1.0 Title Page

Statistical Analysis Plan

Study M14-193

A Multicenter, Open-Label Study of Adalimumab in Japanese Subjects with Generalized Pustular Psoriasis

Incorporating Administrative Change 1,2,3 and 4

Date: 25 Apr 2017

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List of Abbreviations

AAA	Anti-adalimumab Antibody
ADA	Adalimumab
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine Transaminase
ANA	Antinuclear Antibody
AST	Aspartate Transaminase
BCG	Bacillus Calmette-Guérin
BUN	Blood Urea Nitrogen
CDC	Centers for Disease Control and Prevention
CRA	Clinical Research Associate
CRF	Case Report Form
CRP	C-Reactive Protein
dsDNA	Double-stranded Deoxyribonucleic Acid
ECG	Electrocardiogram
EU	European Union
eCRF	Electronic Case Report Form
eow	every other week
ew	every week
FDA	Food and Drug Administration
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMA	Granulocyte and Monocyte absorbent Apheresis
GPP	Generalized Pustular Psoriasis
hs-CRP	high-sensitivity C-Reactive Protein
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
IRB	Institutional Review Board
JDA	Japanese Dermatological Association
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Drug Regulatory Activities

MTX	Methotrexate
NRI	Non-Responder Imputation
PA	Posterior-anterior
PASI	Psoriasis Area and Severity Index
PD	Premature Discontinuation
PGA	Physician's Global Assessment
PK	Pharmacokinetics
POR	Proof of Receipt
PML	Progressive Multifocal Leukoencephalopathy
PPD	Purified Protein Derivative
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SDP	Study Designated Physician
TB	Tuberculosis
TNF	Tumor Necrosis Factor

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by the AbbVie Global Statistics Department for adalimumab study Protocol M14-193 dated 06 April 2017, that incorporates administrative changes 1,2,3, and 4. (original protocol: 08 June 2015). It provides details to further elaborate statistical methods as outlined in the protocol and describes analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS version 9.3 (SAS Institute Inc.) under the UNIX operating system or in the PC environment.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

The primary objective is to investigate efficacy, safety and pharmacokinetics of adalimumab in Japanese subjects with Generalized Pustular Psoriasis (GPP).

4.2 Design Diagram

This study is a 52-week trial. The study will include a 30-day screening period, 52-week open-label active treatment period, and a subsequent 70-day follow-up period after the last dose.

Subjects will be Japanese patients diagnosed as GPP with total skin score of at least 3 and erythema with pustule (skin score of at least 1) in Japan Dermatology Association (JDA) severity index of GPP in GPP Medical Care Guideline 2014.

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be enrolled and treated subcutaneously with adalimumab 80 mg at the Baseline for initial dose and then 40 mg eow on and after Week 2 until Week 50. Dose-escalation to 80 mg eow is allowed if subjects have inadequate response (i.e., minimal improvement, unchanged or worsened) on or after Week 8. Dose reduction is not allowed throughout the study period for the dose-escalated subjects.

The primary efficacy variable is the proportion of subjects achieving Clinical Response (CR) at Week 16. CR is defined as the reduction of skin score of at least 1 (if the subject's Baseline skin score is 3) or at least 2 (if the subject's Baseline skin score is 4 or higher) relative to Baseline, according to JDA severity index of GPP in GPP Medical Care Guideline 2014.

Study visits will occur at Baseline (Week 0), Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52, and at the Premature Discontinuation visit if the subject discontinues prior to Week 52. No open label extension (OLE) study is planned after this 52-week study.

Adverse events will be collected throughout the study. Subjects who complete this study or who decide to withdraw the study participation will have a Day 70 follow-up phone call following their last dose of study drug to determine the status of any ongoing adverse events (AEs) or serious adverse events (SAEs), or the occurrence of any new AEs or SAEs.

Figure 1. Study Schematic

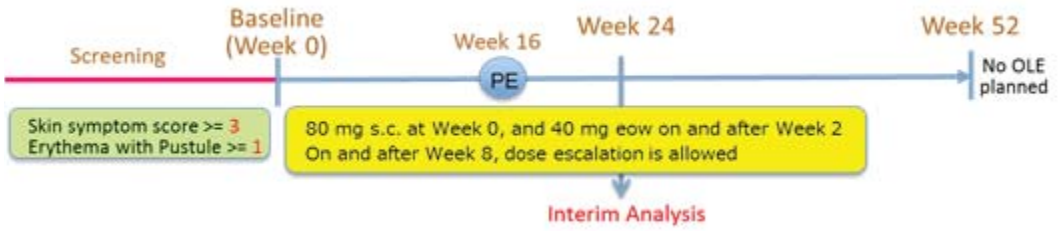

Table 1. Study Activities:

Activity	Screening (Day –30 to Day –1)	Baseline[a] (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call
Informed Consent	X																	
Assign Subject ID Number	X																	
Subject Background	X																	
Inclusion/Exclusion Criteria	X	X[b]																
Medical/Surgical History	X	X[b]																
Prior and Concomitant Therapy Assessment	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Alcohol Use	X																	
Tobacco Use	X																	
Physical Exam[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chest X-Ray[d]/12-Lead ECG[e]	X															X[f]	X[g]	
TB Screening[h]	X																	
Vital Signs	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Tests	X[j]	X[k]														X[k]		
General Labs[l]: Blood Chemistry and Hematology	X	X[m]	X	X	X	X	X		X			X				X	X[s]	

Table 1. Study Activities: (Continued)

