abbvie

1.0   **Title Page**

Statistical Analysis Plan

Study M14-233

A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Adalimumab for the Induction and Maintenance of Clinical Remission in Chinese Patients with Moderately to Severely Active Crohn's Disease and Elevated High-Sensitivity C-Reactive Protein

Date: 26 Oct 2017

Version 1.0

2.0 Table of Contents

List of Tables

List of Figures

3.0   Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by the AbbVie Global Statistics Department for study Protocol M14-233 Amendment 1 dated 21 October 2015. It provides details to further elaborate statistical methods outlined in the protocol and describes analysis conventions to guide the statistical programming work.

This is the SAP for Protocol M14-233 final analysis which includes both the 8-week double-blind (DB) treatment period and 18-week open-label (OL) treatment period.

This analysis plan describes the efficacy analyses as well as the safety analysis. These analyses will be performed after the final database lock of the study.

This document describes the analysis of data except pharmacokinetic, pharmacogenetic, and mRNA variables, which will be analyzed separately. It takes into account ICH Guidelines E3 and E9.

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 Objectives, Design and Procedures

4.1   Objectives

The primary objective of this study is to assess the efficacy and safety of adalimumab in inducing (at Week 4) and maintaining (at Week 26 in Week 8 responders) clinical remission, defined as Crohn's Disease Activity Index (CDAI) < 150, in Chinese subjects with moderately to severely active CD and elevated hs-CRP.

Additional objectives are to assess the effect of adalimumab treatment on other efficacy outcomes, including clinical response, steroid free remission, and improvement in quality of life.

4.2   Design Diagram

This is a Phase 3, randomized, double-blind, placebo controlled, multicenter study of adalimumab in anti-TNF naïve Chinese subjects with moderately to severely active CD ($220 \leq CDAI \leq 450$) and elevated hs-CRP (≥ 3 mg/L). The study consists of an 8-week DB period followed by an OL period of 18 weeks. Subjects will be randomized in a 1:1 ratio to receive adalimumab or placebo at Baseline. Subjects randomized to adalimumab at Week 0 will receive blinded adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and Week 6. Subjects randomized to placebo at Week 0 will receive blinded placebo at Week 0 and Week 2, then will receive blinded adalimumab 160 mg at Week 4 and 80 mg at Week 6. At Week 8, all subjects will enroll in an 18-week OL period to receive adalimumab 40 mg every other week (eow). No drug will be administered at the final study visit.

The study was designed to enroll approximately 200 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

The study duration will be up to 39 weeks, and will include a screening period of up to 35 days, an 8-week double blind treatment period, an 18-week OL period and a 70-day follow-up period. All subjects will have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing AEs. The 70-day follow-up phone call will not be required for any subject who initiates adalimumab therapy not supplied in the context of Study M14-233 after the end of study participation.

At or after Week 12, any subject who experiences inadequate response may increase dose to OL adalimumab 80 mg eow. If the subject has received OL 80 mg eow therapy and continues to demonstrate inadequate response, he or she should be withdrawn from the study per PI discretion.

Subjects may discontinue adalimumab treatment at any time during study participation. Subjects who end study participation early will have a Premature Discontinuation Visit.

A schematic of the study design is shown in Figure 1.

Figure 1. **Study Design**
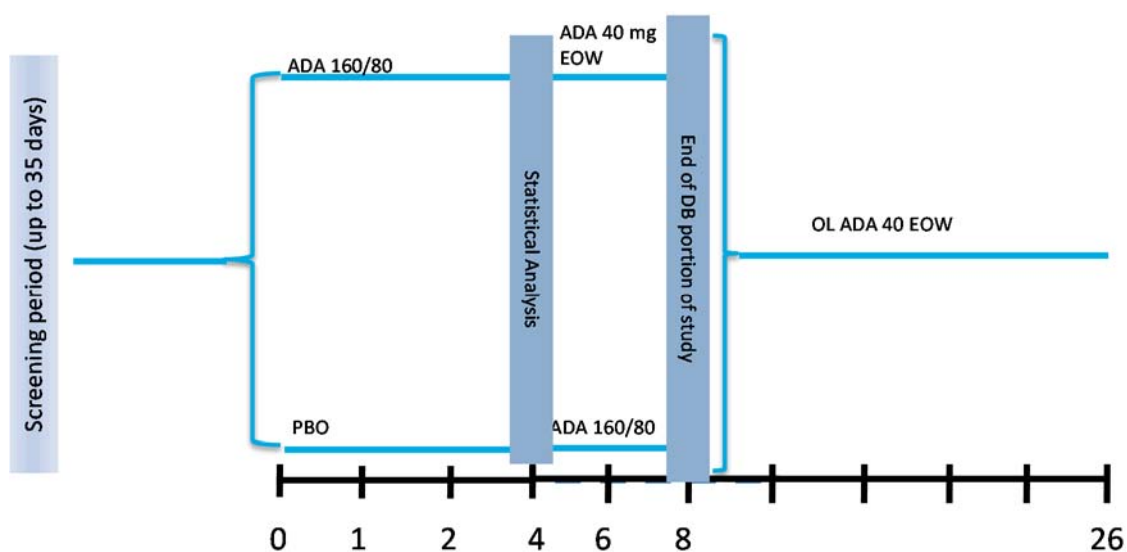
The study activities are presented in Table 1.

