1.0 Title Page

Statistical Analysis Plan

Study W14-406

Concomitant Longitudinal Evaluation of Adalimumab with Methotrexate in the Real World: the CLEAR Study

Date: 29 March 2017

Version 1.0

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3.0 Introduction

This analysis plan describes the statistical analyses to be completed for Study Protocol W14-406 dated 22 April 2016, which incorporates protocol Amendments 1 and 2.

This statistical analysis plan (SAP) provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work. Pharmacokinetics analysis will be described in separate documents.

The SAP will be signed off before the study database is locked. Analyses will be performed using SAS® version 9.4 (SAS Institute, Inc., Cary, NC 27513) or higher on a Hewlett Packard workstation using the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective of this study is to determine the proportion of primary and secondary sub-optimal responders to adalimumab (ADA) monotherapy (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on investigator assessment) with a PGA $\geq$ 3 and a PASI $\geq$ 5 who have a satisfactory response (defined as highly or completely satisfied with subject's therapy using the satisfaction questionnaire) after 16 weeks of treatment with adalimumab and methotrexate (ADA/MTX) combination therapy, based on investigator and subject satisfaction assessments.

The secondary objective of this study includes:

- To determine the proportion of primary and secondary sub-optimal responders to ADA monotherapy (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on investigator assessment) with a PGA $\geq$ 3 and a PASI $\geq$ 5 who reach PASI 50, PASI 75 and PASI 90 16 weeks after initiation of ADA/MTX combination therapy.

- To define the demographic and clinical profile of subjects benefiting from ADA/MTX combination therapy.
- To determine the magnitude, timing, and maintenance of the benefit of adding MTX to ADA by assessing investigator/subject satisfaction with treatment, PGA, PASI, and Dermatology Life Quality Index (DLQI) at 8, 16, and 24 weeks after addition of MTX to therapy.
- To determine change in DLQI from baseline in subjects initiated on ADA/MTX treatment.
- To determine change in serum levels of ADA following addition of MTX and to characterize a possible correlation with changes in investigator/subject satisfaction with treatment, PGA, PASI and DLQI over the study period. Serum levels will be evaluated at baseline (initiation of ADA/MTX) and at Weeks 8, 16 and 24.

4.2 Design Diagram

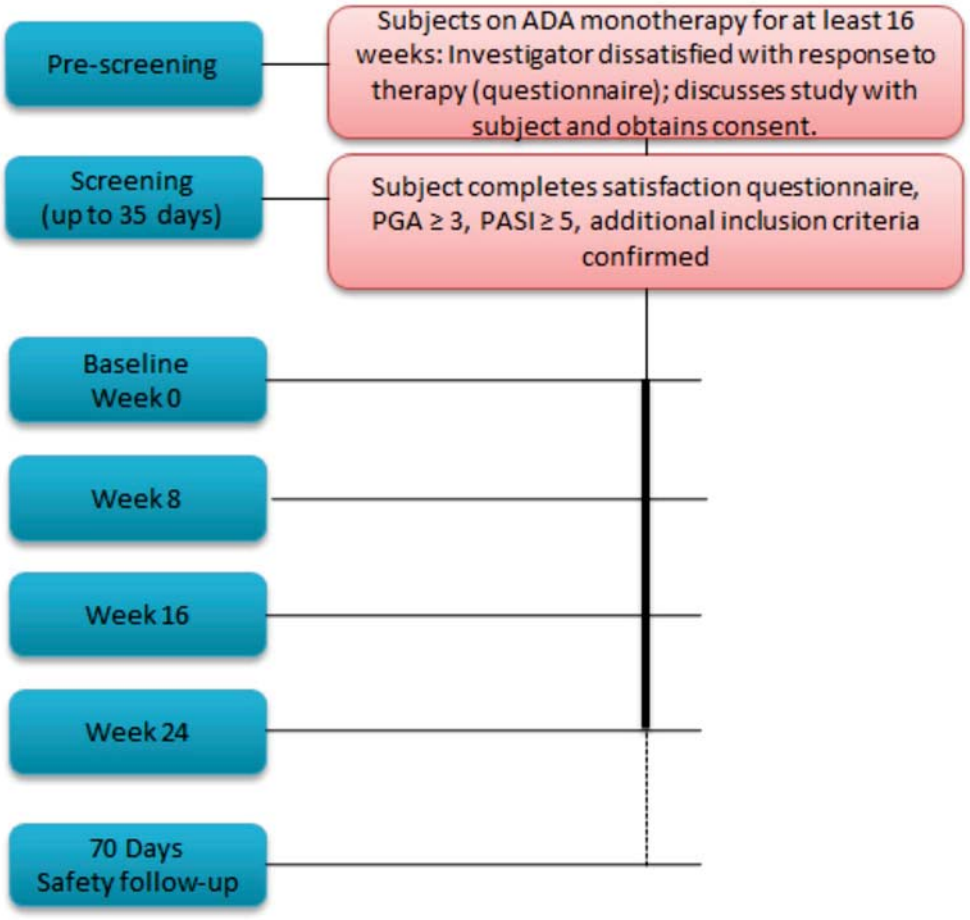
This is a multicenter, single arm, open label longitudinal study. The study entails a screening period up to 35 days, a 24-week treatment period and a 70-day safety follow-up period.