Activity	Screening (Day –30 to Day –1)	Baseline[a] (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call
Urinalysis[n]	X	X			X		X		X			X				X		
HIV Screen[o]	X																	
Hepatitis B Screen[p]	X																	
Hepatitis C Screen	X																	
Antinuclear Antibody (ANA)/Anti-Double-Stranded DNA (dsDNA)[q]	X																	
Photography[r]		X	X	X	X	X	X		X			X				X		
GPP Skin Score and BSA, Systemic/Laboratory Score	X	X	X	X	X	X	X		X			X				X	X[s]	
PGA	X	X	X	X	X	X	X		X			X				X	X[s]	
PASI Score	X	X	X	X	X	X	X		X			X				X	X[s]	
DLQI		X			X		X		X			X				X		
SF-36		X			X		X		X			X				X		
Dispense Study Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[s]	
Administer Study Drug[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[s]	
PK Measurements[u]		X	X	X	X	X	X		X			X				X	X[s]	
AAA Measurements[u]		X			X		X		X			X				X	X[s]	

Table 1. Study Activities: (Continued)

Activity	Screening (Day –30 to Day –1)	Baseline[a] (Day 1)	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52 or Premature Discontinuation Visit	Unscheduled Study Visit	70-Day Call
Monitor Adverse Events[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Follow-Up Phone Call																		X[w]

Footnote for Table 1;

a. The Baseline visit date will serve as the reference for all subsequent visits. A ± 7-days window is permitted around scheduled study visits.

b. Update inclusion/exclusion, medical/surgical history, and prior and concomitant therapy information to assure subject eligibility.

c. Physical examinations performed at Screening, Week 24 and Week 52/PD Visits will be full physical examinations. Physical exams performed at all other visits will be symptom-based.

d. Chest x-ray (CXR) includes posterior-anterior [PA] **and** lateral views. Subjects with normal chest x-ray within 90 days of Screening will not require a repeat chest x-ray, if documentation is available.

e. Subjects with normal ECG within 90 days of Screening will not require a repeat ECG, if documentation is available.

f. Subjects will have a repeat CXR or ECG at Week 52 or the appropriate Premature Discontinuation visit, only if in the opinion of the investigator, clinically significant AEs develop during the study that warrant a repeat.

g. Subjects can have a repeat CXR/ECG at any time during the study as warranted based on the opinion of the Investigator.

h. Subjects with negative latent TB test(s) (In case a subject received both a PPD test and IGRA, both must be negative) within 90 days of Screening will not require a repeat latent TB test, if documentation is available. PPD skin test is to be read 48 to 72 hours after placement.

i. Height will be measured at the Screening only.

j. All females of childbearing potential will have a serum pregnancy test at the Screening that is performed at the central laboratory.

Table 1. Study Activities: (Continued)

k. All females of childbearing potential will have a urine pregnancy test at the Baseline and Week 52 or Premature Discontinuation visits at the central laboratory. Any subject with a positive urine pregnancy test must have a negative serum test performed at the central laboratory prior to start of the treatment in the study. Urine pregnancy test at the Baseline will be performed also at site to confirm negative result on site. If the result at site is positive, treatment with study drug should not be started until the serum pregnancy test at the central laboratory is confirmed negative.

l. Subject should be fasting. Please refer to the laboratory manual for further instructions.

m. Laboratory assessments will only need to be repeated at the Baseline if the time between blood sampling for Screening and Baseline is greater than 14 days, or if the subject's health status has changed to warrant a repeat test.

n. Dipstick urinalysis will be conducted by the central laboratory at all required study visits. A microscopic analysis will be performed in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

o. Subjects will be tested for HIV and documented that the test has been performed. This testing is to be done at the central laboratory. A subject will not be eligible for study participation if test results indicate a positive HIV infection. AbbVie will not receive results from the testing and not be made aware of any positive result.

p. Subjects will be tested for the presence of the Hepatitis B Virus (HBV) at Screening. A positive result for the hepatitis B surface antigen (HBs Ag) will be exclusionary. Samples that are negative for HBs Ag will be tested for surface antibodies (HBs Ab) and core antibodies (HBc Ab Total). Subjects with HBs Ag (–), HBs Ab (–), and HBc Ab Total (+) require PCR qualitative testing for HBV DNA. Any HBV DNA PCR result that meets or exceeds detection sensitivity will be exclusionary.

q. Anti-dsDNA will be measured if ANA is positive.

r. Photographs of skin lesion will be taken at the time points above in subjects who agree to do in the pre-selected sites.

s. When dose escalation is decided on unscheduled visit or on any visit when the data collection is not planned, the investigator must assess skin lesion (GPP skin score, BSA, PGA and PASI score), and perform blood sampling for laboratory test and PK/AAA prior to dose escalation. Body temperature will come from Vital Signs. Additional study drug dispense may be necessary, if appropriate.

t. Administration of study drug will be performed after all assessments and examinations scheduled for that day have been completed. Study drug will be administered every other week in the investigator's office or at subject's home after training of self-injection to ensure proper technique.

u. Blood samples for the measurement of adalimumab and AAA concentrations will be collected prior to dosing.

v. All AEs reported from the time of study drug administration until 70 days following discontinuation of study drug administration will be collected. SAEs and protocol-related nonserious AE will be collected from the time the subject signed the study-specific informed consent until 70 days following discontinuation of study drug administration.

w. Site personnel will contact all subjects by phone 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AE/SAEs.

4.3 Sample Size

GPP is designated as the specified rare and intractable disease in Japan and patient number is quite limited. Assuming the Clinical Response rate of adalimumab in GPP is similar to PASI 75 response in plaque psoriasis, 50% to 60% as expected response rate in adlimumab treatment and 10% as a threshold response rate is hypothesized.