Table 1.   Study Activities

Activity	Screening (35 Days)	Day −21[a]	Day −7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Informed Consent	X																		
Inclusion/Exclusion[d]	X	X	X																
Medical/Surgery History[d]	X			X															
Alcohol and Tobacco Use	X																		
Previous and Concomitant Medication[d]	X	X	X	X	X	X	X	X	X^y	X	X^y	X	X^y	X	X^y	X^y	X	X	
Vital Signs[e]	X			X	X	X	X	X	X^y	X	X^y	X	X^y	X	X^y	X^y	X	X	
Dispense Subject CDAI Diary[f]	X																		
Physical Examination[g]	X			X	X	X	X	X						X			X	X	
Physician TB evaluation	X	X	X	X	X	X	X	X	X^y	X	X^y	X	X^y	X	X^y	X^y	X	X	
TB Screening[h]	X				X	X	X	X		X		X		X			X		
Chest x-ray[i]	X							X				X					X		
Initiate TB Prophlyaxis[j]																			
ECG[k]	X	X																	

Table 1.   Study Activities (Continued)

Activity	Screening (35 Days)	Day −21[a]	Day −7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Chemistry and Hematology	X	X	X	X	X	X	X	X		X		X		X			X	X	
Urinalysis[l]	X		X	X		X		X		X				X			X	X	
Pregnancy Tests[m]	X			X													X	X	
Hepatitis B Screen, HCV, and HIV[n]	X																		
hs-CRP	X		X	X	X	X	X	X		X		X		X			X	X	
C. difficile toxin	X																		
Antinuclear antibody (ANA)/ Anti-double-stranded DNA (anti ds-DNA)[o]	X																		
Stool Sample (fecal calprotectin)				X		X		X		X							X		
Human Antichimeric Antibodies (HACA)/ Infliximab Concentrations				X															
Adalimumab Concentration[p]				X		X		X		X	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[p]		
AAA Concentration[p]				X		X				X	X[q]	X[q]	X[q]	X[q]	X[q]	X[q]	X[p]		

Table 1.   **Study Activities (Continued)**

Activity	Screening (35 Days)	Day −21[a]	Day −7[a]	Baseline (Wk 0)[b]	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26/ Premature Discontinuation	Unscheduled Visit	70-Day Follow-Up Call[c]
Optional Pharmacogenetic Marker[t]				X													X[s]		
Optional biomarker mRNA[t]				X													X[s]		
Crohn's Disease Activity Index (CDAI)		X		X	X	X	X	X	X[y]	X	X[y]	X	X[y]	X	X[y]	X[y]	X	X	
Start Corticosteroid Taper[t]						X													
Monitor Adverse Events[u]	X	X	X	X	X	X	X	X	X[y]	X	X[y]	X	X[y]	X	X[y]	X[y]	X	X	X
Study Drug Dispensing/ Administration[v]				X	X	X	X	X	X[w]	X	X[w]	X	X[w]	X	X[w]	X[w]		X[x]	
Inflammatory Bowel disease Questionnaire (IBDQ)				X													X		

a. Day −21 and Day −7 visits are required for subjects who initiate TB prophylaxis during the screening period. If a subject does not initiate TB prophylaxis, these visits are not required.

b. The Baseline (Week 0) visit date will serve as the reference for all subsequent visits. A ± 3-day window is permitted around scheduled study visits.

c. Subjects will be contacted 70 days following study drug discontinuation for an assessment of any new or ongoing AEs, except those subjects who initiate adalimumab therapy not supplied in the context of the clinical trial after the end of study participation.

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

e. Height will be measured at Screening only.

Table 1.   **Study Activities (Continued)**

f. Diary should be brought back to the site at every visit.

g. Physical examination performed at Screening, Week 4, Week 8, and Week 26/Premature Discontinuation Visits are full physical examinations and those performed at all other visits are symptom-based and TB symptoms are discussed.

h. Subjects with negative QuantiFERON-TB Gold In-Tube test within 35 days of Screening will not require a repeat test, if documentation is available. Subjects with a negative QuantiFERON-TB Gold In-Tube test during the Screening Period will have repeated QuantiFERON-TB Gold In-Tube test at Weeks 2, 4, 6, 8, 12, 16, 20, and 26/PD, unless the Investigator has decided to initiate TB prophylaxis in that subject. For subjects with an indeterminate result during the Screening period, a repeat Screening period test should be performed unless the Investigator decides to initiate TB prophylaxis. If the repeat testing result during the Screening period is negative the QuantiFERON-TB Gold In-Tube test result is considered negative, but if the repeat testing result is indeterminate or positive TB prophylaxis should be initiated at least 3 weeks before Baseline.

    Subjects who have a negative QuantiFERON-TB Gold In-Tube test result during Screening and later develop a positive result will be withdrawn from the study. Subjects who have a negative QuantiFERON-TB Gold In-Tube test result during Screening and later develop an indeterminate result will have repeat testing and will be withdrawn from the study if the repeat testing confirms indeterminate or positive results.

i. Chest x-ray includes posterior-anterior (PA) and lateral views. Subjects with a normal (or one with non-clinically significant findings) CXR within 35 days of Screening would not require a repeat CXR, if documentation is available. All subjects will have repeated CXRs performed to evaluate for TB during the study at Weeks 8, 16, and 26/Premature Discontinuation. A chest CT scan may be used instead of the CXR at investigator discretion. If CXR or chest CT scan was obtained within 4 weeks of Premature Discontinuation, a repeat CXR/chest CT scan is not required.

j. If during Screening the subject has positive QuantiFERON-TB Gold In-Tube test or signs of latent TB in the CXR (or chest CT scan), subject will start and continue at least a 21-day course of TB prophylaxis treatment prior to Baseline (Week 0). Use of TB prophylaxis in subjects with negative TB screening is permitted if warranted based on the opinion of the investigator, but must be started during Screening in this case (i.e., TB prophylaxis should not be initiated after randomization). Subjects who initiate TB prophylaxis should continue the prophylaxis regimen for the duration of the subject's participation in the study (up to the 70 day follow call). Subjects with signs of active TB are excluded from trial participation.

k. Subjects with a normal (or one with non-clinically significant findings) ECG within 90 days of Screening would not require a repeat ECG, if documentation is available.

l. Dipstick urinalysis will be completed by the central laboratory at all required visits. 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.

m. Serum pregnancy test will be performed on all women of childbearing potential at Screening. Urine pregnancy test will be performed at Baseline (Week 0) Visit, and the Week 26/Premature Discontinuation Visit for all women of childbearing potential. The frequency can be increased up to every visit as per local regulations. If any urine pregnancy test is positive, a serum pregnancy test will be performed by the central laboratory.