At screening, subjects who provide written consent will complete a satisfaction questionnaire. PGA and PASI will be determined, and inclusion/exclusion criteria will be assessed. Data collected at a screening visit will include: subject demographics, disease history, vital signs, laboratory investigations and PGA, PASI and DLQI scores.

A 24-week single arm, open label treatment period during which subjects are treated by ADA/MTX. Starting at the baseline visit (Day 0), subjects will continue to self-administer ADA (40 mg eow) and will have oral MTX added to their treatment at a dose to be defined by the investigator (between 10 mg and 25 mg per week). All subjects will also receive the non-investigational medicinal product oral folic acid as a dietary supplement since MTX acts as a folic acid antagonist. The folic acid tablets will be provided by the investigator at a dose of 1.0 mg per day. The required folic acid dose

must be taken every day of the week except on the day when MTX is taken. The investigator will provide specific instructions on the number of folic acid tablets each subject should take. At site Visits 8, 16 and 24 weeks after initiation of ADA/MTX, the following parameters will be assessed: investigator assessment of disease status (using a satisfaction questionnaire); subject self-assessment of disease status (using a satisfaction questionnaire); PGA; PASI; DLQI; AEs; serum levels of ADA. A schematic of the study design is shown in Figure 1:

Figure 1. Study Design Schematic



The 70-day safety follow-up period begins from the last dose of ADA, except those subjects that continue on ADA therapy after the end of study participation. Subjects will be discontinued from the study if they withdraw consent or if they are deemed unsuitable to continue for any reason by the investigator in consultation with the AbbVie Medical Monitor.

4.3 Sample Size

This study was planned to have a 30 month recruitment period where it was anticipated that approximately 200 subjects will be recruited. With this sample size the proportion of responders, defined as the proportion of subjects with a highly or completely satisfied response after 16 weeks of ADA/MTX therapy, based on an investigator assessment and subject self-assessment, can be estimated within ± 4.9% with 95% confidence when the point estimate is 15%, within ± 6.4% with 95% confidence when the point estimate is 30%, or within ± 6.9% with 95% confidence when the point estimate is 50%. Additional accuracy estimates are provided in the table below.

Table 1. Accuracy Estimates with a Sample Size of 200 Subjects

Estimated Proportion of Responders (%)	Accuracy Estimate (%)
5	3.0
10	4.2
15	4.9
20	5.5
25	6.0
30	6.4
35	6.6
40	6.8
45	6.9
50	6.9

Note: Proportion of responders can be estimated with ± accuracy with 95% confidence. The size of the 95% Confidence Interval would be 2× Accuracy.

Due to the enrollment plan change (enroll 50 patients or as the number of enrollment by 31 December 2016), updated accuracy estimates with a sample size of 50 subjects, about the proportion of subjects with a highly or completely satisfied response after 16 weeks of ADA/MTX therapy based on an investigator assessment and subject self-assessment, are provided in the table below.