A sample size of 6 to 10 provides over 90% power to detect the difference between expected Clinical Response rate (50 to 60%) and threshold response rate (with no medication, 10%) in GPP, using a one sample Chi-square test with 2.5% one-sided significance level. In case of using Fisher's exact test, an exact binomial test with a nominal 0.025 one-sided significance level will have 82% power to detect the difference between the threshold proportion of 10% and the expected proportion of 50%.

Therefore, the target number of subjects is set 10 subjects, taking the study feasibility into consideration.

4.4 Interim Analysis

An interim analysis of the primary endpoint and secondary efficacy variables as well as safety data collected from Baseline through Week 24 will be performed after the last subject in FAS population completes the 24-week period of the study. A database lock will be performed and any discrepant data will be clarified before the lock.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Full Analysis Set:

Full Analysis Set (FAS) population includes all subjects who complied with GCP and received at least one dose of study drug and had at least one post-treatment efficacy assessment. FAS is the primary population for the efficacy analysis. In general, efficacy analysis will be performed for all subjects regardless dose escalation.

Safety Dataset:

The Safety set consists of all subjects who received at least one injection of study drug.

Dose Escalation Dataset:

This set consists of all subjects who escalated the study dose from 40 mg eow to 80 mg eow on or after Week 8. In order to evaluate the effect of dose escalation, these subjects will be analyzed for the efficacy and safety (AEs only) using the data prior- and post-dose escalation date, separately.

Pharmacokinetic assessments will be conducted on all subjects who were administered at least one dose of study drug and have at least one post-dose sample collected for the determination of serum adalimumab concentration.

5.2 Variables Used for Stratification of Randomization

Not applicable.

6.0 Analysis Conventions

Unless otherwise specified, the efficacy and safety continuous variables will be summarized using the descriptive statistics (including mean, standard deviation, median, minimum and maximum), and for qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation.

All statistical analyses will be conducted at a two-sided significance level of 0.050 or a one-sided significance level of 0.025 (when rounded to 3 decimal places).

6.1 Definition of Baseline

The baseline visit date is the date when the first dose of study drug is received and

referred to as Day 1. The baseline value for a variable is defined as the last non-missing value on or before the date of the first dose of study drug.

6.2 Definition of Final Observation Value

For subjects who did not discontinue the study before Week 24, final observation is the last non-missing observation collected after the first dose of study drug and on the dose of study drug at Week 24. Final observation for the interim analysis at Week 24 is defined as the last non-missing observation collected after the first dose of study drug and within 70 days after the last dose of study drug for subjects who discontinued the study before Week 24.

Final observation for the final analysis at Week 52 is defined as the last non-missing observation collected after the first dose of study drug and within 70 days after the last dose of study drug.

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

Rx Days are calculated for each time point of interest and it provides a quantitative measure of days between the event and the first dose date. That is, the Rx Day is calculated as the event date minus the date of first dose of study drug plus 1. The Rx Day will be a negative value when the time point of interest is prior to the date of first dose of study drug, and the Rx Day will be a positive value when the time point of interest is after the first dose date. By this calculation algorithm the first dose day is Rx Day 1, while the day prior to the date of first dose is defined as Rx Day –1 (there is no Rx Day 0). Rx days are used to map actual study visits to the protocol specified study visits.

6.4 Definition of Analysis Windows

Since subjects do not always adhere to the study visit schedule, the following rules will be applied to assign actual visits to protocol-specified visits including early termination visits.

For each study visit mentioned in the protocol, a nominal or target day will be selected to represent the corresponding visit along with a window around the target day. Windows will be selected in a non-overlapping fashion so that a date collected on the CRF does not correspond to multiple visit windows. Moreover, windows will not discard any post baseline measurement recorded on the CRF. If a subject had two or more actual visits in one visit window, the visit closest to the target will be used as the study visit for that window. If two visits are equal distance from the target, then the later visit will be used for reporting.

The protocol specified visits and corresponding time windows used in the analyses are presented in Table 2, Table 3, Table 4 and Table 5.

The following visit windows will be used for the analysis of assessment of each efficacy variables which are collected at baseline visit and Week 52 Visit or early termination (ET).

Table 2. Visit Windows for Analysis of Efficacy Variables, General Laboratory Parameters (Blood Chemistry and Hematology)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Day 1	1	≤ 1
Week 2	15	2 – 22
Week 4	29	23 – 43
Week 8	57	44 – 71
Week 12	85	72 – 99
Week 16	113	100 – 141
Week 24	169	142 – 211
Week 36	253	212 – 309
Week 52	365	310 – 421

Table 3. Visit Windows for Analysis of DLQI, SF-36, Laboratory Parameters (Urinalysis)

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Day 1	1	≤ 1
Week 8	57	2 – 85
Week 16	113	86 – 141
Week 24	169	142 – 211
Week 36	253	212 – 309
Week 52	365	310 – 421

Table 4. Visit Windows for Analysis of Vital Signs

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Day 1	1	≤ 1
Week 2	15	2 – 22
Week 4	29	23 – 43
Week 8	57	44 – 71
Week 12	85	72 – 99
Week 16	113	100 – 127
Week 20	141	128 – 155
Week 24	169	156 – 183
Week 28	197	184 – 211
Week 32	225	212 – 239
Week 36	253	240 – 267
Week 40	281	268 – 295
Week 44	309	296 – 323
Week 48	337	324 – 351
Week 52	365	352 – 379

Visit Windows for Dose Escalation Analysis Set

The study days for the analysis of dose escalation effect will be calculated with reference to the dose escalation date.

Study Day = Date of evaluation – date of dose escalation + 1.

