 ADA assessment will be displayed by analysis group at each scheduled time point after first infusion of analysis period. For summary, time point will be assigned to 'Week XX' by every scheduled time points when the assessment date of each visit is in 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 for the safety analysis set. 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 for the safety analysis set.

## 11 Efficacy Analysis

Efficacy will be summarized for the efficacy analysis set and the efficacy – ADA positive/negative subset.

Efficacy 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 'Week 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). For calculation of proportion by time point, the denominator will be the number of patients who perform assessments at each time point.

### 11.1 DAS28

Disease activity score in 28 joints (DAS28) will be calculated in two ways using the following two equations:

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

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

Where:

TJC28 = number of tender joints (0-28): tender joint count (TJC)
SJC28 = number of swollen joints (0-28): swollen joint count (SJC)
ESR = ESR measurement (mm/h)
CRP = CRP measurement (mg/L)
GH = Patient Global Assessment of Disease Activity measured on VAS (0 – 100 mm)

Disease activity will be indexed as follows:

- Remission: DAS28 < 2.6
- Low Disease Activity: 2.6 ≤ DAS28 < 3.2
- Moderate Disease Activity: 3.2 ≤ DAS28 ≤ 5.1
- High Disease Activity: 5.1 < DAS28

Tables for proportion of patients in each disease activity categories (based on DAS28 (ESR) and DAS28 (CRP)) and descriptive statistics of DAS28 (ESR) and DAS28 (CRP) will be provided separately by analysis group at each scheduled time point during analysis period.

For Korean patients, DAS28 scores will be calculated substituting missing ESR or CRP at Visit 1 with result at Screening. For European patients, DAS28 score populated automatically in eCRF will be used. Patients' other DAS28 components, scores and disease activity categories from each scheduled time point will also be listed regardless of period and analysis group. The DAS28 will be displayed to two decimal places.

### 11.2 EULAR Response Criteria

The European League Against Rheumatism (EULAR) response criteria categorizes the DAS28 response (i.e., good, moderate, or none) based on changes in DAS28 from baseline.

**Table 1. European League Against Rheumatism Response Criteria**

| | **DAS28 Improvement from baseline** | | |
|---|---|---|---|
| **Present DAS28** | >1.2 | >0.6 and ≤1.2 | ≤0.6 |
| ≤3.2 | Good response | Moderate response | No response |
| >3.2 and ≤5.1 | Moderate response | Moderate response | No response |
| >5.1 | Moderate response | No response | No response |

Frequencies and percentages for the EULAR response categories (based on both DAS28 (ESR) and DAS28 (CRP)) during analysis period will be summarized by analysis group at every scheduled time point. The EULAR response categories by analysis group will be listed in the DAS28 listing.

### 11.3 Health Assessment Questionnaire (HAQ) Estimate of Physical Ability

The arthritis-related functional disability will be measured using the disability index of the HAQ, a validated, self-administered form that assesses functional ability in a number of relevant areas, including the ability to dress, rise from bed, eat, walk, maintain personal hygiene, reach, grip and other activities on a scale ranging from 0 (without any difficulty) to 3 (unable to do). Scores range from 0 to 3, with higher scores indicating worse disability.

There are 8 categories within the Health Assessment Questionnaire:

- Dressing and Grooming (Questions 1, 2)
- Arising (Questions 3, 4)
- Eating (Questions 5, 6, 7)
- Walking (Questions 8, 9)
- Hygiene (Questions 10, 11, 12)
- Reach (Questions 13, 14)
- Grip (Questions 15, 16, 17)
- Activities (Questions 18, 19, 20)

The answer to each question will be scored as follows: Without any difficulty = 0, With some difficulty = 1, With much difficulty = 2, Unable to do = 3.

In order to compute the disability index:

(1) A score will be obtained for each category by taking the highest score recorded from the questions within the category. The maximum score is taken regardless of missing values in questions, i.e. at least one question must have an assigned score. If all questions have missing values, the score is recorded as missing.

(2) Additionally, an adjustment score is added for each category for use of aids/devices and/or help from another person using the tables below. If the score for a category is 0 or 1 after step (1), and any of the aids/devices/help from another person fields are marked, the score should be increased to 2. If a patient's highest score for that category is 2 or 3 already, it remains 2 or 3.