Table 1. **Study Activities (Continued)**

n. 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. For subjects who are negative for HBs Ag but are positive for core antibodies (HBc Ab Total), HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary. Anti-Hepatitis C will be performed at Screening and will be exclusionary. All subjects will be tested for HIV-1 and documented that the test has been performed. This testing is to be done at a central laboratory. A subject will not be eligible for study participation if confirmatory testing for anti-HIV-1 antibody is positive. AbbVie will not receive results from the testing and not be made aware of any positive result. If the subject had negative anti-HIV-1 test results from the central lab, these tests will not be required to be repeated if the results were obtained within 50 days of the re-screening visit provided that in the meanwhile nothing has changed in the patient's medical history or risk behaviors. If the subject had negative HBV and Anti-Hepatitis C test results from the central lab, these tests will not be required to be repeated if the results were obtained within 35 days of the re-screening visit.

o. Anti-double-stranded deoxyribonucleic acid (anti-dsDNA) performed if ANA result is positive.

p. Blood samples for the measurement of adalimumab and anti-adalimumab antibody (AAA) concentrations will be collected prior to dosing. If the subject Prematurely Discontinues, blood samples for the measurement of adalimumab and AAA concentrations will be collected.

q. Blood samples for the measurement of adalimumab and anti-adalimumab antibody (AAA) concentrations will be collected prior to dosing ONLY if the subject qualifies for dose escalation.

r. Pharmacogenetic and Biomarker mRNA samples are optional. A separate consent must be signed prior to the sample draw.

s. Samples are to be obtained if subject discontinues the study at or after Week 8.

t. Subject will begin mandatory corticosteroid taper at Week 4. If the Investigator feels that the steroid taper is not advisable for a particular subject at Week 4, he/she must be withdrawn from the study.

u. Collection of Serious Adverse Events (SAEs) and protocol-related nonserious adverse events begins the day the subject signs the informed consent. Collection of AEs begins on Day −7 for subjects who initiate TB prophylaxis.

v. Administration of drug should be performed after all assessments and examinations scheduled for that day have been completed as much as possible. Starting at or after Week 12 and if the subject qualifies for dose escalation (criteria defined in Section 5.3.1.1 of Protocol Amendment 1 and per investigator discretion), the subject may receive 80 mg of adalimumab eow.

w. Dosing may occur onsite by appropriate site staff or the subject or their qualified designee can administer doses when not at the site.

x. For damaged or replacement study drug, subject should stay on their dosing schedule established by the Baseline (Week 0) visit.

y. Procedure should be performed if subject doses onsite, if subject doses at home these procedures are not required.

4.3   Sample Size

The Week 4 primary efficacy endpoint is defined as the proportion of subjects achieving CDAI < 150. Based on the adalimumab China Phase 2 CD Study M14-232 (no placebo group in that study), the remission rate at Week 4 was 67% in the adalimumab 160/80 mg treatment group and 40% in the adalimumab 80/40 mg treatment group. In Western CD Study CLASSIC I (Study M02-403), the Week 4 remission rate was 40% in the adalimumab 160/80 mg treatment group and 8% in the placebo group among subjects with elevated hs-CRP at baseline (hs-CRP $\geq$ 3 mg/L). Considering that the placebo effect in China Phase 3 study will potentially be higher than the Western placebo rate, and the treatment effect in the adalimumab 160/80 mg treatment group will potentially be lower than the China Phase 2 CD study, the assumption of remission rates at Week 4 for this study is 24% and 47% for placebo and the adalimumab 160/80 mg treatment groups, respectively, with the expected treatment difference of 23%. A sample size of 100 subjects per arm (total 200 subjects) will provide power of 90% to detect a 23% treatment difference in the primary efficacy endpoint between the adalimumab 160/80 mg treatment group and placebo (1:1 randomization ratio), using two-sided Fisher's exact test at a 0.05 significance level.

If the overall Week 8 response rate is 50%, it is expected that approximately 100 subjects who are Week 8 responders will enter the open-label maintenance period and comprise the analysis population for Week 26 endpoints. Based on the observed Week 26 remission rate in Western CD Study M02-404 in anti-TNF naïve subjects with elevated CRP at baseline (hs-CRP $\geq$ 3 mg/L) who responded to adalimumab induction therapy (52% [34/66]) for the adalimumab 40 mg EOW treatment group the sample size of 100 subjects will allow $\geq$ 99% power to detect remission rate at Week 26 of 52% against a clinically meaningful remission rate of 30% using one-sample Exact test at a two-sided 0.05 significance level. The remission rate of 30% was obtained using the upper bound of the 95% CI of the adult placebo rate from the Western CD Study M02-404 in the same subgroup of subjects.

Prior to the completion of Study M14-233 study enrollment, assessment of the sample size based on the blinded data (overall event rate at Week 4) will be conducted.

4.4 Interim Analysis

No interim analysis is planned for this study.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

The following populations will be used for analyses in this study:

Intent-to-Treat (ITT) set includes all subjects who are randomized. ITT subjects will be analyzed as randomized. ITT set is the primary population for the efficacy analysis during the DB and OL treatment periods.

The Safety set consists of all enrolled subjects who received at least one injection of study drug. The safety set will be analyzed as treated, according to treatment the subject actually received. The safety set will be used only for safety analysis.

The Any Adalimumab set consists of all enrolled subjects who received at least one injection of adalimumab.

5.2 Variables Used for Stratification of Randomization

At Baseline (Week 0), subjects were randomized in a 1:1 ratio to receive adalimumab or placebo. The randomization was stratified by Crohn's disease severity (CDAI $\leq$ 300, > 300) at Baseline (Week 0) and corticosteroid use at Baseline.

6.0   Analysis Conventions

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 or Week 0. 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.

When analyzing laboratory parameters and vital signs on the Any Adalimumab analysis set, the Baseline Visit date is the date when the first dose of adalimumab is received and will be counted as Day 1 or Week 0. The baseline value for a laboratory or vital sign measurement is defined as the last non-missing value on or before the date of the first dose of adalimumab.