Table 5. Visit Windows for GPP skin score relative to dose escalation

Scheduled Week	Nominal Day	Time Window (Rx Day Range)
Day 1 (= date of dose escalation)	1	≤ 1
Week 2	15	2 – 22
Week 4	29	23 – 36
Week 6	43	37 – 50
Week 8	57	51 – 64
Week 10	71	65 – 78
Week 12	85	79 – 92
Week 14	99	93 – 106
Week 16	113	107 – 120
Week 18	127	121 – 134
Week 20	141	135 – 148
Week 22	155	149 – 162
Week 24	169	163 – 176
Week 26	183	177 – 190
Week 28	197	191 – 204
Week 30	211	205 – 218
Week 32	225	219 – 232
Week 34	239	233 – 246
Week 36	253	247 – 260
Week 38	267	261 – 274
Week 40	281	275 – 288
Week 42	295	289 – 302
Week 44	309	303 – 316

6.5 Definition of Missing Data Imputation

The following methods will be used to impute missing values in the efficacy analyses. In general, missing Baseline and safety data will not be imputed. In addition, an observed case analysis will be performed.

Baseline Value is Missing

Subjects will be excluded from analysis of change from baseline if baseline evaluation is missing.

Non-Responder Imputation (NRI)

The NRI approach is used for binary efficacy variables. These variables can take values of 'Achieved' or 'Not Achieved' or may be missing for any reason including discontinuation from study. According to the NRI imputation approach, all missing value will be considered as 'Not Achieved.'

Last Observation Carried Forward (LOCF)

For continuous variables, the following rules will be used for the LOCF approach:

1. Baseline and pre-baseline values will not be used to impute the missing post-baseline values.
2. Missing values after Study Day 1 will be imputed using the latest non-missing values after Day 1 and prior to the missing value. If there are no non-missing values after baseline, then the LOCF value will be missing.

Observed Cases (OC)

Observed case analysis will be performed such that missing values will not be imputed.

Imputation of Missing Dates

For baseline, efficacy, and safety parameters, if the day and/or month are missing, the following conventions will be used to impute the missing dates:

- 01 for missing start day
- End of month for missing end day

- January 1st for missing start month
- December 31st for missing end month

In case of missing or partially missing dosing dates, the dates will not be imputed.

In case of missing or partially missing adverse event start and stop dates, the dates will be imputed by comparing to the first dosing date so that the corresponding adverse events will be made treatment-emergent, whenever possible.

Rounding

Rounding will be performed only for presentation of results. No rounding will be performed before or during computations. The ROUND function of SAS will be used to round results for presentation.

The mean and median will be rounded for presentation to one decimal more than the data were entered into the database. For example, mean systolic blood pressure will be presented to one decimal place (125.2 mmHg) when it is recorded to integer level in the database (110 mmHg). The standard deviation will be rounded to two decimal places more than the data were entered into the database (e.g., 25.31 mmHg for systolic blood pressure). The minimum and maximum values will be presented as entered into the database.
Percentages will be rounded for presentation to one decimal place; e.g., the proportion 0.1244 will be reported in percent as 12.4.

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

7.1 Demographic and Baseline Characteristics

For the subjects in FAS, demographic information and baseline values will be summarized by descriptive statistics. Categorical data will be summarized by number and

percent; and quantitative data will be presented by the number of subjects, mean, standard deviation, minimum value, median, and maximum value.

The following demographic and baseline values will be summarized.

Continuous variables:

- Age (years)
- Body Weight (kg)
- Body Height (cm)
- Body mass Index (kg/m2)
- Blood Pressure (systolic/diastolic) (mmHg)
- Pulse (bpm)
- Respiratory Rate (rpm)
- Body Temperature (°C)
- Duration of Generalized Pustular Psoriasis (GPP) [years: [Date of first dose of study drug – Date of first diagnosis of GPP]/365.25]
- Body Surface Area (BSA; percent [%])
- Psoriasis Area and Severity Index (PASI) score [0.0-72.0]
- Dermatology Life Quality Index (DLQI) [0-30]
- Short Form 36 Health Survey (SF-36)

Categorical variables:

- Sex [male/female]
- Race
- Ethnicity
- Age categories [< 65, ≧ 65]
- Age categories [< 30, 30 - < 50, ≧50]
- Body Weight categories [Median]

- Medical History (using MedDRA, Version 19.1)
- Tobacco [Current, Former, Never, Unknown]
- Alcohol use [Current, Former, Never, Unknown]
- PASI [< 10, 10 - < 30, ≧30]
- BSA [< 10%, 10 - < 25%, 25 - < 50%, 50 - < 75%, 75 - < 100%]
- Tuberculin PPD skin test result
- Chest x-ray finding [finding, calcified granulomas, pleural scarring,
- pleural thickening, sign of active TB, previous TB infection]Antinuclear antibody (ANA) [positive/negative]
- Anti-double stranded DNA (dsDNA) [positive/negative]
- Physician's Global Assessment (PGA) [clear (score=0), minimal (score=1), mild (score=2), moderate (score=3), severe (score=4), very severe (score=5)]

7.2 Medical History

For the FAS population, the medical history data will be summarized and presented using body systems and conditions/diagnoses 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.

In addition, the medical history data for each subject will be provided in the listing.

Chest X-Ray Results

All subjects undergo a standard chest x-ray of chest (including a posterior-anterior [PA] and lateral views) at the screening visit. Finding status (Normal, Abnormal), findings on calcified granulomas (Absent, Present), pleural scarring/thickening (Absent, Present), signs of active TB (Yes, No), and findings indicative of previous TB infection (Yes, No) will be summarized by number and percentage of subjects with these findings.

TB Test Results

Results of Tuberculin PPD skin test or Interferon-Gamma Release Assay (IGRA; QuantiFERON-TB Gold In-Tube test or T-SPOT TB test) at screening visit will be summarized by results.