Table 2. Accuracy Estimates with a Sample Size of 50 Subjects

Estimated Proportion of Responders (%)	Accuracy Estimate (%)
5	6.0
10	8.3
15	9.9
20	11.1
25	12.0
30	12.7
35	13.2
40	13.6
45	13.8
50	13.9

Note: Proportion of responders can be estimated with ± accuracy with 95% confidence. The size of the 95% Confidence Interval would be 2× Accuracy.

4.4 Interim Analysis

No interim analysis is planned for this study.

5.0 Analysis Populations

5.1 Definition of Analysis Populations

Intent-to-Treat (ITT) Populations

The Intent-to-Treat population will be used for all efficacy analyses, which is defined as all subjects who receive at least one dose of study ADA and at least one dose of MTX during the study.

The primary efficacy analyses will also be conducted for the following sub-populations:

- ITT Subjects who are defined as primary sub-optimal responders at baseline based on Investigator assessment.
- ITT Subjects who are defined as secondary sub-optimal responders at baseline based on Investigator assessment.

Safety Populations

The Safety Population will be used for all safety analysis, which is defined as all subjects who received at least one dose of study ADA and one dose of MTX during the study. In this study, the safety population is the same as the ITT Population.

Notations for Treatment Groups

- ADA/MTX: Subjects who received ADA and MTX as study drugs.

6.0 Analysis Conventions

6.1 Definition of Baseline

The last non-missing measurement collected on or before the maximum date of either the first dose of ADA or the first dose of MTX will be used as baseline for the summary of demographics and disease characteristics, the safety analyses, and the efficacy analyses.

6.2 Definition of Final Observation

Final observation is defined as the last non-missing observation collected within 70 days following the last dose of study ADA.

6.3 Definition of Rx Days (Days Relative to the First Dose of Study Drug)

We define the maximum date of either the first dose of study ADA or the first dose of MTX during the study as Rx Day 1 (RxDY 1). Other Rx days (RxDY) are calculated for each time point as the number of days between Rx Day 1 and the specific time point. Rx

days are positive values when the time point of interest is after Rx Day 1. Rx days are negative values when the time point of interest is prior to Rx Day 1. For example, the day prior to Rx Day 1 is defined as Rx Day –1 (there is no Rx Day 0). Rx days will be calculated and displayed in all presentations of data in listing format.

6.4 Definition of Analysis Windows and Data Handling Conventions

All time points and corresponding time windows are defined based on Rx Days.

For visit-wise efficacy analyses, analysis time windows are constructed using the following algorithm:

1. Determine the nominal Rx day for each scheduled visit (e.g., Week 8 [8 weeks after baseline visit] equals Rx Day 57);
2. Determine the window around a specific nominal Rx day by adding or subtracting half of the interval between adjacent scheduled visits (e.g., days between Baseline and Week 8 is 56). The threshold between adjacent scheduled visits is determined by splitting the interval evenly between the visits.
3. If more than one assessment is included in a time window the assessment closest to the nominal day will be used. If there are two observations equidistant to the nominal day, the latest one will be used in analyses. If more than one assessment is included on the same day, then the worst assessment on that day will be used in analyses.
4. If a subject does not have an assessment in a particular visit window due to the inability to follow the visit schedule, but has assessments in the same study period both before and after the visit window, then the worst of the two will be used for the visit. Of note, this convention will be applied to the non-responder imputation method only.

Analysis windows have been specified for the analysis of efficacy, laboratory parameters, study drug injections and vital signs for efficacy and safety populations in Table 3, Table 4, Table 5 and Table 6. In order to include all post baseline data, the first post baseline interval starts on the day after the date of first study drug injection in each period (Rx Day 2) for all efficacy variables.

Table 3. Windows for High-Sensitivity C-Reactive Protein (hs-CRP; Safety Population)

Scheduled Week	Nominal Day (Rx Day)	Interval
Baseline	1	≤ 1
Week 24	169	2 ~ 337[a]

a. Minimum of Rx Day 337 and 70 days after the last dose of study ADA.

