1.0 Title Page

Statistical Analysis Plan

Study M14-496

A Phase 4 open-label randomized controlled study COmparing the effectiveness of adalimumab iNTROduction and methotrexate dose escaLation in subjects with Psoriatic Arthritis (CONTROL)

Date: 10 June 2019

Version 1.0

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3.0 Introduction

This Statistical Analysis Plan (SAP) was created based on Study Protocol M14-496 Amendment 3 dated 03 June 2019.

This statistical analysis plan describes the statistical analyses to be completed by the Data and Statistical Science Department for Study M14-496. It provides the details to further elaborate statistical methods as outlined in the protocol before the Part 1 database lock. However, features of the study and the data collected may suggest that deviations from the approach presented in this analysis plan are appropriate, and exploratory analyses can be added. A detailed description of any substantive modifications to this SAP will be included in the final clinical study report (CSR). Serum adalimumab (ADA) concentration and anti-ADA antibodies (AAA) will be studied by a pharmacokinetics group, the corresponding analysis plan is documented separately and is not in the scope of this SAP. A final CSR is planned after the study is completed.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Background

4.1 Objective

The primary objective is to compare the effectiveness based on the achievement of minimal disease activity (MDA) at Week 16 between subjects who had ADA introduced and those that had methotrexate (MTX) escalated to the highest recommended dose of 20 - 25 mg every week (ew) or highest tolerable dose up to 25 mg ew after inadequate disease control on the initial MTX therapy.

The secondary objectives are:

- To compare the effectiveness at Week 16 between subjects who had ADA introduced and those that had MTX escalated to the highest recommended

dose of 20 - 25 mg ew or highest tolerable up to 25 mg ew based on the following clinical, functional and quality of life measures:

- Psoriatic Arthritis Disease Activity Score (PASDAS)
- Disease Activity in Psoriatic Arthritis (DAPSA) score
- Psoriatic Arthritis Impact of Disease (PsAID) score
- American College of Rheumatology (ACR) 20/50/70 response
- Disease Activity Score 28 (DAS28)-CRP
- Psoriasis Area and Severity Index (PASI)
- Health Assessment Questionnaire Disability Index (HAQ-DI)
- Short Form Health Survey 36 (SF-36) scores: physical component summary (PCS) and mental component summary (MCS)
- Dermatology Life Quality Index (DLQI)
- Leeds Enthesitis Index (LEI)
- Tender dactylitic digit count

- To evaluate the achievement of MDA at Week 32 on each of the four different treatment groups involving ADA and/or MTX in Part 2 of the study.

4.2 Study Design

4.2.1 Study Design and Design Diagram

This interventional Phase 4 open-label, randomized, controlled, parallel-group, multicenter study will be conducted in two (2) parts, each of 16-week duration.

Part 1 (Day 1 - Week 16) is to compare the achievement of MDA on ADA introduced in combination with MTX versus MTX alone escalated to the highest recommended dose of 20 - 25 mg ew[1,2] or highest tolerable dose up to 25 mg ew, whatever feasible, in PsA subjects inadequately controlled after the initial course of MTX at 15 mg ew. Part 1 will be open-label, randomized, controlled, parallel group.

Part 2 (Week 16 - 32) is to evaluate the effectiveness of four (4) different treatment regimens consisting of ADA and/or MTX in maintaining or attaining MDA, as applicable.

Part 2 will be open-label, parallel group. Subjects will be assigned into the four treatment arms based on their MDA status at Week 16 and initial randomized treatment. Starting at Week 24, there will be rescue treatment option based on not achieving MDA and investigator's judgment.

The study is designed to enroll approximately 240 subjects at approximately 60 sites to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Following a screening period of up to 30 days, subjects meeting the selection criteria will be randomized in a 1:1 ratio to either of the two (2) arms and treated for 16 weeks in Part 1:

- Arm 1/Part 1: ADA 40 mg eow in combination with MTX 15 mg ew (ADA 40 mg eow + MTX 15 mg ew),
- Arm 2/Part 1: MTX escalated to 20 - 25 mg or highest tolerable dose ew (MTX 20 - 25 mg or highest tolerable dose ew).

After the assessment of MDA at Week 16 (primary endpoint), subjects will be assigned to one of the four (4) treatment arms based on the achievement of MDA and initial randomized treatment, and treated for additional 16 weeks in Part 2 as follows:

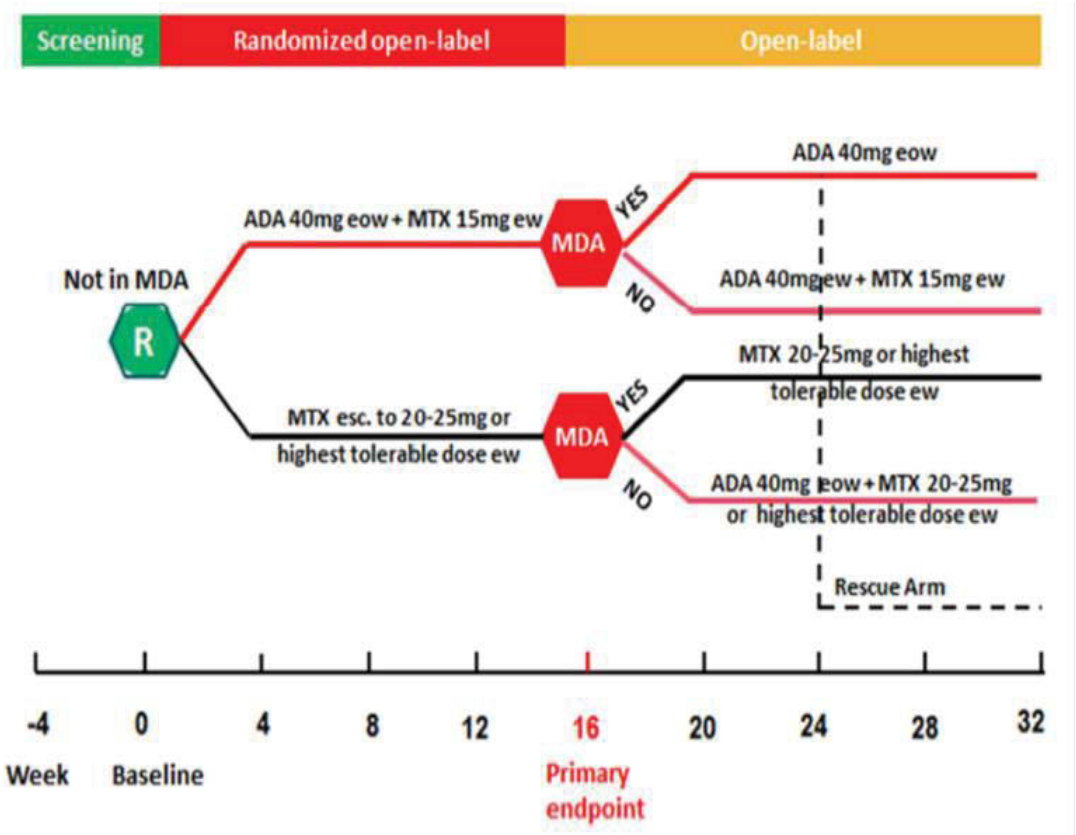
- Arm 1/Part 2: Subjects achieving MDA at Week 16 on ADA 40 mg eow plus MTX 15 mg ew, will have MTX completely withdrawn at Week 16 and continue receiving ADA as monotherapy (ADA 40 mg eow),
- Arm 2/Part 2: Subjects not achieving MDA at Week 16 on ADA 40 mg eow plus MTX 15 mg ew, will have ADA escalated to 40 mg ew in combination with MTX 15 mg ew (ADA 40 mg ew plus MTX 15 mg ew),
- Arm 3/Part 2: Subjects achieving MDA at Week 16 on MTX escalated to 20 - 25 mg or highest tolerable dose ew, will continue with the same MTX dose (MTX 20 - 25 mg or highest tolerable dose ew),
- Arm 4/Part 2: Subjects not achieving MDA at Week 16 on MTX escalated to 20 - 25 mg or highest tolerable dose ew, will receive ADA 40 mg eow in

combination with MTX 20 - 25 mg or highest tolerable dose ew (ADA 40 mg eow plus MTX 20 - 25 mg or highest tolerable dose ew).

Subjects in Arms 1 - 4 of Part 2 of the study will have the option of being rescued, starting at Week 24 and based on the subject not achieving MDA and the Investigator's judgment. The selection of the rescue treatment regimen will be at the discretion of the Investigator, but should involve ADA and/or MTX and should not involve prohibited medications per the protocol.

A schematic of the study design is shown below in Figure 1:

Figure 1. A schematic of the study design



4.2.2 Variables used for Stratification at Randomization

Randomization was stratified by the duration of prior MTX treatment at 15 mg ew: ≤ 3 months and > 3 months.

4.3 Endpoint

4.3.1 Primary Efficacy Endpoint

The primary endpoint is the proportion of subjects achieving MDA at Week 16 on ADA 40 mg eow plus MTX 15 mg ew as compared with subjects on MTX alone escalated to 20 - 25 mg or highest tolerable dose ew.

MDA in PsA is defined as fulfilling at least 5 of the 7 following criteria:[3,4]

- TJC ≤ 1 (out of TJC68 assessed in this study)
- SJC ≤ 1 (out of SJC66 assessed in this study)
- PASI ≤ 1 or BSA ≤ 3
- Patient's assessment of pain VAS ≤ 15
- Patient's global assessment of disease activity (PtGA) VAS ≤ 20
- HAQ-DI score ≤ 0.5
- Tender entheseal points ≤ 1 (out of 8 assessed in this study)

4.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- At Week 16:
  - Change from baseline in PASDAS
  - Change from baseline in DAPSA score
  - Change from baseline in PsAID score
  - Proportion of subjects achieving ACR 20/50/70 response
  - Change from baseline in DAS28-CRP score

- Proportion of subjects achieving PASI 75/90/100 response (for subjects with BSA ≥ 3% at baseline)
- Change from baseline in HAQ-DI score
- Changes from baseline in SF-36PCS and SF-36MCS
- Change from baseline in DLQI score
- Change from baseline in Leeds Enthesitis Index (LEI) (for subjects with presence of enthesitis at baseline)
- Change from baseline in tender dactylitic digit count (for subjects with presence of dactylitis at baseline)

- The proportion of subjects in MDA at Week 32.

4.3.3 Exploratory Efficacy Endpoints

Clinical Efficacy

Clinical efficacy outcomes listed under the secondary endpoints (refer to Section 4.3.2) will be analyzed as exploratory endpoints at Week 32 on the 4 different treatment regimens.

Ultrasound

- The change in Global OMERACT-EULAR synovitis score (GLOESS) from baseline to Week 16 in randomized treatment groups of Part 1 of the study.
- The change in OMERACT enthesitis score from baseline to Week 16 in randomized treatment groups of Part 1 of the study.
- The change in Global OMERACT-EULAR synovitis score (GLOESS) from Week 16 - 32 in the 4 arms of Part 2 of the study.
- The change in OMERACT enthesitis score from Week 16 - 32 in the 4 arms of Part 2 of the study.

4.3.4 Safety Endpoint

The following safety evaluations will be performed during the study: concomitant medication review, adverse event (AE) monitoring, vital signs, and laboratory tests.

4.3.5 Pharmacological Endpoint

For subjects receiving ADA, blood samples will be collected for determination of ADA serum concentrations and the presence of anti-ADA antibodies (AAA). Analysis will be conducted separately and not in the scope of this SAP.

4.4 Sample Size Justification

The study is powered to detect the difference in MDA response rates at Week 16 between ADA + MTX 15 mg and MTX escalated dose groups. Assuming an MDA response rate of 40% in the ADA + MTX group and 20% in the escalated MTX group, a total sample size of 240 subjects, 120 subjects per arm, will provide at least 90% power to detect the difference between the two treatment groups at a significance level of 2-sided 0.05, accounting for 10% dropout.