- Tuberculin PPD skin test (Negative [Induration < 5 mm], Positive [Induration ≥ 5 mm])
- IGRA (Negative, Positive, Indeterminate)

ECG Results

ECG results at screening will be presented as frequency distribution showing results as Normal, Abnormal (Not clinically significant), Abnormal (Clinically significant) and Unable to evaluate/missing.

Pregnancy Tests

Pregnancy information collected at screening (serum test), baseline and Week 52/premature discontinuation (urine test) visits will be listed.

Pharmacokinetic

Adalimumab trough serum concentrations will be reported at each time point using descriptive statistics. The relationship between adalimumab concentrations and Clinical Response will be determined as appropriate.

Immunogenicity

AAA will be evaluated for each subject and rates of AAA positive will be calculated. As appropriate, the effect of AAA on adalimumab pharmacokinetics, efficacy variable(s), and treatment-emergent adverse events may be evaluated.

7.3 Prior and Concomitant Therapy

Prior and concomitant therapy using drug generic name coded using WHO Drug dictionary (version 2016Q1) will be summarized by the generic name with counts and percentages.

8.0 Patient Disposition

Subject disposition will be presented for subjects in the safety analysis set using the following information

- Number and percent of subjects in various analysis sets by investigator and site number
- For the interim analysis at Week 24, number and percent of subjects completing Week 24 and discontinuing on or before Week 24 visit
- For the interim analysis at Week 24, subject disposition including the number and percent of subjects who prematurely discontinued the study (on or before Week 24) by primary reason and by any reason
- For the final analysis at Week 52, number and percent of subjects completing Week 52 and discontinuing before Week 52 visit
- For the final analysis at Week 52, subject disposition including the number and percent of subjects who prematurely discontinued the study (before Week 52) by primary reason and by any reason
- Number and percent of subjects by visit

Summary of protocol deviations will be provided.

The number and percentage of screened subjects who screen failed and the reasons for screen failure (inclusion/exclusion criteria, withdrew consent, lost to follow-up, and/or other) will be summarized. A CSR listing of reason for screen failure will be provided for all subjects who screen failed.

9.0 Study Drug Exposure and Compliance

For the Safety Analysis Set population, study drug exposure will be summarized through the study as follows:

9.1 Study Drug Exposure

The duration (days) of exposure to study drug will be summarized using the number of subjects treated, mean, standard deviation, minimum, median, and maximum. Duration of exposure is defined the number of days since first dose of study drug through the last dose date plus 14 days. For interim analysis at Week 24, the Week 24 dosing date will be used instead of last dose plus 14 days only for ongoing subjects. In addition, the number and percentage of subjects exposed to study drug will be summarized for the following duration intervals.

1 – 15 days
16 – 29 days
30 – 57 days
58 – 85 days
86 – 113 days
114 – 141 days
142 – 169 days
170 – 197 days
198 – 225 days
226 – 253 days
254 – 281 days
282 – 309 days
310 – 337 days
338 – 365 days
> 365 days

Exposure to study drug (total patient years) will be summarized.

Cumulative Dose (mg)

Cumulative dose is derived as dose per administration times the number of injections given during the study. Cumulative dose will be summarized using the number of subjects treated, mean, standard deviation, minimum, median, and maximum.

The Number of Study Drug Injections

The number of injections received at each scheduled time point by subject will be summarized with numbers.

9.2 Compliance

Compliance (%) is defined as the number of adalimumab injections received divided by the number of adalimumab injections planned (rounded to 0.1) during the subject's participation in the study. For subjects who discontinued the study, planned study drug injections counted until the last dose date or the date of last efficacy or vital sign measurement.

9.3 Study Drug Dose

80 mg starting at Baseline (Week 0) and 40 mg eow on and after Week 2 until Week 50. Dose escalation to 80 mg eow is allowed for subjects who do not have appropriate response and meeting dose escalation criteria on or after Week 8. Dose reduction is not allowed after dose escalation until the study end. Treatment of study drug will not occur at Week 52.

The number of adalimumab injections received by subjects will be summarized.

10.0 Efficacy Analysis

10.1 General Considerations

This study is an open-label study without any comparator. The significant level is not defined, and descriptive statistics will be provided. These include the number of

observations, mean, standard deviation, minimum, median, and maximum for continuous variables; and number and percent for discrete variables. The exact 95% confidence intervals will be provided for the proportions. The analysis will be performed using SAS® (SAS Institute Inc., Cary, NC, USA). All efficacy analyses will be performed on the FAS.

10.2 Efficacy Analysis

This section provides the details of the primary efficacy analysis for the study.

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects achieving Clinical Response (CR) at Week 16. CR is defined as reduction of skin score of at least 1 (if the subject's Baseline skin score is 3) or at least 2 (if the subject's Baseline skin score is 4 or higher) relative to Baseline, according to JDA severity index of GPP in GPP Medical care guideline 2014 in Japan.

Table 6. The clinical response categories were defined according to the total skin score at Baseline

Skin score at Baseline \ Reduction in skin score	Skin Score = 0	≥ Δ 3	Δ 2	Δ 1	Δ 0	Increase in Skin Score
4 – 9	Remission	Improvement	Improvement	Minimal improvement	Unchanged	Worsened
3	Remission	Remission	Improvement	Improvement	Unchanged	Worsened

Imputation Method Used for the Primary Efficacy Analysis

Missing data will be imputed using the non-responder imputation (NRI) approach. For details on missing data imputation methods, refer to Section 6.

10.3 Secondary Efficacy Analyses

Discrete variables will be summarized by counts and percentages, and continuous variables will be summarized by descriptive statistics on the items below at each visit.

The subjects who have missing data for any reason such as early terminated subjects will be included into analysis using NRI for discrete variables or LOCF for continuous variables.