Definition of Final Observation

Final observation in the 4-week DB placebo controlled treatment period is defined as the last non-missing observation collected within 70 days following the last dose of study drug or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233 for subjects who discontinue the study before Week 6, and on or before the day of the first dose of study drug at Week 6 for subjects who continues the study.

Final observation in the DB/OL period for the Any Adalimumab set is defined as the last non-missing observation collected within 70 days following the last dose of study drug, or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233.

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

Rx Days are calculated for each time point of interest and provide a quantitative measure of days between the event and Day 1 (which can be the day of the first dose of study drug or the day of the first dose of adalimumab, depending on the analysis). That is, the Rx Day is calculated as the event date minus Day 1 plus 1. The Rx Day will be a negative value when the time point of interest is prior to Day 1, and the Rx Day will be a positive

value when the time point of interest is after Day 1. 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.

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 equidistant from the target, then the later visit will be used for reporting. For efficacy related analyses, if multiple measurements for a particular parameter are collected on the same day for the same subject, the average of those measurements will be used. For safety related analyses, if multiple measurements are made for a particular laboratory or vital sign parameter on the same day for the same subject, the average of the values will be used in the analyses. For summaries and listings of shift from baseline and potentially clinically significant values all values will be considered in the analyses.

Table 2.   Visit Windows for Analysis of CDAI and Vital Sign

Scheduled Week	Nominal Day	Time Window (Rx Day A Range)
Week 0 DB	1[a]	≤ 1
Week 2 DB	15	2 – 22
Week 4 DB	29	23 – 36
Week 6 DB	43	37 – 50
Week 8 DB	57	51 – 64[b]
Week 10 OL	71	65[c] – 78
Week 12 OL	85	79 – 92
Week 14 OL	99	93 – 106
Week 16 OL	113	107 – 120
Week 18 OL	127	121 – 134
Week 20 OL	141	135 – 148
Week 22 OL	155	149 – 162
Week 24 OL	169	163 – 176
Week 26 OL	183	177 – 190

Rx Day A = date of visit – date of first study drug injection in double-blind treatment period + 1

a.   Date of first study drug injection in double-blind treatment period.

b.   For Week 8 DB, visit window was from Rx Day 51 to Rx Day 64 or the date of the first injection in OL period (if applicable), whichever comes first.

c.   For Week 10 OL, visit window was from Rx Day 65 or the date of the first injection in OL period + 1 (if applicable), whichever comes first, to Rx Day 78.

Table 3.   **Visit Windows for Analysis of hs-CRP, Chemistry and Hematology**

Scheduled Week	Nominal Day	Time Window (Rx Day A Range)
Week 0 DB	1[a]	≤ 1
Week 2 DB	15	2 – 22
Week 4 DB	29	23 – 36
Week 6 DB	43	37 – 50
Week 8 DB	57	51 – 71[b]
Week 12 OL	85	72[c] – 99
Week 16 OL	113	100 – 127
Week 20 OL	141	128 – 162
Week 26 OL	183	163 – 190

Rx Day A = date of visit – date of first study drug injection in double-blind treatment period + 1

a.   Date of first study drug injection in double-blind treatment period.

b.   For Week 8 DB, visit window was from Rx Day 51 to Rx Day 71 or the date of the first injection in OL period (if applicable), whichever comes first.

c.   For Week 12 OL, visit window was from Rx Day 72 or the date of the first injection in OL period + 1 (if applicable), whichever comes first, to Rx Day 99.

Table 4.   **Visit Windows for Analysis of Urinalysis**

Scheduled Week	Nominal Day	Time Window (Rx Day A Range)
Week 0 DB	1[a]	≤ 1
Week 4 DB	29	2 – 43
Week 8 DB	57	44 – 71[b]
Week 12 OL	85	72[c] – 112
Week 20 OL	141	113 – 161
Week 26 OL	183	162 – 190

Rx Day A = date of visit – date of first study drug injection in double-blind treatment period + 1

a.   Date of first study drug injection in double-blind treatment period.

b.   For Week 8 DB, visit window was from Rx Day 37 to Rx Day 71 or the date of the first injection in OL period (if applicable), whichever comes first.

c.   For Week 12 OL, visit window was from Rx Day 72 or the date of the first injection in OL period + 1 (if applicable), whichever comes first, to Rx Day 112.

Table 5.   Visit Windows for Analysis of Fecal Calprotectin and IBDQ

Scheduled Week	Nominal Day	Time Window (Rx Day A Range)
Week 0 DB	1[a]	≤ 1
Week 4 DB	29	2 – 43
Week 8 DB	57	44 – 71[b]
Week 26 OL	183	72[c] – 190

Rx Day A = date of visit – date of first study drug injection in double-blind treatment period + 1

a.   Date of first study drug injection in double-blind treatment period.

b.   Rx Day 71 or the date of the first injection in OL period (if applicable), whichever comes first.

c.   For Week 26 OL, visit window was from Rx Day 72 or the date of the first injection in OL period + 1 (if applicable), whichever comes first, to Rx Day 190.

Vital signs and laboratory measurements will also be presented on the Any Adalimumab set using the visit windows in the following tables.

Table 6.   Visit Windows for Analysis of CDAI and Vital Sign (Any Adalimumab)

Visit Week	Nominal Day	Time Window (Rx Day B Range)
Week 0	1[a]	≤ 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

Rx Day B = date of visit – date of first dose of adalimumab + 1

a.   Date of first dose of adalimumab in double-blind treatment period.

Table 7. **Visit Windows for Analysis of hs-CRP, Chemistry and Hematology (Any Adalimumab)**

Visit Week	Nominal Day	Time Window (Rx Day B Range)
Week 0	1[a]	≤ 1
Week 2	15	2 – 22
Week 4	29	23 – 36
Week 6	43	37 – 50
Week 8	57	51 – 71
Week 12	85	72 – 99
Week 16	113	100 – 127
Week 20	141	128 – 162
Week 26	183	163 – 190

Rx Day B = date of visit – date of first dose of adalimumab + 1

a. Date of first dose of adalimumab in double-blind treatment period.