4.5 Part 1 Analysis

Part 1 database lock is planned when all randomized subjects have completed Week 16 of the study. The 16-week study results (through Week 16) will be based on this database lock.

4.6 Multiplicity Testing Procedures for Type-I Error Control

There is only one primary endpoint in this study and therefore multiplicity adjustment is not applicable.

4.7 Missing Data Imputation

The following missing data imputation will be performed for efficacy analysis.

Non-Responder Imputation (NRI) Approach

To account for missing data for the binary efficacy endpoints, a non-responder imputation approach (NRI) will be used, e.g., subjects who have missing data at a specific visit will be treated as non-responder for that visit, or who prematurely discontinue or have been rescued will be considered as a non-responder for all subsequent visits.

Mixed-Effects Model Repeated Measures (MMRM)

The repeated measure analysis will be conducted using mixed models based on observed data at all visits. For the MMRM analysis (of continuous variables), data collected after premature discontinuation of study drug will be excluded. The mixed model includes treatment, visit, treatment-by-visit interaction, and the stratification factor of duration of prior MTX use (≤ 3 months or > 3 months) as fixed effects, subject as random effect and baseline measurement as a covariate. An unstructured variance covariance matrix will be used. The parameter estimations assume data being missing at random (MAR) and using the method of restrictive maximum likelihood (REML).

Observed Cases (OC)

The OC analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the OC analysis for that visit. In addition, OC will not include values after subject have rescue visit or after premature discontinuation of study drug.

5.0 Analysis Populations and Important Subgroups

5.1 Analysis Populations

Intent-to-Treat Population Part 1

The Intent-To-Treat Part 1 (ITT Part 1) population comprises all subjects who were randomized and received at least one dose of the study medication during the Part 1 period. The data collected up to Week 16 will be included and analyzed by the treatment

group assignment given at the time of randomization, even if the subject does not receive the correct treatment, is not compliant to the protocol procedures, or does not follow the protocol until completion.

Intent-to-Treat Population Long Term

The Intent-To-Treat Long Term (ITT LT) population comprises all subjects who entered Part 2 period and received at least one dose of Part 2 study medication. The data collected from randomization and up to Week 32 will be included and analyzed by the four treatment regimens as follows:

- ADA 40 mg eow + MTX 15 mg ew/ADA 40 mg eow
- ADA 40 mg eow + MTX 15 mg ew/ADA 40 mg ew + MTX 15 mg ew
- MTX 20 - 25 mg or highest tolerable dose ew
- MTX 20 - 25 mg or highest tolerable dose ew/ADA 40 mg eow + MTX 20 - 25 mg or highest tolerable dose ew

Per Protocol Population

In order to evaluate the impact of major protocol violations on the results of the trial, additional analysis of the primary effectiveness variable may be conducted on the per protocol population, which consists of all ITT Part 1 subjects who entered the randomized period of the study and did not meet any major protocol violation during the Part 1 of the study. The determination of major protocol violation will be finalized prior to the final database lock.

Safety Population Part 1

The Safety population Part 1 consists of all subjects who received at least one dose of the study medication during the Part 1 period. The data collected up to Week 16 will be included and analyzed by the two "As treated" treatment groups in Part 1. "As treated" is determined by the treatment a subject received during majority of the subject's drug exposure time in the analysis period, regardless of the treatment randomized.

Safety Population Part 2

The Safety population Part 2 consists of all subjects who received at least one dose of the Part 2 study medication. The data collected from Week 16 to Week 32 will be included and analyzed by "as treated" treatment groups that subjects received when entering in Part 2. The data collected after the initiation of the rescue medication will be summarized separately, and not be included in the analysis.

"As treated" treatment groups are defined as follows:

1. ADA 40 mg eow
2. ADA 40 mg ew + MTX 15 mg ew
3. MTX 20 - 25 mg or highest tolerable dose ew
4. ADA 40 mg eow + MTX 20 - 25 mg or highest tolerable dose ew

Rescue Population

The Rescue population consists of all subjects who received at least one dose of the rescue medication after Week 24 visit. The data collected after the initiation of the rescue medication will be summarized separately by the Part 2 treatment groups as well as overall.

5.2 Subgroup

Age, gender, BMI, race, region, prior MTX use (> 3 months or ≤ 3 months) will be the subgroups for the subgroup analysis.

6.0 Efficacy Analyses

6.1 General Considerations

There are two sets of planned efficacy analysis: Part 1 analysis and long-term analysis.

Part 1 Efficacy Analysis

Standard efficacy analysis by the randomized treatment groups (ADA 40 mg eow + MTX 15 mg ew, MTX 20 - 25 mg or highest tolerable dose ew) will be performed on the efficacy data up to Week 16 based on ITT Part 1 population. Formal statistical inference will be generated with missing data handling, and statistical testing will be conducted at $\alpha = 0.05$ level (2-sided). Results from this set of analysis will be used as the key efficacy findings of this study.

No protocol-defined rescue will occur prior to the time point.

Long Term Efficacy Analysis

Long term efficacy analysis from baseline to Week 32 will be performed based on the ITT LT Population by the 4 treatment regimens as described in Section 5.1. Descriptive statistics will be summarized by the four treatment regimens. The between-treatment comparison is not applicable for the long term analysis. No missing data imputation will be performed for long term efficacy analysis.

Rescue handling will be applied for long term efficacy analysis. The data collected after the initiation of the rescue medication will be summarized separately.

6.2 Primary Efficacy Analysis

The primary endpoint is the proportion of subjects achieving MDA at Week 16. The null hypothesis is that there is no difference in the rate of MDA between the two randomized treatment groups of ADA 40 mg eow + MTX 15 mg ew and MTX 20 - 25 mg or highest tolerable dose ew; the alternative hypothesis is that the rates of MDA between the two groups are different.

Point estimate and 95% CI using normal approximation will be provided for the rate of MDA for each randomized treatment group. Treatment comparisons will be made between the randomized treatment groups using a Cochran-Mantel-Haenszel (CMH)

test[5,6] (refer to Appendix A), adjusting for the stratification factor which is the duration of prior MTX 15 mg ew use of ≤ 3 months or > 3 months. Point estimate of the treatment difference and the associated 95% CI using normal approximation will also be presented. To account for missing data for the primary endpoint, a non-responder imputation approach (NRI) will be used, e.g., subjects who discontinue during Part 1 with missing data will be imputed as a non-responder (NRI) in the subsequent visits.