- Proportion of subjects achieving Clinical Response (expect Week 16, which is the primary endpoint).
- Proportion of subjects achieving remission.
- Change from the Baseline in total GPP score (skin and systemic/laboratory test).
- Change from the Baseline in JDA severity index of GPP.
- Change and Percent change from the Baseline in total skin score.
- Change from the Baseline in total systemic/laboratory test score.
- Change from the Baseline in score of erythema area (overall) and BSA (BSA of GPP).
- Change from the Baseline in score of erythema area with pustule and BSA.
- Change from the Baseline in score of edema area and BSA.
- Change from the Baseline in Body temperature.
- Change from the Baseline in WBC.
- Change from the Baseline in hs-CRP.
- Change from the Baseline in serum Albumin.
- Proportion of subjects achieving "Mild" in JDA severity index of GPP for patients with "Moderate" or "Severe" at the Baseline.
- Proportion of subjects achieving Treatment Success in PGA (reduction of 2 grades).
- Change from the Baseline in PGA grade.
- Proportion of subjects achieving PGA 0/1 for patients with PGA grade at least 2 at Baseline.
- Proportion of subjects achieving PASI 90.

- Proportion of subjects achieving PASI 75.
- Proportion of subjects achieving PASI 50.
- Change and Percent change from the Baseline in PASI score.
- Proportion of subjects achieving DLQI = 0.
- Change from the Baseline in DLQI score.
- Change from the Baseline in SF-36 score.
- Proportion of subjects taking systemic co-medication for GPP (etretinate, MTX, oral steroids, cyclosporine).
- Proportion of subjects taking topical co-medication for GPP (corticosteroid, vitamin D3, tacrolimus).

10.4 Handling of Multiplicity

No adjustment for multiplicity will be done.

10.5 Efficacy Subgroup Analysis

The subgroup analysis listed below is planned for the subgroups shown. Proportion of subjects achieving Clinical Response (remission and improvement) at Weeks 16, 24, and 52.

- Dose escalation: (without dose escalation, with dose escalation)
- Previous infliximab experience (infliximab naïve, prior exposure to infliximab)

For all subject in Dose Escalation Set will be summarized as:

- Proportion of subject achieving Clinical Response by dose escalation.

11.0 Safety Analysis

11.1 General Considerations

Unless otherwise specified, all safety analysis will be performed on the Safety dataset.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as events that begin or worsen either on or after the first dose day of the study medication and within 70 days after the last dose of the study medication. Treatment-emergent AEs will be summarized separately for the first half period (Week 0 to Week 24), the second half period (Week 24 to Week 52), and entire period (Week 0 to Week 52).

For the interim analysis at Week 24, treatment-emergent adverse events are defined as any event with an onset or worsening on or after the first dose of study drug and on or prior to the Week 24 dosing date for subjects who continued in the study after Week 24, and up to 70 days after the last dose of study drug for subjects who discontinued prior to Week 24 visit.

Treatment-emergent adverse events will be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The system organ classes will be presented in alphabetical order and the preferred terms will be presented in alphabetical order within each system organ class.

For the Dose Escalation set, TEAEs will be reported before the date of dose escalation and also on or after the date of dose escalation, separately.

Adverse Event Overview

The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories.

- Any treatment-emergent adverse event

- Any treatment-emergent adverse event that was rated as possibly related to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent severe adverse event
- Any treatment-emergent serious adverse event
- Any treatment-emergent adverse event leading to discontinuation of study drug
- Any treatment-emergent serious adverse event that was rated as possibly related to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent adverse event leading to death
- Any treatment-emergent adverse event of special interest
- Any Deaths

Adverse Events by SOC and PT

The number and percentage of subjects experiencing adverse events will be tabulated according to the primary MedDRA system organ class (SOC) and preferred term (PT). Subjects reporting more than one adverse event for a given MedDRA PT 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 MedDRA 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.

The following AEs will be summarized using the conventions described above:

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event that was rated as possibly related to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent adverse event by maximum severity
- Any treatment-emergent adverse event by maximum relationship to study
- Any treatment-emergent serious adverse event
- Any treatment-emergent adverse event leading to discontinuation of study drug

- Any treatment-emergent serious adverse event that was rated as possibly related to study drug by the investigator (Reasonable Possibility)
- Any treatment-emergent adverse event leading to death
- Any treatment-emergent adverse event of special interest

Adverse Events by Maximum Severity

Adverse events 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 adverse 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.

Adverse Events by Maximum Relationship

Adverse events will also be summarized by maximum relationship to study, 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 adverse 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, respectively.

Adverse Event Rates per 100 Patient Years of Study Drug Exposure

Incidence rates per 100 patient years of exposure to study drug will be presented for adverse event overviews and for adverse events by SOC and PT.

The treatment-emergent adverse event rate per 100 patient years of exposure will be calculated overall, for each primary SOC, and each PT. For this calculation, 1 year will be considered to be 365.25 days. The numerator of the overall rate, the SOC rate, or the PT rate, will be the total number of treatment-emergent adverse events reported overall,

for the SOC, or for the PT, respectively; i.e., a subject can be counted more than once overall, for a SOC, and for a PT. The denominator of the rates will be the total number of days exposed to study drug summed across all treated subjects divided by 365.25, and rounded to one decimal place. The adverse event rate per 100 subject-years of exposure will be calculated as [(numerator/denominator)]*100. The number of adverse events reported (numerator), the total number of years of study drug exposure (denominator), and the adverse event rate per 100 subject-years will be presented overall, for each SOC, and for each PT.