Table 8. **Visit Windows for Analysis of Urinalysis (Any Adalimumab)**

Visit Week	Nominal Day	Time Window (Rx Day B Range)
Week 0	1[a]	≤ 1
Week 4	29	2 – 43
Week 8	57	44 – 71
Week 12	85	72 – 112
Week 20	141	113 – 161
Week 26	183	162 – 190

Rx Day B = date of visit – date of first dose of adalimumab + 1

a. Date of first dose of adalimumab in double-blind treatment period.

Table 9.   **Visit Windows for Analysis of Fecal Calprotectin and IBDQ (Any Adalimumab)**

Visit Week	Nominal Day	Time Window (Rx Day B Range)
Week 0	1^a	≤ 1
Week 4	29	2 – 43
Week 8	57	44 – 71
Week 26	183	72 – 190

Rx Day B = date of visit – date of first dose of adalimumab + 1

a.   Date of first dose of adalimumab in double-blind treatment period.

Definition of Missing Data Imputation

The following imputation methods will be used to impute missing values in the efficacy analyses. In addition, an observed case analysis will be performed.

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.'

Subjects who dose-escalate from OL adalimumab 40 mg eow to OL adalimumab 80 mg eow due to disease flare or non-response will be imputed as 'Not Achieved' in the analysis of binary efficacy variables.

For the analysis of Week 26 efficacy variables only for dose-escalated subjects, the remission/response status will be determined based on the observed data at Week 26 after the dose escalation.

Last Observation Carried Forward (LOCF)

For all variables (discrete/categorical/response variables and continuous variables), except for the endpoint defined for dose-escalated subjects only, 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.

3. For subjects who dose-escalate to OL adalimumab 80 mg eow, the last non-missing value before dose escalation will be used for LOCF values at the following visits.

For the endpoints defined for dose-escalated subjects only, the last non-missing value through the entire study will be used for LOCF values at the following visits.

Observed Case (OC)

Observed case analysis will be performed such that missing values will not be imputed. Data from subjects who dose-escalate to OL adalimumab 80 mg eow will be considered missing after the point of dose escalation. These data will not be imputed and will not be included in the numerator or denominator.

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

Rule for CDAI Calculation

Up to 14 day of diaries will be recorded in eCRF or CDAI calculation for each visit. Diary entries will be evaluated for the CDAI calculation for each visit. For each CDAI subscore, the available scores from the most recent diary days (at least 4 days, up to

7 days) prior to actual day of the study visit will be summed, and then multiplied by the corresponding multiplier to get subtotal score. If available diary entries are fewer than 7 days, the subtotal score will be calculated as (summed total available score/number of days) × 7 × corresponding multiplier. The three subscores (number of liquid/very soft stools, abdominal pain rating, and general well-being) will then be rounded to one decimal. The final CDAI is rounded to a whole number.

If a subject has fewer than 4 days of diary data, the total CDAI score will not be calculated and will be considered missing.

If a subject has any subscore missing, the corresponding total CDAI score will be missing.

Definition of Clinical Remission

CDAI < 150.

Definition of Clinical Response

Decrease in CDAI $\geq$ 70 points from Baseline.

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

7.1 Demographic and Baseline Characteristics

For subjects in analysis ITT set, 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 n, mean, standard deviation, minimum value, median, and maximum value.

For ITT analysis set, demographics and baseline values will be compared between treatment groups and a p-value will be provided. In general, continuous variables will be analyzed using analysis of variance (using SAS procedure 'PROC GLM') with treatment group as factor. Categorical variable will be analyzed using chi-square test or Fisher's exact test if $\geq$ 20% of the cells have expected cell count < 5.

The following demographic and baseline values will be summarized.

Continuous Variables:

- Age (years)
- Body weight (kg)
- Height (cm)
- Body Mass Index (kg/m^2)
- Blood Pressure (Systolic/Diastolic) (mmHg)
- Pulse (bpm)
- Respiratory Rate (RPM)
- Temperature (°C)
- CDAI score
- Crohn's Disease Duration (years)
- hs-CRP (mg/L)
- Fecal Calprotectin (µg/g)
- Albumin Concentration (mg/mL)
- IBDQ score

Categorical Variables:

- Sex (male, female)
- Age ($\leq$ median, > median)
- Baseline Fecal Calprotectin ($\leq$ median, > median)
- Baseline Corticosteroid Use (yes, no)
- Baseline Immunosuppressant Use (yes, no)
- hs-CRP at Baseline ($< 10, \geq 10$ mg/L)
- hs-CRP at Baseline ($\leq$ median, > median)
- Crohn's Disease Severity (CDAI ≤ 300, > 300) at Baseline
- Baseline CDAI ($\leq$ median, > median)
- Weight ($\leq$ median, > median)

- Baseline Albumin Concentration (≤ median, > median)

- Disease Duration (≤ median, > median)

- Tobacco Use (user, ex-user, never used, unknown)

- Alcohol Use (drinker, ex-drinker, non-drinker, unknown)

7.2   Medical History

Medical and Surgical History: A complete medical and surgical history (which includes CD-onset date), history of tobacco and alcohol use, will be obtained from each subject during the Screening Period. An updated medical history will be obtained at the Baseline (Week 0) Visit to ensure that the subject still qualifies. Medical history will be summarized using body system and condition/diagnosis for ITT analysis by treatment group. No statistical tests will be performed.

Chest X-Ray Results: All subjects undergo a standard chest x-ray (including a posteroanterior [PA] and lateral view) or chest CT during the Screening Period. Number and percent of subjects with presence or absence of finding for the previous TB infection, calcified granulomas, pleural scarring/thickening, and other findings will be presented by treatment group. No statistical tests will be performed.

TB Test Results: QuantiFERON TB Gold test at Screening Visit will be summarized. QuantiFERON-TB tests will be described as positive, negative or indeterminate. No statistical tests will be performed.