Rx day relative to the maximum date of either the first dose of study ADA or the first dose of MTX during the study.

Table 4. Windows for All Other Efficacy and Safety Analyses (ITT/Safety Populations)

Scheduled Week	Nominal Day (Rx Day)	Interval
Baseline	1	≤ 1
Week 8	57	2 ~ 85
Week 16	113	86 ~ 141
Week 24	169	142 ~ 197[a]

a. Minimum of Rx Day 197 and 70 days after the last dose of study ADA.

Rx day relative to the maximum date of either the first dose of study ADA or the first dose of MTX during the study.

Table 5. Windows for ADA Injection (Safety Population)

Scheduled Week	Nominal Day (Rx Day)	Interval
Baseline	1	≤ 1
Week 2	15	2 ~ 22
Week 4	29	23 ~ 36
Week 6	43	37 ~ 50
…	…	…
Week K	K × 7 + 1	K × 7 – 5 ~ K × 7 + 8
Week 22	155	149 ~ 162

Rx day relative to the first dose date of study ADA during the study.

Table 6. Windows for MTX Administration (Safety Population)

Scheduled Week	Nominal Day (Rx Day)	Interval
Baseline	1	≤ 1
Week 1	8	2 ~ 11
Week 2	15	12 ~ 18
Week 3	22	19 ~ 25
…	…	…
Week K	K × 7 + 1	K × 7 – 2 ~ K × 7 + 4
Week 23	162	159 ~ 165

Rx day relative to the first dose date of MTX during the study.

6.5 Missing Data Imputation

No global imputation is taking place at the database level. Efficacy and safety related imputations, as applicable, are outlined in Section 10.1 and Section 11.1, respectively.

6.6 Rounding of Numeric Results

Rounding will be performed for presentation of results. No rounding will be performed before or during analyses.

The mean and median will be rounded for presentation to 1 decimal more than the data were entered into the database. The standard deviation will be rounded to 2 decimal

places more than the data that were entered into the database. The minimum and maximum values will be presented as entered into the database.

Probabilities will be rounded to 3 decimal places before assignment of statistical significance and will be presented in rounded format. Probabilities that round to zero or are reported by SAS as zero will be presented as "< 0.001."

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

7.1 Demographic and Baseline Characteristics

All demographic and baseline variables will be described with summary statistics. Categorical data will be summarized using the frequency and percentage; continuous data will be summarized using the mean, standard deviation, median, first quartile, third quartile, minimum, and maximum. The number of non-missing values will also be summarized.

All summaries will be presented for the ITT Population. No statistical tests will be performed.

The following demographic and baseline parameters will be summarized.

Demographic

- Sex [male, female]
- Age [years]
- Age category [< 40, 40 – 64, ≥ 65]
- Body weight [kg] – overall and by gender
- Height [cm]
- Body mass index [kg/m^2]
- BMI Category [< 25 , 25 – < 30, ≥ 30]
- Race
- Ethnicity

Tobacco/Nicotine and Alcohol Use

- Tobacco/Nicotine Use [current, former, never, unknown]
- Alcohol Use [current, former, never, unknown]

Baseline Characteristics

- Duration of Ps: The duration of Ps will be calculated relative to the date of screening visit (i.e., duration = [date of screening visit – date of onset] + 1. Duration of Ps will be expressed in years, by dividing the result in days by 365.25.
- Psoriatic arthritis (PsA) status [yes, no]
- Duration of Psoriatic arthritis (PsA): The duration of PsA will be calculated relative to the date of screening visit (i.e., duration = [date of screening visit – date of onset] + 1. Duration of PsA will be expressed in years, by dividing the result in days by 365.25.
- Family history of psoriasis [yes, no]

Baseline Characteristics – Efficacy Assessments

- Psoriasis Area and Severity Index (PASI)
- Physician's Global Assessment of Skin Psoriasis (PGA-S)
- Dermatology Life Quality Index (DLQI)
- Body Surface Area affected by Psoriasis (BSA)
- Satisfaction Questionnaire – Investigator
- Satisfaction Questionnaire – Subject
- Hi-sensitivity C-reactive Protein (hs-CRP)