Adverse Events of Special Interest (AESI)

The analysis of treatment-emergent adverse events of special interest based on Standardized MedDRA Queries (SMQs) or Company MedDRA Queries (CMQs) will be presented for the adverse event overviews and for adverse events by SOC and PT.
The final analyses will follow the latest version of Product Safety Statistical Analysis Plan (PSSAP).
The current list of AEs of special interest in PSSAP (version 5.0, dated 20Jan2016) for treatment with adalimumab is:

- Any Infections AE
- Any Serious Infection AE
- Any Legionella Infection AE
- Any Diverticulitis AE
- Any Opportunistic Infection AE (Excluding Oral Candidiasis and TB)
- Any Oral Candidiasis AE
- Any Tuberculosis AE
- Any Active Tuberculosis AE
- Any Latent Tuberculosis AE
- Any Parasitic Infection AE
- Any Reactivation of Hepatitis B AE
- Any Progressive Multifocal Leukoencephalopathy (PML) AE
- Any Malignancy AE

- Any Lymphoma AE
- Any Hepatosplenic T-Cell Lymphoma AE (HSTCL)
- Any Non-Melanoma Skin Cancer (NMSC) AE
- Any Melanoma AE
- Any Leukaemia AE
- Any Other Malignant AE (Excluding NMSC, Melanoma, Lymphoma, HSTCL, and Leukemia)
- Any Allergic Reaction AE (Including Angioedema/Anaphylaxis)
- Any Lupus-Like Reactions and Systemic Lupus Erythematosus AE
- Any Vasculitis AE
- Any Cutaneous Vasculitis AE
- Any Non-Cutaneous Vasculitis AE
- Any Sarcoidosis AE
- Any Autoimmune Hepatitis AE
- Any Myocardial Infarction Related AE
- Any Cerebrovascular Accident Related AE
- Any Congestive Heart Failure Related (CHF) AE
- Any Pulmonary Embolism Related AE
- Any Interstitial Lung Disease AE
- Any Intestinal Perforation AE
- Any Pancreatitis AE
- Any Stevens-Johnson Syndrome AE
- Any Erythema Multiforme Related AE
- Any Worsening/New Onset of Psoriasis AE
- Any Demyelinating Disorder AE (Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis and Others)
- Any Amyotrophic Lateral Sclerosis AE
- Any Reversible Posterior Leukoencephalopathy Syndrome (RPLS) AE
- Any Hematologic Disorders AE (Including Pancytopenia)

- Any Liver Failure and Other Liver Event AE (Except Gall Bladder Related Events)
- Any Humira Administration Related Medication Errors AE
- Any Injection Site Reaction AE
- Any AE Leading to Death
- Any AE Leading to Discontinuation of Study Drug
- Any Deaths

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

11.2.2 Listing of Adverse Events

The following additional summaries of adverse events will be prepared.

- Listing of treatment-emergent adverse events
- Listing of subject numbers associated with each PT for treatment-emergent adverse events
- Listing of treatment-emergent serious adverse events
- Listing of pre-treatment serious adverse events
- Listing of treatment-emergent adverse events that led to discontinuation of study drug
- Listing of treatment-emergent fatal adverse events.
- Listing of deaths
- Listing of treatment-emergent adverse events of special interest

11.3 Analysis of Laboratory Data

Laboratory test variables are specified in Table 7. Laboratory test variables will use standard units.

Table 7. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis[a]
Hematocrit Hemoglobin Red Blood Cell count White Blood Cell count Neutrophils (Stab, Seg) Bands (Stab) Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase/alanine transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase/aspartate transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin hs-CRP	Specific gravity Ketones pH Protein Blood Glucose
Additional Blood Samples Collected		
β-hCG (serum pregnancy test) QuantiFERON-TB Gold or T-SPOT TB (IGRA) HIV HBV HCV ANA anti-dsDNA – *if ANA positive* Pharmacokinetic, Anti-adalimumab antibody		

a. A microscopic analysis will be performed by the central laboratory, in the event the dipstick results show protein, ketones or blood greater than negative or glucose greater than normal.

11.3.1 Variables and Criteria Defining Abnormality

The liver specific laboratory tests include the serum glutamic-pyruvic transaminase (SGPT/ALT), serum glutamic-oxaloacetic transaminase (SGOT/AST), alkaline

phosphatase and total bilirubin. Each of these laboratory values will be categorized as follows:

1. < 1.5 ULN,
2. ≥ 1.5 × ULN TO < 3 × ULN,
3. ≥ 3 × ULN TO < 5 ULN,
4. ≥ 5 × ULN TO < 8 ULN, and
5. ≥ 8 × ULN,

where ULN is the upper normal limit.

Shift tables showing shift from Baseline to maximum and final values 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 4 criteria:

1. ALT ≥ 2.5 × ULN, or
2. AST ≥ 2.5 × ULN, or
3. Alkaline Phosphatase ≥ 2.5 × ULN, or
4. Total Bilirubin ≥ 1.5 × ULN.

For selected laboratory parameters (Hematology: Hemoglobin, Platelet count, WBC, Neutrophils, Lymphocytes; Clinical Chemistry: ALT, AST, Alkaline Phosphatase, γ-GTP, Total Bilirubin, Albumin, CPK, Creatinine, Uric Acid, Calcium, Sodium, Potassium, Inorganic Phosphorus, Magnesium, Glucose, Cholesterol, Triglycerides) with Common Toxicity Criteria (CTC), Potentially Clinically Significant (PCS) Laboratory Findings (Common Toxicity Criteria CTC [Version 4.0] Grades 3 and 4) will be assessed.