TB Prophylaxis: History of use of TB prophylaxis or initiation of TB prophylaxis will be summarized.

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. No statistical tests will be performed.

7.3   Previous Treatment and Concomitant Medications

The previous and concomitant medications are defined in the protocol. Based on generic medication names, these categories of medications used by subjects before and during the study will be summarized by number and percent for ITT analysis set for the treatment groups. No statistical tests will be performed.

The number and percent of subjects using Crohn's disease specific medications including corticosteroids, aminosalicylates, immunomodulators (azathioprine, mercaptopurine, methotrexate, or other), and antibiotics within 90 days prior to Baseline, and at Baseline will be tabulated. The number and percentage of subjects using CD-specific immunomodulators at any time prior to Baseline will also be tabulated.

8.0   Patient Disposition

Subject disposition will be presented for subjects in the ITT analysis set using the following information by treatment group:

- Number and percent of subjects by treatment group and by investigator and/or site number in DB and OL periods
- Number and percent of subjects completing the DB Week 0 – 4, Week 0 – 8 and OL Week 8 – 26, and discontinuing during the DB Week 0 – 4, Week 0 – 8 and OL Week 8 – 26 visits, respectively
- Subject disposition, including the number and percent of subjects who prematurely discontinued during the DB Week 0 – 4, 0 – 8, and OL Week 8 – 26, respectively, by primary reason and by any reason

Summary of protocol deviations will be provided.

9.0   Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized using the mean, standard deviation, minimum, median, and maximum. Exposure to study drug (total patient years) will be summarized for each treatment group using Safety Analysis Set.

- Total exposure for DB placebo controlled period = date of Week 4 injection – date of first study drug dose, for subjects who did not prematurely discontinue before Week 4; If a subject discontinued at or before Week 4, then exposure is defined as "date of last injection prior to Week 4 – date of first injection + 14 days or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233, whichever comes first."

The number of injections received at each schedule time point will be summarized with number and percent for each treatment group using Safety Analysis Set.

Compliance (%) is defined as the number of injections received divided by the number of injections planned (rounded to 0.1) during the subject's participation in Study M14-233 and multiplied by 100 (rounded to 0.1%). Treatment Compliance will be summarized for the safety analysis set using descriptive statistics. Subjects with missing data for the number of injections returned will be excluded from the summary.

10.0   Efficacy Analysis

10.1   General Considerations

All statistical tests will be two-sided with the significance level of 0.05. 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 analysis will be performed using SAS$^{®}$ (SAS Institute Inc., Cary, NC, USA).

10.2   Primary Efficacy Analyses

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

Primary Efficacy Variables:

Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 4.

Analysis Data Set for the Primary Efficacy Analysis:

The primary efficacy analysis will use the ITT analysis data set.

Imputation Method Used for the Primary Efficacy Analysis:

The primary efficacy analysis will use the NRI method to impute the missing values at Week 4. Subjects with missing primary endpoint data at Week 4 will be classified as "no clinical remission."

Statistical Method of the Primary Efficacy Analysis:

The comparison for the difference between the treatment groups on the primary efficacy variable will be performed using the Cochran-Mantel-Haenszel (CMH) test and will be stratified by Crohn's disease severity (CDAI $\leq$ 300, > 300) at Baseline and corticosteroid use at Baseline. A CMH based two-sided 95% confidence interval for the difference between the treatment groups will be calculated. Missing CDAI will be imputed using the non-responder imputation (NRI) approach. Subjects who dose escalate will be imputed using NRI for visits after dose escalation. The last observation carried forward (LOCF) method will also be used as the sensitivity analyses.

10.3   Secondary Efficacy Analyses

The Week 26 efficacy endpoint is proportion of subjects who achieve clinical remission at Week 26 (CDAI < 150) in subjects who achieved clinical response (decrease in CDAI $\geq$ 70 points from Baseline) at Week 8. The one sample Exact test will be performed by comparing it to the clinically meaningful remission rate of 30%, and the two-sided 95% CI will be provided.

Key secondary efficacy endpoints include:

- Proportion of subjects who achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 4.
- Proportion of subjects who achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who achieved decrease in

CDAI ≥ 70 points from Baseline plus at least 30% reduction in hs-CRP from Baseline at Week 8.

● Proportion of subjects who discontinue corticosteroid use and achieve clinical remission (CDAI < 150) at Week 26 in subjects who were taking steroids at Baseline and who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

● Proportion of subjects who discontinue corticosteroid use and achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who were taking steroids at Baseline and who achieved decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 8.

● Proportion of subjects who achieve clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 4.

● Proportion of subjects who achieve decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 4.

● Proportion of subjects who achieve CDAI < 150 and hs-CRP < 3 mg/L at Week 4.

● Proportion of subjects who achieve CDAI < 150, hs-CRP < 3 mg/L at Week 26 in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

● Proportion of subjects who achieve IBDQ remission (IBDQ ≥ 170 points) at Week 4.

● Proportion of subjects who achieve IBDQ remission at Week 26 in subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

● Change from Baseline in fecal calprotectin level at Week 4.

● Proportion of subjects who achieve CDAI < 150, hs-CRP < 3 mg/L and fecal calprotectin < 250 µg/g at Week 4.

● Proportion of subjects who achieve CDAI < 150, hs-CRP < 3 mg/L and fecal calprotectin < 250 µg/g at Week 26 in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

Additional secondary endpoints include:

- Proportion of subjects with clinical remission (CDAI < 150) over time.
- Proportion of subjects with CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline over time.
- Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) over time.
- Proportion of subjects with decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline over time.
- Change from Baseline in CDAI over time.
- Change from Baseline in hs-CRP level over time.
- Change from Baseline in fecal calprotectin level over time.

The analysis over time will be performed for the DB placebo-controlled period (Week 0 to Week 4), with comparisons between active treatment and placebo groups. The analysis over time will also be performed for Any Adalimumab set (the entire study on or after the first dose of adalimumab), with only summary statistics for adalimumab treatment.