Vital Signs

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse (bpm)

- Respiratory rate (rpm)
- Body temperature (°C)
- ECG (Normal, Abnormal – not clinically significant, Abnormal – clinically significant, Unable to evaluate)

Chest X-Ray, TB Test and BCG Vaccination History

- Chest x-ray (Normal, Abnormal, Missing)
- Calcified granulomas (Absent, Present, Missing)
- Pleural scarring (Absent, Present, Missing)
- Pleural thickening (Absent, Present, Missing)
- Signs of active TB (No, Yes, Missing)
- PPD TB test (< 5 mm, ≥ 5 mm, missing)
- Quantiferon TB test (Negative, Indeterminate, Positive, Missing)
- Enrolled on TB Prophylaxis (No, Yes, Missing)
- TB History – at higher risk (No, Yes, Missing)
- BCG immunization (No, Yes, Unknown)
- Active or latent TB (No, Yes, Missing)

The following variables will be presented in listing format:

- Physical Examination
- Pregnancy Test

7.2 Medical History

Medical history will be summarized using body systems and condition/diagnosis as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Prior Treatment and Concomitant Medications

The number and percent of subjects who received a prior or concomitant medication will be tabulated by the generic name assigned by the World Health Organization (WHO) Dictionary.

A prior medication is defined as any medication taken prior to the maximum date of either the first dose of study ADA or the first dose of MTX during the study. A concomitant medication is defined as any medication that started prior to the aforementioned date and continued to be taken after the maximum date of either the first dose of study ADA or the first dose of MTX or any medication that started on or after the date of the first dose of study drug, but not after the last study ADA dose date during the study.

Prior Ps treatment received and discontinued (including reason for discontinuation) prior to screening will be summarized as well.

7.4 Protocol Deviation

Number and percentage of subjects who reported at least 1 of the following protocol deviation categories will be provided:

- Inclusion/exclusion criteria deviations
- Developed withdrawal criteria but was not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment

7.5 Inclusion/Exclusion Criteria

Number and percentage of subjects who did not meet inclusion/exclusion criteria will be reported.

8.0 Patient Disposition

The summary of subject disposition for the ITT Population will include:

- Number of subjects in the ITT population
- Number and percentage of subjects who complete the entire study
- Number and percentage of subjects who prematurely discontinue from study
- Number and percentage of subjects who remain on ADA/MTX combo after completion from study
- Number and percentage of subjects who remain ADA only after completion from study

In addition, the reasons for premature discontinuation (primary reason and all reasons) will be summarized with frequencies and percentages. Subjects with multiple reasons for premature discontinuation will be counted once in the calculation of the number and percentage of total discontinuations ("Premature Discontinuation").

9.0 Study Drug Exposure and Compliance

Summary of study drug exposure and compliance will be provided.

The study drug exposure (days) will be summarized with the mean, standard deviation, minimum, first quartile, median, third quartile and maximum, for ADA and for MTX. Study drug exposure will be summarized as follows.

Study Drug Exposure (in Days) for ADA:

- Date of last study ADA injection – Date of first study ADA injection + 14 days.

Study Drug Exposure (in Days) for MTX:

- Date of last dose of MTX – Date of first dose of MTX + 7 days.

Compliance (%), which is defined as the number of injections received divided by the number of injections planned for ADA, and as the doses received divided by the doses planned for MTX, during the subject's participation in the study (rounded to 0.1%), will be summarized separately. In addition, at each scheduled time point, the number of ADA

injections and MTX doses received and compliance will be summarized with frequencies and percentages.

When computing compliance at each scheduled time point, the denominator for each week will include all subjects in each analysis population who have not prematurely discontinued prior to the scheduled study drug injection. The date of prematurely discontinuation will be taken from vital sign dataset.