The following table describes the Criteria for Potentially Clinically Significant Laboratory Findings:

Table 8. Potentially Clinically Significant Laboratory Findings

Laboratory Parameter	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hemoglobin – Low (G/L)	< LLN – 100	< 100 – 80	< 80	–
Hemoglobin – High (G/L)	CH > 0.0 – 20	CH > 20 – 40	CH > 40	–
Platelet count (× 10^9/L)	< LLN – 75	< 75 – 50	< 50 – 25	< 25
WBC (× 10^9/L)	< LLN – 3.0	< 3.0 – 2.0	< 2.0 – 1.0	< 1.0
Neutrophils (× 10^9/L)	< LLN – 1.5	< 1.5 – 1.0	< 1.0 – 0.5	< 0.5
Lymphocytes (× 10^9/L)	< LLN – 0.8	< 0.8 – 0.5	< 0.5 – 0.2	< 0.2
ALT	> ULN - 3.0 × ULN	> 3.0 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
AST	> ULN - 3.0 × ULN	> 3.0 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20.0 × ULN
Alkaline phosphatase	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
γ-GTP	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
Total bilirubin	> ULN - 1.5 × ULN	> 1.5 - 3.0 × ULN	> 3.0 - 10.0 × ULN	> 10.0 × ULN
Albumin (G/L)	< LLN – 30	< 30 – 20	< 20	–
CPK	> ULN – 2.5 × ULN	> 2.5 × ULN – 5.0 × ULN	> 5.0 × ULN – 10.0 × ULN	> 10.0 × ULN
Creatinine*	> ULN – 1.5 × ULN; or > 1 - 1.5 × BL	> 1.5 – 3.0 × ULN or > 1.5 – 3.0 × BL	> 3.0 – 6.0 × ULN or > 3.0 × BL	> 6.0 × ULN
Uric Acid (MCMOL/L)	> ULN – 590	–	–	> 590
Calcium – Low (MMOL/L)	< LLN – 2.0	< 2.0 – 1.75	< 1.75 – 1.5	< 1.5
Calcium – High (MMOL/L)	> ULN – 2.9	> 2.9 – 3.1	> 3.1 – 3.4	> 3.4
Sodium – Low (MMOL/L)	< LLN – 130	–	< 130 – 120	< 120

Table 8. Potentially Clinically Significant Laboratory Findings (Continued)

Laboratory Parameter	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Sodium – High (MMOL/L)	> ULN – 150	> 150 – 155	> 155 – 160	> 160
Potassium – Low (MMOL/L)	< LLN – 3.0	–	< 3.0 – 2.5	< 2.5
Potassium – High (MMOL/L)	> ULN – 5.5	> 5.5 – 6.0	> 6.0 – 7.0	> 7.0
Inorganic Phosphorus (MMOL/L)	< LLN – 0.8	< 0.8 – 0.6	< 0.6 – 0.3	< 0.3
Magnesium - Low (MMOL/L)	< LLN – 0.5	< 0.5 – 0.4	< 0.4 – 0.3	< 0.3
Magnesium - High (MMOL/L)	> ULN – 1.23	–	> 1.23 – 3.30	> 3.30
Glucose – Low (MMOL/L)	< LLN – 3.0	< 3.0 – 2.2	< 2.2 – 1.7	< 1.7
Glucose – High (MMOL/L)	> ULN – 8.9	> 8.9 – 13.9	> 13.9 – 27.8	> 27.8
Cholesterol (MMOL/L)	> ULN – 7.75	> 7.75 – 10.34	> 10.34 – 12.92	> 12.92
Triglycerides (MMOL/L)	1.71 – 3.42	> 3.42 – 5.7	> 5.7 – 11.4	> 11.4

CH = change in ULN or change in baseline, if baseline > ULN; ULN = upper limit of normal range; LLN = lower limit of normal range; BL = baseline;

* = identify by ULN if baseline is normal else use BL if baseline is abnormal;

11.3.2 Statistical Methods

Mean changes from baseline to each post-baseline visits (as defined in Table 1) and final value in continuous laboratory parameters will be summarized with the baseline mean, visit mean, change from baseline mean, standard deviation, minimum value, median, and maximum value.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. Cross (shift) tables from baseline to the minimum/maximum/final values according to the normal range will be provided for each hematology, clinical chemistry parameter and urinalysis parameters. The shift tables will cross tabulate the frequency and percentage of subjects with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

Incidence of abnormal laboratory values for hematology, clinical chemistry parameter and urinalysis parameters will be provided.

Scatter plot of Baseline values versus the final values in laboratory parameters will be provided.

11.4 Analysis of Vital Signs and Weight

The following vital signs are measured at the designated study visits in Table1.

- Blood Pressure (Systolic/Diastolic) (mmHg)
- Pulse (bpm)
- Respiratory rate (rpm)
- Body temperature (°C)
- Body Weight (kg)

11.4.1 Statistical Methods

For each vital sign and weight variable, analyses of the mean change from baseline to each post-baseline value will be presented for the Safety Dataset using the descriptive statistics including 95% confidence interval based on standard normal distribution.

12.0 Summary of Changes

No major changes were made to the analysis plan. Minor correction are as follows.

12.1 Summary of Changes Between the Latest Version of Protocol and the Current SAP

12.2 Summary of Changes Between the Previous Version and the Current Version of the SAP

- Corrected the information of protocol version and updated the SAP version in section 3.0.
- The sentence, This is the first version of SAP for Protocol M14-193., was removed.
- Add Efficacy Assessment Criteria table for clinical response in section 10.2 based on Administrative change 4.

13.0 Appendix

14.0 Reference

Document Approval

Study M14193- Statistical Analysis Plan Version 2.0 - 25Apr2017 (E3 16.1.9)

Version: 2.0 **Date:** 24-May-2017 02:22:50 AM **Company ID:** 05242017-00F9F681531935-00002-en

Signed by:	Date:	Meaning Of Signature:
[redacted]		Approver
		Approver