Exploratory endpoints include:

- Proportions of subjects who achieve CDAI < 150 at Week 26 in subjects who did not achieve clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

For categorical endpoints with comparison between the treatment groups, the difference in proportions of subjects between treatment groups will be analyzed using the CMH test adjusted for stratification variables. Additionally, the CMH based two-sided 95% confidence interval for the difference in proportions will be provided. For categorical endpoints with comparison to the clinically meaningful constant rate, the one sample Exact test will be performed and the two-sided 95% CI will be provided. The NRI imputation method will be used for subjects with missing data at the time point

evaluated. Subjects who dose-escalate will be imputed using NRI for visits after dose escalation. The LOCF method will also be used as the sensitivity analyses.

Change from Baseline in continuous endpoints will be analyzed using Analysis of Covariance (ANCOVA) model including factor for treatment group, stratification factors and Baseline values. For analyses of changes from Baseline variables, both LOCF and observed case analyses will be performed. The LOCF analysis is considered primary for inferential purposes.

10.4　　　　Handling of Multiplicity

No adjustment for multiplicity will be done.

10.5　　　　Efficacy Subgroup Analysis

The subgroups listed below will be used in subgroup analyses of the primary endpoint.

- Sex (male, female)
- Age ($\leq$ median, > median)
- Baseline fecal calprotectin ($\leq$ median, > median)
- Baseline fecal calprotectin ($\leq$ 250 µg/g, > 250 µg/g)
- Baseline corticosteroid use (yes, no)
- Baseline immunosuppressant use (yes, no)
- hs-CRP at Baseline (< 10 and $\geq$ 10 mg/L)
- hs-CRP at Baseline (< 30 and $\geq$ 30 mg/L)
- hs-CRP at Baseline ($\leq$ median, > median)
- Crohn's disease activity (CDAI $\leq$ 300, > 300) at Baseline
- Baseline CDAI ($\leq$ median, > median)
- Weight ($\leq$ median, > median)
- Baseline albumin ($\leq$ median, > median)
- Disease duration ($\leq$ 3 years, > 3 years)
- Disease duration ($\leq$ median, > median)

11.0   Safety Analysis

11.1   General Considerations

Safety analyses will include reporting of adverse events, laboratory, and vital sign measurements. Safety analyses will be carried out using the Safety set for the DB placebo controlled period (Week 0 to Week 4), and will be carried out using the Any Adalimumab set for the DB/OL period of Any Adalimumab (the entire study on or after the first dose of adalimumab up to 70 days after the last dose of adalimumab, or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233). The safety analyses results through Week 4 will be presented using two treatment groups (i.e., ADA160/80 versus placebo). The safety analysis on the Any Adalimumab set will be presented for all the subjects as one adalimumab treatment group.

Comparisons between active treatment and placebo groups will be performed for the DB placebo controlled period using the safety analysis set. The safety variable will be summarized by treatment according to the treatment a subject actually received. The differences between treatment group and placebo in safety parameters will be evaluated using two-sided tests at the significance level of 0.100.

For the any adalimumab analysis Set, only summary statistics will be provided for adalimumab treatment.

Missing safety data will not be imputed.

11.2   Analysis of Adverse Events

11.2.1   Treatment-Emergent Adverse Events

Treatment-emergent AEs will be summarized separately for the DB placebo-controlled period and for the DB/OL period of Any Adalimumab.

Treatment-emergent AEs during placebo-controlled DB period are defined as events that begin or worsen either on or after the first dose of study drug and up to the first dose of

study drug at Week 4, or within 70 days after the last dose of study drug, or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233, for subjects who discontinued prior to Week 4. Treatment-emergent AEs during DB/OL period of Any Adalimumab are defined as events that begin or worsen either on or after the first dose of adalimumab in DB or OL period, and within 70 days after the last dose of study drug, or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233.

An overview of treatment-emergent AEs, including AEs of special interest such as adverse events leading to death and adverse events leading to early termination, AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 20.0 or later) preferred term and system organ class, AEs by maximum relationship to study drug, and AEs by maximum severity will be summarized by number and percentage.

The number and percent of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories. Comparisons of the percent of subjects experiencing an adverse event between adalimumab and placebo during the DB placebo controlled period will be performed using Fisher's exact tests. Only *P* values < 0.100 when rounded to three digits will be presented.

- Any treatment-emergent adverse event.
- Any treatment-emergent adverse event with a Reasonable Possibility of being related to study drug by the investigator.
- 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 adverse event leading to death.
- Any treatment-emergent adverse event of special interest.
- Any deaths.

Adverse events with missing or unknown relationship to study drug will be categorized as having a reasonable possibility of being study drug-related. Adverse events with missing or unknown severity will be categorized as severe.

Treatment-emergent adverse events will be summarized as follows:

- Grouped by System Organ Class and Preferred Term.
- A by-subject listing will be provided.
- Grouped by System Organ Class, Preferred Term and maximum Severity.
- Grouped by System Organ Class, Preferred Term and maximum Relationship to Study Drug.
- Grouped by System Organ Class and Preferred Term with subject numbers.

Treatment-emergent AEs occurring for more than 5% of the subjects in any of the treatment arms will be summarized by MedDRA PT in decreasing frequency of adalimumab treatment arm.

In treatment-emergent AE tables, a subject who reports more than one treatment-emergent AE in different system organ classes will be counted only once in the overall total. A subject who reports two or more different preferred terms which are in the same SOC will be counted only once in the SOC total. A subject who reports more than one treatment AE with the same preferred term will be counted only once for that preferred term using the most extreme incident (i.e., most "severe" for the severity tables and most "related" for the relationship tables).

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 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.

Treatment-emergent AEs will be summarized for any adalimumab set by event rate per 100 patient-years, defined as

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

where total patient years is defined as the sum of the study drug exposure of all subjects, as defined in an earlier section, normalized by 365.25, and rounded to 1 decimal place.

