1.0 Title Page

Statistical Analysis Plan

Final Analysis

Study M06-807

A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Efficacy and the Long-Term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Crohn's Disease Who Have Demonstrated a Clinical Response in the M06-806 Study

Date: 11 Apr 2017

Version 4.0

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3.0 Introduction

This document describes the final analysis plan for statistical analysis of the Study M06-807 "A Multi-Center, Open-Label Study of the Human Anti-TNF Monoclonal Antibody Adalimumab to Evaluate the Efficacy and the Long-term Safety and Tolerability of Repeated Administration of Adalimumab in Pediatric Subjects with Crohn's Disease Who Have Demonstrated a Clinical Response in the M06-806 Study."

The study design and analyses presented in this document are based on the last amended study protocol (Amendment 7) dated 26 May 2015. It takes into account ICH Guidelines E3 and E9. This statistical analysis plan (SAP) will provide details to further elaborate statistical methods as outlined in the protocol and describe analysis conventions to guide the statistical programming work.

The present statistical analysis plan describes the final analysis for safety and efficacy of Study M06-807.

The AbbVie Global Statistics Department will perform the statistical analysis, using the current version of the SAS® software under the UNIX operating system.

3.1 Scope of the Analysis

The first interim analysis was completed using data on or before 30 November 2010 to obtain preliminary results on the longer term safety and efficacy of adalimumab in pediatric Crohn's disease (CD), beyond the 52 weeks of the parent Study M06-806. The principal purpose of the first interim analysis was to evaluate the safety of the study drug. The efficacy variables, clinical remission and clinical response based on Pediatric Crohn's Disease Activity Index (PCDAI) and Crohn's Disease Activity Index (CDAI) were summarized over time. Information on demographic, baseline characteristics and prior/concomitant medications of the enrolled subjects were also provided.

The second interim analysis was performed using data on or before 31 July 2011. Similar variables on safety, efficacy, demographic, baseline characteristics and prior/concomitant

medications of the enrolled subjects were provided. In addition, the dose de-escalation population which consists of all subjects who have responded well to treatment and had dose and/or frequency decrease per protocol Amendment 4 were examined.

The third interim analysis was performed using data with an associated cutoff date of 31 January 2015. In addition to the analyses performed in the second interim analysis, corticosteroid-free remission and concomitant corticosteroid-free remission were added as new efficacy variables. Subgroup analysis was conducted on some safety and efficacy variables.

The final analysis will be performed using final data.

4.0 Study Objectives, Design and Procedures

4.1 Objective

As per the study protocol, the objective of the study is to evaluate the long-term maintenance of clinical response, safety and tolerability of repeated administration of adalimumab in pediatric subjects with CD who participated in, and successfully completed, Protocol M06-806 through Week 52 and enrolled in Protocol M06-807.

4.2 Study Design

This study is a multicenter, open-label study of the human anti-TNF monoclonal antibody adalimumab. Thirty-one sites participated in Study M06-807. Approximately 130 pediatric subjects were expected to enroll in this study; final enrollment was 100 subjects.

Subjects were allowed to enroll in Study M06-807 if they participated in and successfully completed Protocol M06-806 through Week 52. A subject must have been a responder at any time point during Study M06-806. A responder was defined as a subject who had a PCDAI that was at least 15 points lower than the Study M06-806 baseline PCDAI.

All subjects were on open-label maintenance therapy during Study M06-807. Subjects who enrolled into the study from blinded therapy in Study M06-806 received open-label therapy at a dose dependent on their body weight. Subjects who weighed ≥ 40 kg at Baseline (the Week 52 visit of Study M06-806) received 40 mg eow of adalimumab, while subjects who weighed < 40 kg at Baseline received 20 mg eow of adalimumab. Beginning at Week 8, subjects who had a disease flare may have been switched to ew treatment at the same dose of adalimumab received while on eow treatment. A disease flare was defined as an increase in the Pediatric Crohn's Disease Activity Index (PCDAI) of ≥ 15 points when compared to the PCDAI obtained at the subject's previous visit.