10.0 Efficacy Analysis

10.1 General Considerations

Point estimates and 95% confidence intervals (CIs) based on normal approximation will be provided for the discrete efficacy variables such as the proportion of responders to ADA/MTX. Change and percent change from baseline variables will be estimated using an appropriate estimation from a Mixed Model and statistical tests of change from baseline equal to zero will be carried out at the 0.05 significance level; 95% confidence intervals will also be provided.

Descriptive statistics will be provided. These include the number of observations, mean, and standard deviation for continuous variables and counts and percentages for discrete variables. Baseline and visit means at each scheduled visit will also be provided for change and percent change from baseline continuous variables.

Missing data will be imputed using the following methods for the efficacy analyses:

- Non-Responder Imputation (NRI): The NRI analysis will categorize any subject who has missing value at a specific visit as non-responder (or "dissatisfied" in satisfaction variables) for that visit. NRI will be the primary approach in analyses of categorical variables.
- Mixed-effect Model Repeat Measurement (MMRM): A mixed-effect model will be developed for continuous endpoint repeated measured at Baseline, Week 8, 16, and 24; controlling for time and subject ID. The fixed effects will be used to report the visit means at corresponding visits. Change and percent

change from baseline will be determined accordingly. MMRM will be the primary approach in analyses of continuous variables.

- Last Observation Carried Forward (LOCF): The LOCF analyses will use the completed evaluation from the previous visit to impute missing data at later visits. Baseline efficacy evaluations will not be carried forward. LOCF will be a sensitivity approach in analyses of continuous variables and categorical variables.

All efficacy variables will be analyzed for the ITT population overall, and separately by primary sub-optimal responders and secondary sub-optimal responders at baseline.

10.2 Efficacy Variables

10.2.1 Primary Efficacy Variable

The primary efficacy endpoints will be:

- Based on investigator assessment, the proportion of subjects achieving a satisfactory response at Week 16 (satisfactory response is defined as highly or completely satisfied with therapy based on responses to the satisfaction questionnaire).
- Based on subject self-assessment, the proportion of subjects achieving a satisfactory response at Week 16 (satisfactory response defined as highly or completely satisfied with therapy based on responses to the satisfaction questionnaire).

10.2.2 Secondary Efficacy Variables

Secondary efficacy variables included:

- Based on investigator assessment, the proportion of subjects achieving a satisfactory response at scheduled visits other than Week 16
- Based on subject self-assessment, the proportion of subjects achieving a satisfactory response at scheduled visits other than Week 16
- Proportion of subjects achieving PASI 50/75/90/100 at all scheduled visits

- Change and percent change from baseline in PASI at all scheduled visits.
- Proportion of subjects achieving a clinical response defined as a PGA of "Clear" or "Minimal" at all scheduled visits
- Change and percent change from baseline in DLQI at all scheduled visits
- Based on investigator assessment, the proportion of subjects at each of the five categories of satisfaction at all scheduled visits
- Based on subject self-assessment, the proportion of subjects at each of the five categories of satisfaction at all scheduled visits
- Proportion of subjects achieving a DLQI score of 0 or 1 at all scheduled visits
- Change and percent change from baseline in BSA at all scheduled visits.
- Change from baseline in hs-CRP at all scheduled visits.

10.3 Handling of Multiplicity

No multiplicity adjustment will be applied to the efficacy analyses.

10.4 Efficacy Subgroup Analyses

PASI 50/75/90/100 endpoints will also be analyzed in the following subgroup:

- Subjects on ADA 40 mg eow prior to baseline or 40 mg once weekly prior to wash-out.

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will include reporting of adverse events, laboratory, and vital sign measurements. Safety analyses with group comparison will be carried out using the Safety Population.

Mean changes from baseline in all continuous laboratory parameters and vital signs variables to post-baseline visits will be summarized for the Safety Population. No

statistical tests will be applied. The number of non-missing values will be given. Missing safety data will not be imputed.

11.2 Analysis of Adverse Events

Treatment-emergent adverse events (TEAEs) will be tabulated.

Adverse events that start more than 70 days after the last study ADA injection during the study will not be included in the summaries; however, if reported, these adverse events will be included in the adverse event data listings. A summary of all pretreatment (i.e., event start date is prior to the date of the first study drug injection) serious adverse events will be provided. Adverse events will be summarized by patient year as well.