Sensitivity analyses will be conducted using the same method described above based on observed cases (OC) data.

6.3 Secondary Efficacy Analyses

Part 1 Analysis

A complete list of secondary efficacy endpoints is provided in Section 4.3.2. Binary endpoints will be analyzed in a similar way as the primary endpoint.

For the continuous endpoints, the change from baseline at Week 16 will be analyzed using MMRM with treatment, the stratification factor of duration of prior MTX use (≤ 3 months or > 3 months), visit, and treatment-by-visit interaction as fixed effects, subject as random effect and baseline measurement as a covariate. The MMRM analysis is based on observed data. The LS mean, 95% CI and standard error for each randomized treatment group, the LS mean of the treatment difference and its associated 95% CI and p-value from the MMRM model will be presented.

Long Term Analysis

The achievement of MDA at Week 32 on each of the four different treatment regimens will be evaluated. The proportion of subjects who achieved MDA at Week 32 will be summarized by counts and percentages for the four treatment regimens. Point estimate and 95% CI using normal approximation will be provided for each treatment regimen as well. The subjects who were rescued prior to Week 32 will be considered as non-

responders (MDA = 0) at Week 32. No comparison between treatment regimens will be performed.

6.4 Other Efficacy Analyses

Clinical Efficacy Variables

Binary secondary endpoints described in Section 4.3.2 will be analyzed as exploratory endpoints at Week 32 using count and percentages on each of the four different treatment regimens. Point estimate and 95% CI using normal approximation will be provided as well. The data occurred after initiation of the rescue medication will be imputed using NRI for the subsequent visits in this summary.

Continuous secondary endpoints described in Section 4.3.2 will be analyzed as exploratory endpoints at Week 32 by summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, median, minimum, maximum) for each treatment regimen. All observed data will be used to summarize the continuous exploratory endpoints. The data occurring after initiation of the rescue medication will be overwritten by the last observation prior to treatment rescue (Last observation carried forward: LOCF) for the subsequent visits in this summary.

Ultrasound Variables

For ultrasound assessment at Week 16, analysis will be performed using similar methods to those described for the secondary continuous efficacy endpoints. In addition, baseline weight will also be included as an additional covariate in MMRM. The LS mean, 95% CI and standard error for each randomized treatment group and the LS mean of the treatment difference, its associated 95% CI and p-values will be presented.

For the ultrasound assessment at Week 32, summary statistics (number of subjects, mean, 95% confidence interval, standard deviation, median, minimum, maximum) will be presented for each treatment regimen. All observed data will be used to summarize the

continuous exploratory endpoints. The data occurring after initiation of the rescue medication will be overwritten by LOCF for the subsequent visits in this summary.

Summary of Efficacy Endpoints by Visit

Summary of the primary and secondary efficacy endpoints at the scheduled time points will be presented by two treatment groups in the Part 1 analysis and by four treatment regimens in the long-term analysis. Achievement of each MDA component as binary endpoints will be summarized similarly as well.

For Part 1 analysis, binary efficacy endpoints will be analyzed in a similar way as the primary endpoint and continuous efficacy endpoints will be analyzed from the same MMRM model for the Wk16 endpoints.

For the long term by-visit summary of binary and continuous efficacy endpoints, summary statistics will be provided by the four treatment regimens and by visit. For binary endpoints, subjects who were rescued after Week 24 will be considered as non-responders for all subsequent visits after initiation of the rescue medication in this summary. For continuous efficacy endpoints, the Data occurred after initiation of the rescue medication will be overwritten by LOCF for the subsequent visits in this summary.

6.5 Efficacy Subgroup Analyses

The primary efficacy endpoint will be examined in the subgroups listed in Table 1 below. Point estimate of the treatment differences and 95% CI between the randomized treatment groups will be presented for each subgroup. No p-value will be provided for subgroup analysis. If any of the resulting subgroups for a variable has fewer than 20% of the planned study size (i.e., < 48 subjects), the subgroup analyses for that variable will not be presented.

Table 1. Subgroups for Efficacy Analysis

Subgroup Factor	Categories
Age	< 40, [40, 65), ≥ 65
Sex	Male or Female
BMI	< 25 kg/m^2 or ≥ 25 kg/m^2
Race	White, Non-white
Geographic region	US, Western Europe/Canada, Eastern Europe/Middle East/Africa, Latin America, Japan/Asia/Pacific
Prior MTX usage	≤ 3 months or > 3 months

6.6 Efficacy Analysis for Rescued Patients

For the subjects who take at least of one dose of rescue medication, MDA status will be evaluated after rescue at the Week 28 and Week 32. Point estimate and 95% CI using normal approximation will be provided for the response rate of the MDA by 4 treatment regimens as well as overall. The subjects who are rescued at Week 24 and Week 28 will be summarized separately.

7.0 Safety Analyses

7.1 General Considerations

There will be 2 sets of safety analyses to be performed.

1. Safety analyses during Part 1 (up to Week 16).
2. Safety analyses during Part 2 (Week 16 to Week 32).

Safety analyses will include reporting of adverse events (AEs), laboratory, and vital signs measurements. Treatment-emergent AEs will be summarized and reported. Missing safety data will not be imputed. Part 1 and Part 2 safety analyses will be carried out using the Safety Population Part 1 and Safety Population Part 2, respectively.

Safety Analysis during Part 1 (up to Week 16)

Standard safety analysis by the "as treated" treatment groups of ADA 40 mg eow + MTX 15 mg ew and MTX 20 - 25 mg or highest tolerable dose ew will be performed on safety data up to Week 16. No protocol-defined treatment switching will occur prior to this time point.