Subjects who enrolled into the study from open-label therapy in Study M06-806 continued to receive the same dose they were receiving (i.e., 40 mg ew or 20 mg ew) at the Week 52 visit of Study M06-806.

Subjects who developed a flare while receiving ew open-label therapy or had a PCDAI ≥ 15 points when compared to their Baseline (the Week 52 visit of Study M06-806) PCDAI (regardless of study visit), may have been discontinued from the study at the discretion of the Investigator.

Beginning from Week 8, the dose of adalimumab may have been increased to 40 mg, at the discretion of the Investigator, for subjects whose body weight had increased from < 40 kg to ≥ 40 kg from Baseline (the Week 52 visit of Study M06-806). The site entered the subject's body weight into the Interactive Voice Response System (IVRS) and the dose would have been adjusted, if applicable.

Reductions in concomitant therapy were allowed for Crohn's treatment related toxicities (e.g., leukopenia, anemia, neuropathy) of Grade 3 or higher.

Subjects may have been allowed to decrease prednisone (or equivalent) and budesonide if qualifications were met (Section 5.2.3.2 of protocol for required timing and rate of taper).

Subjects may have been allowed to adjust their Crohn's specific concomitant medications as specified in Section 5.2.3.2 of protocol.

The duration of the study could last up to 408 weeks (approximately 8 years). Subjects who completed, or who early terminated from the study were to be contacted 70 days after their last dose of study drug to obtain information on any ongoing and new adverse events.

This study was to be concluded approximately 12 weeks after the following criteria were satisfied:

- Study drug received country and local (if applicable) regulatory approval for pediatric Crohn's Disease.
- All applicable local reimbursement procedures were completed.

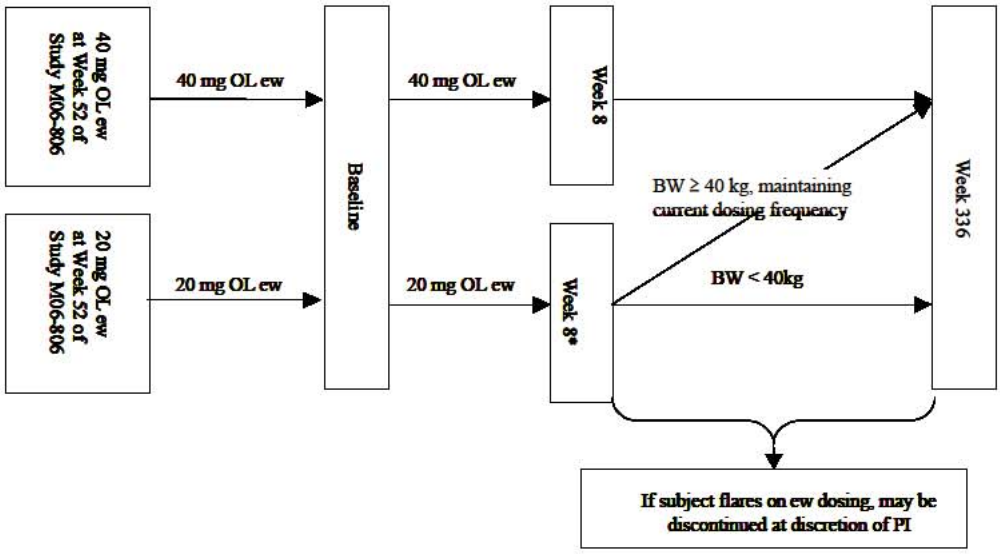
Sites were notified once these criteria were met.

Following country and local (if applicable) regulatory approval and applicable local reimbursement approval of the study drug in a country, subjects should have returned to their next scheduled study visit as specified in the protocol. The termination visit should have been conducted in place of their regular scheduled study visit. These subjects should have been considered as having completed the study.