**Table 2. Aids/Devices Items for HAQ Categories**

| Item | HAQ Category |
|---|---|
| Devices used for dressing (button hook, zipper pull, long handled shoe horn, etc.) | Dressing & Grooming |
| Special or Built up chair | Arising |
| Built up or special utensils | Eating |
| Cane | Walking |
| Walker | Walking |
| Crutches | Walking |
| Wheelchair | Walking |
| Raised toilet seat | Hygiene |
| Bathtub seat | Hygiene |
| Bathtub bar | Hygiene |
| Long handled appliances in bathroom | Hygiene |
| Long handled appliances for reach | Reach |
| Jar opener (for jars previously opened) | Grip |

Note: The assignment of devices to particular disability categories assumes that the devices are used only for their intended purposes

**Table 3. Help from another Person Items for HAQ Categories**

| Item | HAQ Category |
|---|---|
| Dressing & Grooming | Dressing & Grooming |
| Arising | Arising |
| Eating | Eating |
| Walking | Walking |
| Hygiene | Hygiene |
| Reach | Reach |
| Gripping and opening things | Grip |
| Errands and chores | Activities |

(3) A minimum of 6 categories must have a score assigned in order for the HAQ estimate of physical ability to be derived. If there are only scores available for less than 6 categories, the HAQ estimate of physical ability cannot be computed and should be recorded as missing. If there are 6 or more categories with a score assigned, divide the summed category scores (using the adjustment score) by the number of categories answered to obtain the HAQ estimate of physical ability.

Descriptive statistics for actual value of the HAQ estimate of physical ability will be presented by analysis group at each scheduled time point during analysis period. A listing will be provided showing the patient's score for each category and HAQ estimate of physical ability. Listings will also be provided showing the raw scores for each category, the responses to the "Aids/Devices" categories, and the "Help from another person" categories. Additional listing will also be provided by analysis group for visual analogue scale (VAS) result to show the patient's score on the HAQ assessment of pain (0-no pain, 100-severe pain). These listings will all be displayed by analysis group.

## 12 Health-economics Analysis

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

- 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)

The number and percentage of patients with above information at each category will be summarized by analysis group at each scheduled visit during analysis period for the safety analysis set. 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 also be provided displaying descriptive statistics of number of hospitalization days, number of days off and number of working days gained. Listing for health-economics evaluation will be provided by analysis group for the safety analysis set.

## 13 References

[1] EMEA, Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis. 2003.

[2] ICH-E1A, The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Longterm Treatment of Non-Life- Threatening Conditions. 1995

[3] Wietske Kievit, Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register, Rheumatology 2011;50:196–20

[4] 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

[5] 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.

# APPENDIX 1: TABLE OF CONTENTS: SUMMARY TABLES AND LISTINGS

## List of Tables

## List of Listings

## 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 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 (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 | 1. Hepatitis B virus infection in medical history.<br>• Hepatitis B, Hepatitis viral, Hepatitis acute, Hepatitis toxic<br><br>2. Diagnosis possibly related to HBV reactivation (PT term):<br>• Hepatitis B, hepatitis, hepatitis toxic, hepatitis acute, hepatotoxicity, hepatomegaly, hepatic steatosis, liver disorder<br><br>3. Possible relevant abnormal lab results (PT term):<br>• Alanine aminotransferase increased<br>• Aspartate aminotransferase increased<br>• Gamma-glutamyltransferase increased<br>• Blood alkaline phosphatase increased<br>• Hypertransaminasaemia<br>• Transaminases increased<br>• Hyperbilirubinaemia<br>• Hepatic enzyme increased<br>• Liver function test abnormal<br>• Liver function test increased<br>• Blood bilirubin increased<br><br>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. |
| Congestive heart failure | PT: Cardiac failure congestive |
| Opportunistic infections (excluding TB) | 1. SOC: Infections and infestations, and<br>2. Reported SAE, and<br>3. Exclude Tuberculosis, and<br>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.)<br>5. It would be also determined by medical review, separately. |
| Serious infections including sepsis (excluding opportunistic infections and TB) | 1. SOC: Infection and infestations, and<br>2. Reported SAEs, and<br>3. Exclude opportunistic infections and tuberculosis |
| Tuberculosis | Any PTs with tuberculosis |
| Serum sickness (delayed hypersensitivity reactions) | 1. IRRs captured by capture rule in Appendix 2, and<br>2. IRR case which occurs 5 to 14 days after the latest Infliximab infusion, and<br>3. It would be also determined by medical review, separately. |

| | |
|---|---|
| Haematological reactions | PTs:<br>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:<br>Acute cutaneous lupus erythematosus, Chronic cutaneous lupus erythematosus, Cutaneous lupus erythematosus, Systemic lupus erythematous, 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”):<br>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:<br>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,<br>2. Reported as SAE, and<br>3. IRRs which occurred after infliximab-free intervals of more than 16 weeks during a re-induction regimen (Week 0 – Week 6), and<br>4. It would be also determined by medical review, separately. |
| Sarcoidosis/sarcoid-like reactions | 1. PTs: Heerfordt's syndrome, erythema nodosum, or<br>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<br>2. Exclude lymphoma, HSTCL and skin cancer, and<br>3. It would be also determined by medical review, separately. |
| Skin cancer | 1. SOC terms: 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)', and,<br>2. It would be also determined by medical review, separately. |
| Pregnancy Exposure | Any PTs with pregnancy except pregnancy test |
| Infusion reactions associated with shortened infusion duration (in RA) | 1. IRRs captured by capture rule in Appendix 2, and,<br>2. It would be determined by medical review. |
| Infusion related reaction/hypersensitivity/anaphylactic reaction | IRRs captured by capture rule in Appendix 2. |