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAE) are defined as following:

TEAEs are defined as any event with an onset date that is on or after the maximum date of either the first dose of study ADA or the first dose of MTX and no more than 70 days after the last study ADA injection during the study.

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

Adverse event data will be summarized and presented using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) system organ class (SOCs) and preferred terms (PTs).

11.2.1.1 Adverse Event Overview

The number and percentage of subjects experiencing TEAEs will be summarized for the following AE categories:

- Any AE

- Any AE with a Reasonable Possibility of being related to study drug by the investigator
- Any severe AE
- Any serious AE
- Any serious AE with a Reasonable Possibility of being related to study drug by the investigator
- Any AE leading to discontinuation of study drug
- Any AE of special interest
- Any AE Leading to Death
- Any Deaths

Additional AEs may be considered for tabulation/summary based on recommendations for Clinical and Safety as deemed appropriate. Any event with an unknown severity will be considered as severe and any AE with an unknown relationship will be considered as drug-related.

11.2.1.2 Adverse Events by System Organ Class and Preferred Term

TEAEs will be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA version 16.1 or later version) system organ classes (SOCs) and preferred terms (PTs). The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

A subject who reports more than 1 AE in different SOCs will be counted only once in the overall total. A subject who reports more than 1 AE in different PTs, which are in the same SOC, will be counted only once in the SOC total. A subject who reports more than 1 AE with the same PT will be counted only once for that PT using the most extreme incident (i.e., most severe for the severity tables and most related for the relationship tables).

11.2.1.3 Adverse Events by Maximum Severity

TEAEs will also be summarized by maximum severity. If a subject has an adverse event with 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 if the subject has another occurrence of the same adverse event with the most extreme severity "Severe." In this case, the subject will be counted under the "Severe" category.

11.2.1.4 Adverse Events by Maximum Relationship

TEAEs will also be summarized by maximum relationship to study drug, as assessed by the investigator. If a subject has an adverse event with 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 adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

11.2.1.5 Adverse Events by "Reasonable Possibility" of Being Related to Study Drug

TEAEs will also be summarized by relationship defined by "Reasonable Possibility" of being related to study drug, as assessed by the investigator. If a subject has an AE with an unknown relationship, then the subject will be counted in as with "Reasonable Possibility."

11.2.1.6 Serious Adverse Events (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.

11.2.1.7 Adverse Events of Special Interests

The Adverse Events of Special Interests (AESI) categories following the most updated PSAP will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs).

11.2.1.8 Adverse Events by 100 Patient Years

TEAEs will be summarized by event rate per 100 patient years, defined as

$$100 \times \frac{\text{Number of TEAEs}}{\text{Total Patient Years}},$$

where total patient years is defined as the sum of the study drug exposure of all subjects normalized by 365.25, and rounded to one decimal place.

11.3 Analysis of Laboratory Data

11.3.1 Variables and Criteria Defining Abnormality

Clinical laboratory tests conducted in the study are listed in the table below. Laboratory parameters will be reported using the standard international (SI) units.

Note: For urinalysis, only specific gravity and pH will be summarized.

Table 7. Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis	Quantiferon TB Gold	Other
Albumin Alkaline Phosphatase ALT AST Calcium Cholesterol Creatinine Enzymatic Glucose, Random, Serum Phosphate Potassium Sodium Total Bilirubin Total Protein Triglycerides Urea (BUN) Uric Acid	Basophils Eosinophils HCT HGB Lymphocytes Monocytes Neutrophils Platelets RBC WBC	Blood Glucose, Urine Ketones Leukocytes Nitrite pH Protein, Urine Specific Gravity Urine Microscopic	Quantifeton Mit. Minus NIL Quantiferon NIL Quantiferon TB Gold Quantiferon TB minus NIL	ANA Pattern Anti-ds DNA Antinuclear Antibody Hs-CRP HBV DNA PCR Taqman HCG, Quantitative

11.3.2 Statistical Methods

11.3.2.1 Analysis for Continuous Laboratory Data

Mean changes from baseline to post-baseline visits and to the final visit will be summarized with the baseline mean, the visit mean, change from baseline mean, standard deviation, and median.