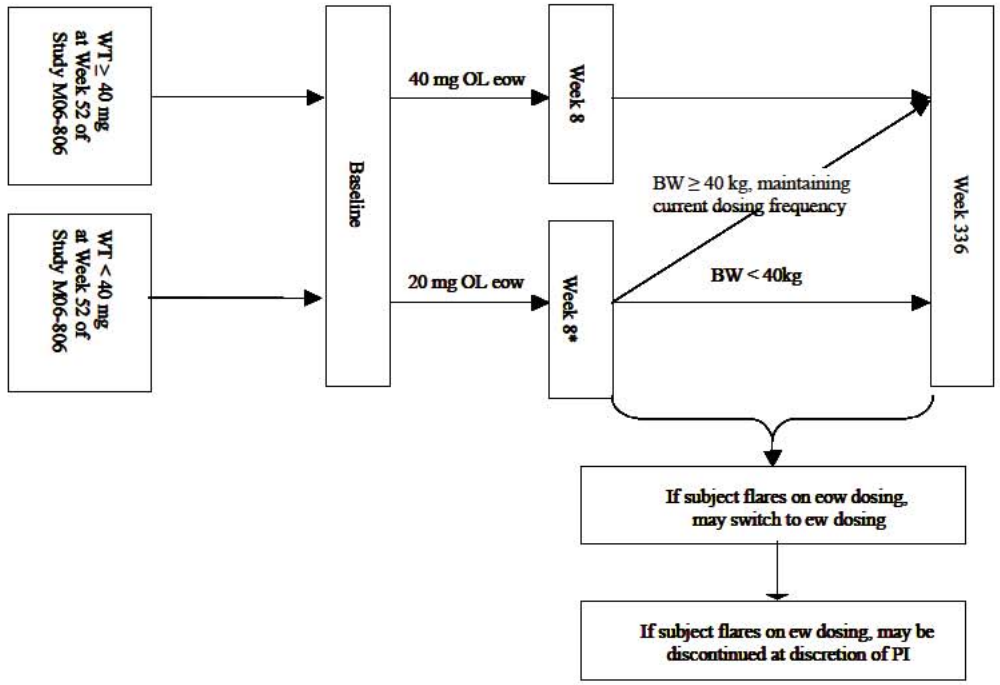
After completion of Study M06-806 and consideration of efficacy, safety and population pharmacokinetic results in conjunction with exposure-response modeling and simulation, it was observed that both the Low-Dose and High-Dose treatment provided evidence of efficacy and safety. Therefore, in order to minimize the systemic exposures to study drug to the lowest doses necessary in children with CD, Amendment 4 provided investigators with the option of dose de-escalation by reducing the dose or switching from ew to eow based on the clinical status of the individual patient. In addition, since the 10 mg eow dose was efficacious in subjects weighing < 40 kg in Study M06-806 patients had the option to be switched to this dose based on their body weight and clinical status at the discretion of the investigator. Subjects who experienced a disease flare may have re-increased their dosage or dose frequency to the next higher treatment level regardless

of prior dose or dose frequency decrease. A schematic of the study design is shown in Figure 1 (prior to Amendment 4) and in Figure 2 (after Amendment 4).