11.2.2   Adverse Events of Special Interest

The following AEs of special interest will be summarized by number and percentage of subjects experiencing an AE of interest. The AEs of interest will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) for the following AE categories:

- Any infection,
- Any serious infection,
- Any legionella infection,
- Any diverticulitis,
- Any opportunistic infection excluding oral candidiasis and TB,
- Any oral candidiasis,
- Any tuberculosis,
- Any active tuberculosis,

- Any latent tuberculosis,
- Any parasitic infection,
- Any reactivation of hepatitis B,
- Any progressive multifocal leukoencephalopathy (PML),
- Any malignancy,
- Any lymphoma,
- Any hepatosplenic T-cell lymphoma (HSTCL),
- Any non-melanoma skin cancers (NMSC),
- Any melanoma,
- Any leukaemia,
- Any malignancy other than lymphoma, HSTCL, leukaemia, NMSC or melanoma,
- Any allergic reaction including angioedema/anaphylaxis,
- Any lupus-like reactions and systemic lupus erythematosus,
- Any vasculitis,
- Any cutaneous vasculitis,
- Any non-cutaneous vasculitis,
- Any sarcoidosis,
- Any autoimmune hepatitis,
- Any myocardial infarction,
- Any cerebrovascular accident,
- Any CHF,
- Any pulmonary embolism,
- Any interstitial lung disease,
- Any intestinal perforation,
- Any intestinal stricture,
- Any pancreatitis,
- Any Stevens-Johnson Syndrome,
- Any erythema multiforme,

- Any worsening/new onset of psoriasis,
- Any demyelinating disorder,
- Any amyotrophic lateral sclerosis,
- Any reversible posterior leukoencephalopathy syndrome (RPLS),
- Any hematologic disorders including pancytopenia,
- Any liver failure and other liver event,
- Any Humira administration related medication error,
- Any injection site reaction.

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

11.3   Analysis of Laboratory Data

Changes from baseline in continuous laboratory parameters will be summarized for each visit. The mean change from baseline will be compared between treatment groups (ADA 160/80 versus placebo) at each time point during the DB placebo-controlled period on the Safety Analysis set. Summaries of mean changes from baseline will be provided on the Any Adalimumab set for the adalimumab treatment.

Mean changes from baseline to post-baseline visits will be summarized with the baseline mean, the visit mean, change from baseline mean, standard deviation and median. The treatment group differences for mean changes from baseline will be analyzed using a one-way ANOVA and between group mean change from baseline with the 95% confidence interval, standard error, and *P* value will be presented.

Shift tables from baseline to the final value according to the normal range will be provided for each hematology, clinical chemistry parameter and urinalysis parameter (specific gravity and pH only).

For selected laboratory parameter with Common Toxicity Criteria (CTC), frequencies and percentages of subjects with post baseline lab values that are Grade 3 or above according

to the CTC toxicity criteria Version 3.0 (or later) will be summarized. Comparisons of the percentage of subjects experiencing a value meeting the criteria between treatment groups will be performed using Fisher's exact tests. Only P values ≤ 0.100 when rounded to three digits will be presented. 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.

11.3.1   Analysis of Liver Specific Laboratory Tests

The liver specific laboratory tests include the serum glutamic-pyruvic transaminase (ALT/SGPT), serum glutamic-oxaloacetic transaminase (AST/SGOT), alkaline phosphatase and total bilirubin. Each of these laboratory values will be categorized as follows:

1. < 1.5 ULN,

2. $\geq 1.5 \times$ ULN TO $< 3 \times$ ULN,

3. $\geq 3 \times$ ULN TO < 5 ULN,

4. $\geq 5 \times$ ULN TO < 8 ULN, and

5. $\geq 8 \times$ 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 $\geq 2.5 \times$ ULN, or

2.   AST $\geq 2.5 \times$ ULN, or

3.   Alkaline Phosphatase $\geq 2.5 \times$ ULN, or

4.   Total Bilirubin $\geq 1.5 \times$ ULN.

11.4   Analysis of Vital Signs

The following vital signs will be summarized at every visit during the study.

- Body Weight (kg)
- Blood Pressure (Systolic/Diastolic) (mmHg)
- Pulse (bpm)
- Respiratory Rate (RPM)
- Temperature (°C)

Changes from baseline in vital sign measurements will be summarized for each visit.

The mean change from baseline will be compared between treatment groups (ADA 160/80 versus placebo) during the DB placebo-controlled period on the Safety analysis set. Summaries of mean changes from baseline will be provided on the Any Adalimumab analysis set.

Mean changes from baseline to post-baseline visits will be summarized with the baseline mean, the visit mean, change from baseline mean, standard deviation and median. The treatment group differences for mean changes from baseline will be analyzed using a one-way ANOVA and the between group mean change from baseline with the 95% confidence interval, standard error, and *P* value will be presented.

12.0   Summary of Changes

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

In the current SAP, safety data will be summarized separately for the DB placebo-controlled period (Week 0 to Week 4) and for the DB/OL periods of Any Adalimumab (during the entire study on or after first dose of adalimumab from Week 0 to 70 days after

the last dose of the study medication, or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233). This is different from the latest version of protocol, which stated that safety data will be summarized separately for the double-blind dosing period (Week 0 to Week 8) and the OL period (Week 8 to 70 days after the last dose of the study medication, or the date subjects initiate adalimumab therapy not supplied in the context of Study M14-233). Per the study design, placebo subjects would receive adalimumab 160/80 mg induction dose from Week 4 to Week 8. Therefore it is appropriate to summarize placebo re-induction period safety data with adalimumab re-induction period safety data from Week 4 to 8, and with OL safety data.

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

This is the first version of the SAP.

13.0 Appendix

14.0 References

Document Approval

Study M14233 - Statistical Analysis Plan Version 1 - 26Oct2017 (E3 16.1.9)

Version: 1.0   **Date:** 30-Oct-2017 06:09:13 PM   **Company ID:** 10302017-00F9F683B05036-00001-en

Signed by:	Date:	Meaning Of Signature:
	26-Oct-2017 02:17:05 PM	Approver
	26-Oct-2017 02:21:10 PM	Author
	30-Oct-2017 06:09:12 PM	Approver