Frequency tables of subjects with treatment-emergent adverse events (TEAEs) by system organ class (SOC) and by preferred term (PT) as in the Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be provided by as-treated treatment groups. Observed values in all continuous laboratory parameters and vital signs variables at each visit will be summarized by "as treated" treatment groups. Frequency tables of subjects meeting criteria for potentially clinically significant vital sign values and for potentially clinically significant laboratory values will be provided by as-treated treatment groups. Missing safety data will not be imputed.

Safety Analysis during Part 2 (Week 16 to Week 32)

Similar standard safety analysis by the "as treated" treatment groups will be performed on safety data from Week 16 to Week 32 based on Safety Population Part 2.

7.2 Analysis of Adverse Events

7.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) will be defined based on the following:

- Part 1: TEAEs will be defined as any event with an onset date that is on or after the first dose of Part 1 study drug, and
  - no more than 70 days after the last dose of ADA and 30 days after the last dose of MTX, if the subject discontinued prematurely from Treatment Part 1 or did not enter the Part 2, or
  - prior to date of first dose of Part 2 study drug if the subject entered Part 2.

- Part 2: TEAEs will be defined as any event with an onset date that is on or after the first dose of Part 2 study drug and with an onset date no more than 70 days after the last dose of ADA or 30 days after the last dose of MTX.

Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the study drug start time and the adverse event start time are collected and the adverse event start time is prior to the study drug start time. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment emergent unless there is other evidence that confirms the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

Adverse event data will be presented by SOCs and PTs using MedDRA Version 21.1 or most up to date version.

7.2.1.1 Adverse Event Overview

The number and percentage of subjects experiencing TEAEs will be summarized for the following AE categories by the two treatment groups in Part 1 and by the four treatment groups in Part 2:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent severe adverse events
- TEAEs reasonably possibly related to study drug
- TEAEs leading to discontinuation of study drug
- TEAE leading to death

Additional AEs may be considered for tabulation/summary based on recommendations from Clinical and Safety as deemed appropriate.

7.2.1.2 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing adverse events will be tabulated by SOC and MedDRA PT by the two treatment groups in Part 1 and by the four treatment groups in Part 2. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

7.2.1.3 TEAEs by Maximum Severity

TEAEs will also be summarized by maximum severity by the two treatment groups in Part 1 and by the four treatment groups in Part 2. If a subject has an AE with an unknown severity, then the subject will be counted in the severity category of unknown, even if the subject has another occurrence of the same event with a severity present. The only exception is that if the subject has another occurrence of the same AE with the most extreme severity – severe. In this case, the subject will be counted under the severe category.

7.2.1.4 TEAEs by Relationship

TEAEs will also be summarized by relationship to study drug, as assessed by the investigator, by the two treatment groups in Part 1 and by the four treatment groups in Part 2. If a subject has a TEAE with an unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same TEAE with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

7.2.1.5 Frequent (≥ 5%) Adverse Events by System Organ Class and Preferred Term

TEAEs occurring for more than 5% of the subjects in any of the two treatment groups in Part 1 or any of the four treatment groups in Part 2 will be summarized by SOC and PT in decreasing frequency separately.

7.2.1.6 Adverse Events of Special Interest

The Adverse Events of Special Interest (AESI) categories by SOC and PT will be summarized and presented by the two treatment groups in Part 1 and by the four treatment groups in Part 2. The details of AESI list and search criteria are stated in Appendix A, which are extracted from Adalimumab Product Safety Statistical Analysis Plan Version 8.0.

7.2.2 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

All serious adverse events (SAEs), deaths, and adverse events leading to discontinuation of study drug will be listed. The number and percentage of subjects experiencing SAEs (including deaths) and adverse events leading to discontinuation of study drug will be tabulated according to the primary MedDRA SOC and MedDRA PT for each treatment group in Part 1 and for each treatment groups in Part 2.

7.3 Analysis of Laboratory Data

7.3.1 Analysis for Continuous Laboratory Data

Observed values of hematology, chemistry, and urinalysis variables which are measured longitudinally will be summarized by visits and by the two treatment groups in Part 1 and by the four treatment groups in Part 2. The following summary statistics of each visit will be presented for each treatment group: sample size, observed mean, standard deviation, minimum, median, and maximum.

Mean change and percent change from baseline in selected laboratory variables will be summarized by the two treatment groups in Part 1 and by the four treatment groups in Part 2 at each visit. Mean difference between the two treatment groups in Part 1 will be compared using one-way ANOVA with treatment as a factor. Mean difference and the associated 95% CIs will be presented at each visit. The selected laboratory variables of clinical interest include: Hematocrit, hemoglobin, Red Blood Cell (RBC) count, White Blood Cell (WBC) count, platelet count, lymphocytes, neutrophils, creatinine, Aspartate aminotransferase (AST), aminotransferase (ALT), Cholesterol, Glucose, Triglycerides.

The last evaluation prior to the first dose of study drug in Part 1 or Part 2 will be used as Baseline for Part 1 or Part 2, respectively.

7.3.2 Shift Table Analyses

Shift tables for changes from Baseline according to the normal range will also be provided for laboratory variable. The baseline and post-baseline laboratory observations will be categorized by grades according to NCI CTC criteria.

For each laboratory variable, shift tables will be generated that cross tabulate the subjects as deemed appropriate by the two treatment groups in Part 1 and by the four treatment groups in Part 2, respectively:

- Category of the baseline value versus category of the final value.
- Category of the baseline value versus maximum category.
- Category of the baseline value versus minimum category.

Note that the minimum/maximum category is used, rather than the category of the minimum/maximum value. The two may be different due to variation in the reference range.

No statistical tests will be performed for this analysis.

7.3.3 Analysis for Potentially Clinically Significant Laboratory Values

For selected laboratory parameters, the criteria for potentially clinically significant laboratory values will be determined by CTC criteria of Grade 3 or above. The number and percentage of subjects meeting the criteria for potentially clinically significant laboratory values will be summarized by the two treatment groups in Part 1 and by the four treatment groups in Part 2.

A listing of all subjects with any laboratory determination during each Part meeting Common Toxicity Criteria (CTC) (Version 3) of Grade 3 or higher will be provided. For each of these subjects, the whole course of the respective parameter will be listed.