Figure 1. Study Schematic

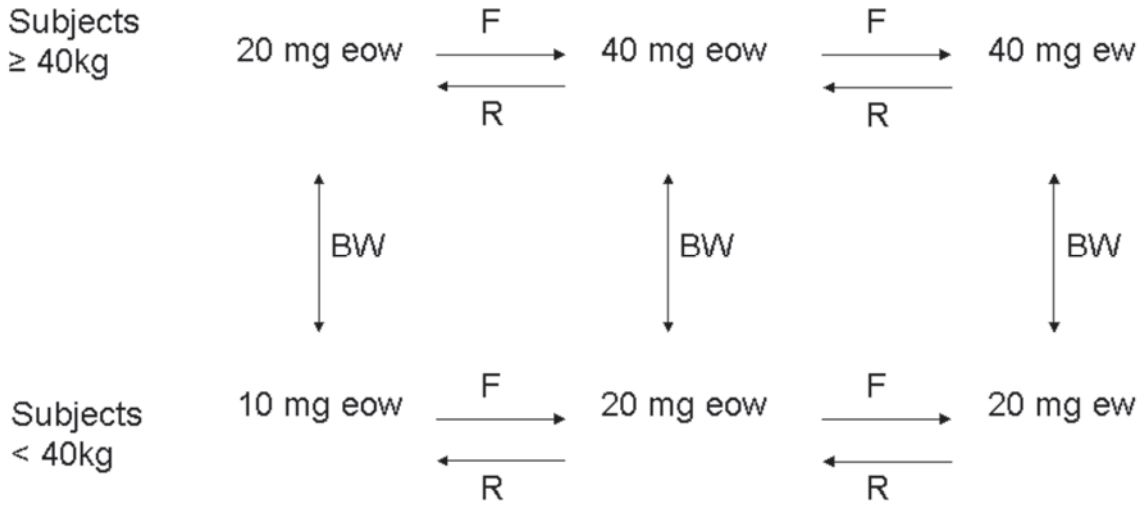


Subjects who enter M06-807 Study from Double-Blind Dosing of M06-806 Study



* At or after Week 8 subjects on 20 mg OL dosing with an increase in BW to ≥ 40 kg may increase their dosing to 40 mg OL at the discretion of the Investigator.

Figure 2. Dosing Schematic After Amendment 4



F: Subjects who have a disease flare may be switched to the next higher treatment level.

R: Subjects who responded to their current treatment may be switched to the next lower treatment level at the discretion of the investigator after discussion with the medical monitor. Response is defined as a) a ≥ 15 points decrease in PCDAI compared to the last observation prior to dose escalation in patients who dose-escalated or b) a ≥ 15 points decrease in PCDAI compared to Baseline of Study M06-806 in patients who did not dose escalate.

BW: Subjects with an increase in body weight to ≥ 40 kg may increase their dose to the next higher level at the discretion of the investigator after discussion with the medical monitor. Subjects with a decrease in body weight to < 40 kg may decrease their dose to the next lower level at the discretion of the investigator after discussion with the medical monitor.

Study procedures were to be performed as summarized in the study schematic presented in Table 1.

Table 1. Study Activities

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Inclusion/exclusion criteria	X									
Informed consent	X									
Previous and concomitant medications	X[a]	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X[a]	X	X	X	X	X	X	X	X	X
Vital signs[c]	X[a]	X	X	X	X	X	X	X	X	X
Physical exam	X[a]	X	X	X	X	X	X	X	X	X
General LAB[d]	X[a]	X	X	X	X	X	X	X	X	X
TB testing (PPD or QuantiFERON-TB Gold)[e]							X			
Urinalysis[f]	X[a]	X	X	X	X	X	X	X	X	X
Erythrocyte sedimentation rate	X[a]	X	X	X	X	X	X	X	X	X
CRP	X[a]				X		X		X	
ANA	X[a]			X						
Anti-dsDNA[g]	X[a]			X						
PCDAI	X[a]	X	X	X	X	X	X	X	X	X
CDAI[h]	X[a]	X	X	X	X	X	X	X	X	X
IMPACT III Questionnaire[i]	X[a]			X	X		X		X	

Table 1. Study Activities (Continued)

Activity	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X[a]	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X[a]	X	X	X	X	X	X	X	X	X
X-ray for bone age[j]	X[a]						X			
Serum bone markers	X[a]				X		X		X	
PK Blood Sample[k]					X		X		X	
Anti-adalimumab blood levels (AAA)[k]					X		X		X	
Adverse events[l]	X[a]	X	X	X	X	X	X	X	X	X
Dispense study drug	X[a]	X	X	X	X	X	X	X	X	X