11.3.2.2 Shift Table Analyses

The laboratory data will be categorized as low, normal, or high based on the normal ranges of the laboratory used in this study. The shift tables will tabulate the number and percentage of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

Shift tables for changes from baseline according to the normal range will be provided for each hematology, clinical chemistry and urinalysis (specific gravity and pH only) parameter. Shifts from baseline to the following endpoints will be considered: minimum value, maximum value and final value. Categories of "low or normal" and "high or normal" will be included at baseline in addition to the categories of "low," "normal," "high" and "missing."

11.3.2.3 Potentially Clinically Significant Laboratory Values

Frequencies and percentages of subjects with post baseline lab values that are Grade 3 or above according to the CTC toxicity criteria will be summarized. A separate listing will be provided that presents all of the subjects and values that are CTC toxicity Grade 3 or above. For each of these subjects, the whole course of the respective parameter will be listed.

Additional summaries will be presented for liver function tests including ALT or serum glutamic-pyruvic transaminase (SGPT), AST or serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, and total bilirubin. Each laboratory value will be categorized as follows:

- $< 1.5 \times$ ULN
- $\geq 1.5 \times$ ULN – $< 3.0 \times$ ULN
- $\geq 3.0 \times$ ULN – $< 5.0 \times$ ULN
- $\geq 5.0 \times$ ULN – $< 8.0 \times$ ULN
- $\geq 8.0 \times$ ULN

where ULN is the upper normal limit.

Shift tables of baseline to the maximum values, and from baseline to final value will be presented using these five categories.

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 four criteria:

- ALT ≥ 2.5 × ULN, or
- AST ≥ 2.5 × ULN, or
- Alkaline phosphatase ≥ 2.5 × ULN, or
- Total bilirubin ≥ 1.5 × ULN

11.4 Analysis of Vital Signs

All analyses will be conducted for subjects in the Safety Population.

11.4.1 Variables and Criteria Defining Abnormality

The following vital sign parameters will be assessed: Systolic blood pressure [mmHg], Diastolic blood pressure [mmHg], Pulse [beats per minute], Respiratory rate [breaths per minute], Body Temperature [°C], Weight [kg]. The following table presents the Criteria for Potentially Clinically Significant Vital Sign Findings.

Table 8. 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/or decrease ≥ 20 mmHg from baseline
	High	Value ≥ 180 mmHg and/or increase ≥ 20 mmHg from baseline
Diastolic Blood Pressure	Low	Value ≤ 50 mmHg and/or decrease ≥ 15 mmHg from baseline
	High	Value ≥ 105 mmHg and/or increase ≥ 15 mmHg from baseline
Pulse	Low	Value ≤ 50 bpm and/or decrease ≥ 15 bpm from baseline
	High	Value ≥ 120 bpm and/or increase ≥ 15 bpm from baseline

11.4.2 Statistical Methods

Mean changes from baseline to post-baseline visits and to the final visit in vital sign parameters will be summarized with the baseline mean, the visit mean, change from baseline mean, standard deviation, median.

Vital signs results satisfying the criteria for potentially clinically significant values will be identified in a listing. For each of these subjects, the whole course of the respective

parameter will be listed. The number and percentage of subjects who have at least one value meeting criteria for potentially clinically significant values will be provided for each selected vital sign parameter.

11.5 Analysis of ECG Parameters

ECG results will be listed in the data listings.

11.6 Analysis for Other Safety Variables

Not applicable.

11.7 Safety Subgroup Analyses

No safety subgroup analyses will be performed.

12.0 Special Statistical Topics

Not applicable.

13.0 List of Tables, Figures and Data Listings that Are to Be Programmed

To be provided in a separate document.

14.0 Summary of Changes

Not applicable now.

Document Approval

Study W14406 - Statistical Analysis Plan Version 1 - 29Mar2017 (E3 16.1.9)

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