A listing of potentially clinically significant liver function laboratory values will be provided. The listing will include all subjects who met any of the following criteria:

- ALT $\geq 3 \times$ ULN
- ALT $\geq 5 \times$ ULN
- ALT $\geq 10 \times$ ULN
- ALT $\geq 20 \times$ ULN
- AST $\geq 3 \times$ ULN
- AST $\geq 5 \times$ ULN
- AST $\geq 10 \times$ ULN
- AST $\geq 20 \times$ ULN
- TBL $\geq 2 \times$ ULN
- ALP $\geq 1.5 \times$ ULN
- ALT and/or AST $\geq 3 \times$ ULN and concurrent TBL $\geq 1.5 \times$ ULN
- ALT and/or AST $\geq 3 \times$ ULN and concurrent TBL $\geq 2 \times$ ULN

7.4 Analysis of Vital Signs and Weight

The vital sign variables are defined in Section 4.3.4.[3] Observed values of vital sign variables which are measured longitudinally will be summarized at each visit by the two treatment groups in Part 1 and by the four treatment groups in Part 2, respectively. Summary statistics such as number of subjects, baseline mean, visit mean, standard deviation, minimum and maximum will be provided.

The criteria for potentially clinically significant vital sign findings are presented in Table 2. The number and percentage of subjects meeting the criteria for potentially clinically significant vital sign values will be summarized by the two treatment groups in Part 1 and by the four treatment groups in Part 2. Vital sign results satisfying the criteria for potentially clinically significant findings will be identified in a listing.

Table 2. Criteria for Potentially Clinically Significant Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Significant Vital Signs
Systolic blood pressure	Low	Value ≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High	Value ≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decrease ≥ 15 mmHg from Baseline
	High	Value ≥ 105 mmHg and increase ≥ 15 mmHg from Baseline
Pulse	Low	Value ≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	Value ≥ 120 bpm and increase ≥ 15 bpm from Baseline
Weight	High	> 7% increase from baseline
	Low	> 7% decrease from baseline

The last evaluation prior to the first dose of study drug in Part 1 or Part 2 will be used as Baseline for Part 1 or Part 2, respectively.

7.5 Analysis of ECG Parameters

No post-baseline ECGs were obtained for this study.

8.0 Summary of Changes

8.1 Summary of Changes Between the Previous Version and the Current Version

Not applicable.

8.2 Summary of Changes in Previous Version

Not applicable.

9.0 Appendix

Appendix A. AESI List and Search Strategies

There are two types of search strategies may be used for categorizing AESI categories are as follow:

- Lowest Level MedDRA Queries (LMQs).
- Standard MedDRA Queries (SMQs)/Company MedDRA Queries (CMQs)/Product-specific MedDRA Queries (PMQs)

LMQs will be the default search strategy unless otherwise stated in the safety analysis request. SMQs/CMQs/PMQs will have limited use as a search strategy, e.g., aggregated safety review or any other special requests as deemed appropriate. LMQs will be used in our study.

The following table includes all AESI for Humira with the LMQ searches.

AESI	LMQ Name	LMQ Search Term Definition
Infection		
All Infection	Infection LMQ	Terms clearly identifying an infection.
Serious Infection	Infection LMQ	All Infections – Subset for SAEs.
Legionella Infection	Legionella Infection LMQ	Terms Legionella infections. Culture and isolation of Legionella from respiratory secretions and/or pleural fluid. Direct fluorescent antibody (DFA) staining that identifies Legionella in respiratory secretions and/or pleural fluid. Four-fold increase in Legionella antibody titer or a single titer of 1:128.
Diverticulitis	Diverticulitis LMQ	Leukocytosis, CT Findings (Phlegmon, free air bubbles, abscess, colonic wall thickening, free fluid, obstruction), Fistulas (colovesica, rectovaginal).

AESI	LMQ Name	LMQ Search Term Definition
Infection (continued)		
Opportunistic Infection Excluding Oral Candidiasis and TB	Opportunistic Infection LMQ	Terms describing unusually severe forms of infections by a microbe typically seen only in immunocompromised individuals e.g., the term 'Herpes sepsis' is included. Investigations for infections that generally occur exclusively in immunocompromised patients e.g., JC virus test positive. Broader terms for infections typically only seen in immunocompromised persons when a more specific term for that infection type is not available e.g., the term 'stomatoccal infection' is included. Terms describing specific forms of fungal infections or tuberculosis infections which typically occur only in immunocompromised patients e.g., the term 'disseminated TB' is included.
Oral Candidiasis	Oral Candidiasis LMQ	Terms describing Oral Candidiasis only.
Tuberculosis		Active tuberculosis and latent tuberculosis combined.
Active Tuberculosis	Active Tuberculosis LMQ	Terms that describe active disease of tuberculosis.
Latent Tuberculosis	Latent Tuberculosis LMQ	Terms that describe positive results for TB screening tests (either skin or blood tests). Terms that describe TB infection or latent infection.
Parasitic Infection	Parasitic Infection LMQ	Protozoal infectious disorders, Helminthic Disorders, and Ectoparasitic infestations. Skin and subcutaneous arthropod and parasitic infestations, Parasitic lower respiratory tract infections. Investigations terms for parasite identification and serology tests.
Reactivation of Hepatitis B	Reactivation of Hepatitis B Viral Infection LMQ	HBVsAg positive, HBeAb positive, PCR test for viral titer, HBVsAb positive, HBVc Ab positive.
Progressive Multifocal Leukoencephalopathy (PML)	Progressive Multifocal Leukoencephalopathy LMQ	PML definitive diagnosis.