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
Inclusion/exclusion criteria										
Informed consent										
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X	X	X		X		X		X	
Vital signs[c]	X	X	X		X		X		X	
Physical exam	X	X	X		X		X		X	
General LAB[d]	X	X	X		X		X		X	
TB testing (PPD or QuantiFERON-TB Gold)[e]	X				X				X	
Urinalysis[f]	X	X	X		X		X		X	
Erythrocyte sedimentation rate	X	X	X		X		X		X	
CRP		X			X		X		X	
ANA		X			X				X	
Anti-dsDNA[g]		X			X				X	
PCDAI	X	X	X		X		X		X	
CDAI[h]	X	X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 96	Week 108	Week 120	Week 132 Call	Week 144	Week 156 Call	Week 168	Week 180 Call	Week 192	Week 204 Call
IMPACT III Questionnaire[i]		X	X		X		X		X	
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X	X	X		X		X		X	
X-ray for bone age[j]		X			X				X	
Serum bone markers[j]		X	X		X		X		X	
PK Blood Sample[k]	X		X		X		X		X	
Anti-adalimumab blood levels (AAA)[k]	X		X		X		X		X	
Adverse events[l]	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X	X	X		X		X		X	

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336	Week 348 Call	Week 360
Inclusion/exclusion criteria													
Informed consent													
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[b]	X		X		X		X		X		X		X
Vital signs[c]	X		X		X		X		X		X		X
Physical exam	X		X		X		X		X		X		X
General LAB[d]	X		X		X		X		X		X		X
TB testing (PPD or QuantiFERON-TB Gold)[e]			X				X				X		
Urinalysis[f]	X		X		X		X		X		X		X
Erythrocyte sedimentation rate	X		X		X		X		X		X		X
CRP	X				X		X		X		X		X
ANA					X								
Anti-dsDNA[g]					X								
PCDAI	X		X		X		X		X		X		X

Table 1. Study Activities (Continued)

Activity	Week 216	Week 228 Call	Week 240	Week 252 Call	Week 264	Week 276 Call	Week 288	Week 300 Call	Week 312	Week 324 Call	Week 336	Week 348 Call	Week 360
CDAI[h]	X		X		X		X		X		X		X
IMPACT III Questionnaire[i]	X		X		X		X		X		X		X
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)	X		X		X		X		X		X		X
X-ray for bone age[j]					X				X				X
Serum bone markers[j]	X		X		X		X		X		X		X
PK Blood Sample[k]	X		X		X		X		X		X		X
Anti-adalimumab blood levels (AAA)[k]	X		X		X		X		X		X		X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X		X		X		X		X		X		X

Table 1. Study Activities (Continued)

Activity	Week 372 Call	Week 384	Week 396 Call	Week 408/ Early Term	Unsched Visit	70-Day Follow-Up Call
Inclusion/exclusion criteria						
Informed consent						
Previous and concomitant medications	X	X	X	X	X	
Urine pregnancy test[b]		X		X	X	
Vital signs[c]		X		X	X	
Physical exam		X		X	X	
General LAB[d]		X		X	X	
TB testing (PPD or QuantiFERON-TB Gold)[e]		X		X		
Urinalysis[f]		X		X	X	
Erythrocyte sedimentation rate		X		X	X	
CRP		X		X	X	
ANA				X		
Anti-dsDNA[g]				X		
PCDAI		X		X	X	
CDAI[h]		X		X	X	
IMPACT III Questionnaire[i]		X		X	X	
Unscheduled outpatient visits, emergency room visits and hospitalizations questionnaire	X	X	X	X	X	

Table 1. Study Activities (Continued)

Activity	Week 372 Call	Week 384	Week 396 Call	Week 408/ Early Term	Unsched Visit	70-Day Follow Up Call
Work Productivity and Impairment Questionnaire: Crohn's Disease (WPAI – CD)		X		X	X	
X-ray for bone age[j]				X		
Serum bone markers[j]		X		X	X	
PK Blood Sample[k]		X		X	X	
Anti-adalimumab blood levels (AAA)[k]		X		X	X	
Adverse events[l]	X	X	X	X	X	X
Dispense study drug		X			X[m]	

a. At the Baseline Visit, the following procedures will be completed as part of Week 52 of the Study M06-806.

b. Performed on all females of child-bearing potential – Urine pregnancy test at all study visits.

c. Vital sign determinations of height, weight, sitting blood pressure, heart rate, respiratory rate, and body temperature will be obtained at each visit.