AESI	LMQ Name	LMQ Search Term Definition
Malignancies		
Malignancies	Malignancies LMQ	All MedDRA terms for malignant or unspecified tumors: • Malignancy related conditions. • Terms for malignancy related conditions. • Terms for therapeutic and diagnostic procedures used to treat malignancies; treated malignancy to be specified. • Some of these procedures are also used for the treatment of non-malignant conditions. • Laboratory tests (incl. the results) that are specific for the malignancies. • To make agreement on "in situ" stage whether they fall under malignancies or not; currently assessed as malignancies. • To make agreement on general terms of "neoplasm;" whether considered as malignancies when no further details provided. • Tumour markers. • Terms related to tumor markers including the result. For European Group on Tumour Markers, please reference the web site at http://ar.iiarjournals.org/content/27/4A/1901.abstract: • Terms related to benign tumors. • Terms related to premalignant conditions. • Treatment and diagnostic procedures that do not specify a malignancy indicated. • Malignancy related therapeutic and diagnostic procedures includes a variety of terms which describe chemotherapy or radiotherapy treatment. Please be aware, however, that there are some terms which relate to chemotherapeutic. Such terms are not linked to chemotherapy or radiotherapy terms.
Lymphoma	Lymphoma LMQ	All terms for malignant or unspecified tumors. Terms for malignancy related conditions. Terms for therapeutic and diagnostic procedures used to treat malignancies. Some of these procedures are also used for the treatment of non-malignant conditions terms related to tumor markers.
Hepatosplenic T-Cell Lymphoma (HSTCL)	Hepatosplenic T-Cell Lymphoma (HSTLC) LMQ	The most specific inclusion criteria is the diagnosis based on T-cell histology for the lymphoma of T-cell receptor type.
Non-Melanoma Skin Cancer (NMSC)	Non-Melanoma Skin Cancer LMQ	"Skin Neoplasms, Malignant and Unspecified" And Add the Preferred Terms. "Squamous Cell Carcinoma" and "Bowen's Disease" to this Search.

AESI	LMQ Name	LMQ Search Term Definition
Malignancies (continued)		
Melanoma	Melanoma LMQ	The most common skin cancers are basal cell carcinoma and squamous cell carcinoma, but this category includes malignancies arising from other types of skin cells (e.g., Merkel cell carcinoma) and appendegeal cells (e.g., eccrine carcinoma).
Leukaemia	Leukemia LMQ	Terms for Lymphoid leukemia (e.g., Acute lymphoblastic leukemia, ALL, Chronic lymphocytic leukemia, CLL). Terms for Myeloid leukemia (e.g., Acute myeloblastic leukemia, AML, Chronic myeloid leukemia, CML, Myeloid sarcoma). Terms for Monocytic leukemia (e.g., Acute monoblastic leukemia, Acute monocytic leukemia, AML, Chronic myelomonocytic leukemia). Terms for Other leukemia s of specified cell type (e.g., Acute erythroid leukemia). Terms for Leukemia of unspecified cell type. Terms for Leukemia in remission.
Other Malignancies Except Lymphoma, HSTCL, Leukemia, NMSC, and Melanoma		If an AE is identified as a "malignancy" in the "Malignancies LMQ" search above but not a "Lymphoma," "HSTCL," "Leukemia," "NMSC," or a "Melanoma," then it belongs to "Other Malignancies" category.
Immune Reactions		
Allergic Reactions Including Angioedema/ Anaphylaxis	Allergic Reactions LMQ	Any terms representing events which include anaphylaxis, allergic events, hypersensitivity, angioedema, angioneurotic edema, urticarial (hives).
Lupus-Like Reactions and Systemic Lupus Erythematosus (SLE)	Lupus-Like Reactions and Systemic Lupus Erythematosus (SLE) LMQ	Lupus erythematosus and associated conditions in both primary and secondary locations in this are included except Lupoid hepatic cirrhosis, which is excluded. Additional terms representing the diagnostic criteria of the American College of Rheumatology (ACR), e.g., Malar rash, Arthritis, Renal disorder, etc.

AESI	LMQ Name	LMQ Search Term Definition
Immune Reactions (continued)		
Vasculitis	Vasculitis LMQ	Terms for primary vasculitides (e.g., Henoch-Schonlein purpura, Behçet's syndrome, or Granulomatosis with polyangiitis (which includes Wegener's granulomatosis). Terms containing vasculitis (e.g., Cutaneous vasculitis, Lupus vasculitis, or Rheumatoid vasculitis). Terms containing arteritis (e.g., Arteritis coronary or Polyarteritis nodosa). Terms containing angiitis (e.g., Microscopic polyangiitis or Thromboangiitis obliterans). Terms for forms of purpura indicative of a vascular condition such as Henoch Schonlein purpura and Chronic pigmented purpura (narrow, which includes Majocchi's purpura) and Palpable purpura (broad). Terms for laboratory test results that may indicate vasculitis (e.g., Antineutrophil cytoplasmic antibody increased).
Cutaneous Vasculitis	Cutaneous Vasculitis LMQ	Terms for vasculitides clearly identifiable as cutaneous (e.g., Cutaneous vasculitis, Skin vasculitis, Majocchi's purpura, Leukocytoclasitc, vasculitis, vasculitis legs, Necrotizing vasculitis, polyangiitis or Vasculitic rash).
Non-Cutaneous Vasculitis		Terms for vasculitides that are NOT in Cutaneous Vasculitis LMQ.
Sarcoidosis	Sarcoidosis LMQ	Sarcoidosis of any organ.
Autoimmune Hepatitis	Autoimmune Hepatitis LMQ	
Cardiovascular/Vascular		
Myocardial Infarction	Myocardial Infarction LMQ	Myocardial Infarction. Terms which included the words 'myocardial infarction, heart attack, cardiac enzymes increased, cardiac troponin increased, CK-MB increased, ECG ST elevation, Q wave abnormal.'
Cerebrovascular Accident	Cerebrovascular Accident LMQ	Terms for conditions specific for cerebrovascular accident disorders irrespective of cause and irrespective of acuteness or chronicity.
Congestive Heart Failure	Congestive Heart Failure LMQ	Terms describing existing cardiac failure in its various forms with or without right/left ventricular specified. A small number of terms for symptoms, signs and investigational findings that are pathognomonic of the condition.
Pulmonary Embolism	Pulmonary Embolism LMQ	Terms that are specifically assigned to describe the condition where an embolic event occurred in the lung of a patient, chronic or acute, arterial or venous.