d. Blood draws should be performed after questionnaire and vital signs determinations and before study drug administration.

e. PPD or QuantiFERON-TB Gold testing at Weeks 48, 96, 144, 192, 240, 288, 336, 384 and 408/ET. No annual TB test should be done at Week 408 or at ET if already done at Week 384 or later.

f. Microscopic urinalysis will be performed at any visit if dipstick UA is abnormal (protein greater than a trace, blood greater than 5 – 10 Ery/ul, moderate or large ketone count or glucose greater than 50 mg/dL).

g. If an ANA result is positive, anti-dsDNA will be performed automatically.

h. For subjects who are age 13 or older at the Study M06-807 Baseline Visit, a CDAI will be completed at each visit.

i. For subjects who are age 10 or older at the Study M06-807 Baseline Visit, an IMPACT III Assessment will be completed at Baseline, Weeks 12, 24, 48, 72, 108, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408/ETC and unscheduled visits.

Table 1. Study Activities (Continued)

j. If the height velocity is 0 and, in the opinion of the investigator, a subject is no longer growing, the x-ray for bone age and the determination of serum bone markers can be omitted.

k. In addition to blood draws every 24 weeks, PK and AAA blood draws to be performed if subject meets flare criteria and dose escalated to ew dosing.

l. All AEs, including SAEs, will be captured throughout the study from the time that the subject signs the Informed Consent Form. SAEs will be captured throughout the 70 day follow-up period (if applicable).

m. If an unscheduled visit is performed to change the frequency or dose of study drug, study drug may be dispensed.

4.3 Sample Size

Subjects who successfully completed Study M06-806 through Week 52 were eligible to participate in this study. One hundred (100) subjects from Study M06-806 were enrolled in this study.

4.4 Analysis

Final analysis will be performed using the final data. The safety, efficacy, demographic, baseline characteristics and prior/concomitant medications of the enrolled subjects will be summarized.

4.5 Derived, Defined and Transformed Variables

For the analysis the following efficacy variables are defined:

1. The clinical remission and response as per PCDAI (to be measured for all subjects) are defined as follows:
   - Clinical response is defined as a decrease from Study M06-806 Baseline in PCDAI ≥ 15 points.
   - Clinical remission is defined as PCDAI ≤ 10.
2. The clinical remission and response as per CDAI (to be measured and analyzed only for subjects 13 years and older at Study M06-806 Baseline) are defined below:
   - Clinical response is defined as a decrease from Study M06-806 Baseline in CDAI ≥ 70 points.
   - Clinical remission is defined as CDAI < 150.
3. The corticosteroid-free remission as per PCDAI (to be measured for all subjects with corticosteroid use at Study M06-806 Baseline) is defined as follows:
   - Discontinued corticosteroids for at least 90 consecutive days prior to the respective visit and PCDAI ≤ 10 at that visit.

4. The corticosteroid-free remission as per CDAI (to be measured and analyzed only for subjects 13 years and older at Study M06-806 Baseline with corticosteroid use at Study M06-806 Baseline) is defined as follows:
    - Discontinued corticosteroids for at least 90 consecutive prior to the respective visit and CDAI < 150 at that visit.
5. The concomitant corticosteroid-free remission as per PCDAI (to be measured for all subjects with corticosteroid use at Study M06-806 Baseline) is defined as follows:
    - Discontinued corticosteroids prior to the respective visit and PCDAI ≤ 10 at that visit.
6. The concomitant corticosteroid-free remission as per CDAI (to be measured and analyzed only for subjects 13 years and older at Study M06-806 Baseline with corticosteroid use at Study M06 806 Baseline) is defined as follows:
    - Discontinued corticosteroids prior to the respective visit and CDAI < 150 at that visit.

5.0 Analysis Populations

5.1 Definition of Analysis Populations

The following two study populations will be used for analyses in this study.

Intent-To-Treat (ITT) Population: The ITT population consists of all subjects who received at least one dose of adalimumab in Study M06-807 and also had at least one non-missing efficacy measurement during the study. The ITT population will be used for efficacy analyses in this study.