AESI	LMQ Name	LMQ Search Term Definition
Respiratory		
Interstitial Lung Disease	Interstitial Lung Disease LMQ	ILDs include inflammatory and fibrotic diseases that ultimately disrupt the alveolar capillary interface, leading to hypoxemia. ILDs usually manifest with a restrictive physiology, but airway involvement can cause obstruction or mixed physiology. ILDs are associated with many clinical settings, including connective tissue disease; occupational, environmental and drug exposures; and primary pulmonary disorders.
Gastrointestinal Events		
Intestinal Perforation	Intestinal Perforation LMQ	Terms for/related to any part of GI Tract, GI ulcers, obstruction, hemorrhage.
Intestinal Stricture in CD[a]	Intestinal Stricture LMQ	Abdominal Pain. Radiographic Findings: Bowl loop distension, gas-fluid level, bowel wall thickening.
Pancreatitis	Pancreatitis LMQ	Terms with the word "pancreatitis" (other than those indicative of chronic conditions). Terms indicative of pancreatic dysfunction (such as pancreatorenal syndrome). Terms for typical complications, e.g., Pancreatic pseudocyst.
Skin and Subcutaneous Tissue Disorders		
Stevens-Johnson Syndrome	Severe Skin Reaction Stevens-Johnson Syndrome LMQ	This falls within the erythema multiforme-toxic epidermal necrolysis spectrum, representing an intermediate severity. All terms and their synonyms specifically linked to erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis are included. No procedure terms or appropriate investigation terms are specific.
Erythema Multiforme	Erythema Multiforme LMQ	Diagnosis terms that represent the condition Erythema Multiforme are included. Terms that represent the signs/symptoms that are specific for Erythema Multiforme and included in the criteria for the diagnosis of Erythema Multiforme are included.
Worsening and New Onset of Psoriasis	Worsening New Onset of Psoriasis LMQ	Psoriasis can present in guttate form, where the lesions are smaller, or involve flexural parts of the body (e.g., axilla, inframammary areas), or involve fingernails or toenails (i.e., nail psoriasis), or involve palms or soles. In pustular psoriasis, the presentation is characterized by sterile pustules on a brightly erythematous base. When pustular psoriasis involves the palms and soles, it is termed palmoplantar pustulosis. Other variants of psoriasis include psoriasiform dermatitis and acrodermatitis continua.

AESI	LMQ Name	LMQ Search Term Definition
Nervous System Disorder		
Demyelinating Disorders Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis and Others	Demyelinating Disorders LMQ	Terms for encephalomyelitis and leukoencephalopathies related to demyelination (e.g., Acute haemorrhagic leukoencephalitis and Progressive multifocal leukoencephalopathy). Trigeminal neuralgia is included in broad terms due to possible association with multiple sclerosis or other demyelinating conditions. Terms representing a disability scale which is highly specific for MS (e.g., Expanded disability status scale score increased).
Amyotrophic Lateral Sclerosis	Amyotrophic Lateral Sclerosis LMQ	There are no specific tests to provide a definite diagnosis of ALS although the presence of upper and lower motor neuron signs in a single limb is strongly suggestive. The diagnosis is based on symptoms and signs as well as a series of tests to assess muscle weakness and atrophy, hyperreflexia, and spasticity which gets progressively worse. For these reasons the search terms recommended for adjudication purposes would need to be consistent with the diagnosis of ALS and not with non-specific findings describing all the different types of motor neuron diseases. Patients may exhibit symptoms and signs of the disease such as hyperreflexia, and spasticity. Tests such as muscle biopsy, nerve conduction velocity, electromyography as well as MRI scans of the brain or spinal cord may also point to a possible diagnosis of ALS although none of these tests are definitive and will therefore not be included in the search.
Amyotrophic Lateral Sclerosis (continued)		ALS-related syndromes include progressive muscular atrophy, primary lateral sclerosis and progressive bulbar palsy will be included in the search.
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	Reversible Posterior Leukoencephalopathy Sydrome (RPLS) LMQ	Reversible Posterior Leukoencephalopathy Syndrome definitive diagnosis. Posterior Reversible Encephalopathy Syndrome definitive diagnosis.
Hematologic Events		
Hematologic Disorders Including Pancytopenia	Hematologic Disorders Including Pancytopenia LMQ	Terms referring to direct alterations of the hematopoiesis. Hematological signs and diagnoses of bone marrow depression. Hematological investigation results of bone marrow depression. Neonatal terms are included in the broad search (the term neonatal does not allow a conclusion whether the condition is of acquired or inherited origin). Certain abnormal terms are included in the broad searches.

AESI	LMQ Name	LMQ Search Term Definition
Hepatic Events		
Liver Failure and Other Liver Events (Except Gall Bladder Related Events)	Liver Events LMQ	Terms representing liver related diagnoses or diagnoses that can be related histological descriptions. Also included are conditions associated with jaundice or cholestasis of possible hepatic origin and therefore excludes terms indicating jaundice caused by haemolytic conditions, such as Jaundice extrahepatic obstructive. Diagnoses associated with pregnancy are included.
Other		
Humira Administration Related Medication Error	Medication Errors LMQ	Medication errors. Product Quality Issues. Terms which included the words Medication errors that relates to 'adalimumab use.'
Injection Site Reactions	Injection Site Reaction LMQ	Terms in the Injection Site Reactions, Infusion Site Reactions, Vaccination Site Reactions. Terms which included the words injection site, infusion site, application site, administration site, and 'vaccination site.' The search is focused on local reactions to injections.

a. In CD program only. Any calculation of AE incident rate will only include patients in the CD program.

10.0 References

1. Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2015;75(3):499-510.
2. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015;386(10012):2489-98.
3. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis. 2010;69(1):48-53.
4. Coates LC. Treating to target in psoriatic arthritis. Curr Opin Rheumatol. 2015;27(2):107-10.
5. Greenland S, Rothman KJ. Introduction to stratified analysis. In Rothman KJ, Greeland S, Lash TL, editors. Modern Epidemiology, 3rd Edition. Philaphdelphia: Lippincott Williams & Wilkins; 2008.
6. Liu GF, Wang J, Liu K, et al. Confidence intervals for an exposure adjusted incidence rate difference with application to clinical trials. Stat Med. 2006;25(8):1275-86.