Safety Population: The safety population consists of all subjects who received at least one dose of adalimumab in Study M06-807. The safety population will be used for safety analyses in this study.

6.0 Analysis Conventions

Definition of Baseline

For the analysis of change and percent change, 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 medication during the parent Study M06-806. Clinical response and remission based on CDAI and PCDAI will also be calculated using the Study M06-806 baseline values. The baseline values of the Study M06-806 will be reported for the subjects enrolled in the Study M06-807.

However, as mentioned in the next section, the visit windows used for the analysis are defined with respect to the first dose date during the Study M06-807.

Definition of Rx Days (Days Relative to the First Dose During Study M06-807)

Rx days are calculated for each time point relative to assigned visit. They are defined as the number of days between the day of the first dose of study drug in Study M06-807 and the specific time point. Rx days are negative values when the time point of interest is prior to the first study drug dose day. Rx days are positive values when the time point of interest is after the first study drug dose day. The day of the first dose of study drug in Study M06-807 is defined as Rx Day 1, while the day prior to the first study drug dose is defined as Rx Day –1 (there is no Rx Day 0).

Definition of Analysis Windows

All time points and corresponding time windows are defined based on Rx days. If more than one assessment is included in a time window the assessment closest to the nominal day should be used. If there were more than one observation with equal distance to the nominal day the latest one will be used in the analyses. 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. Time Window for Measurements Done at Each Office Visit

Assigned Visit	Nominal Day	Time Window (Rx Day Range)
Week 0	1	≤ 1
Week 4	29	2 – 43
Week 8	57	44 – 71
Week 12	85	72 – 127
Week 24	169	128 – 211
Week 36	253	212 – 295
Week 48	337	296 – 379
Week 60	421	380 – 463
Week 72	505	464 – 547
Week 84	589	548 – 631
Week 96	673	632 – 715
Week 108	757	716 – 799
Week 120	841	800 – 925
Week 144	1009	926 – 1093
Week 168	1177	1094 – 1261
Week 192	1345	1262 – 1429
Week 216	1513	1430 – 1597
Week 240	1681	1598 – 1765
Week 264	1849	1766 – 1933
Week 288	2017	1934 – 2101
Week 312	2185	2102 – 2269
Week 336	2353	2270 – 2437
Week 360	2521	2438 – 2605
Week 384	2689	2606 – 2773
Week 408	2857	2774 – 2941

Table 3. Time Window for Analysis of IMPACT III

Assigned Visit	Nominal Day	Time Window (Rx Day Range)
Week 0	1	≤ 1
Week 12	85	2 – 127
Week 24	169	128 – 253
Week 48	337	254 – 421
Week 72	505	422 – 631
Week 108	757	632 – 799
Week 120	841	800 – 925
Week 144	1009	926 – 1093
Week 168	1177	1094 – 1261
Week 192	1345	1262 – 1429
Week 216	1513	1430 – 1597
Week 240	1681	1598 – 1765
Week 264	1849	1766 – 1933
Week 288	2017	1934 – 2101
Week 312	2185	2102 – 2269
Week 336	2353	2270 – 2437
Week 360	2521	2438 – 2605
Week 384	2689	2606 – 2773
Week 408	2857	2774 – 2941

Table 4. Time Window for Analysis of hs-CRP

Assigned Visit	Nominal Day	Time Window (Rx Day Range)
Week 0	1	≤ 1
Week 24	169	2 – 253
Week 48	337	254 – 421
Week 72	505	422 – 631
Week 108	757	632 – 883
Week 144	1009	884 – 1177
Week 192	1345	1178 – 1429
Week 216	1513	1430 – 1681
Week 264	1849	1682 – 1933
Week 288	2017	1934 – 2101
Week 312	2185	2102 – 2269
Week 336	2353	2270 – 2437
Week 360	2521	2438 – 2605
Week 384	2689	2606 – 2773
Week 408	2857	2774 – 2941

The time window for treatment-emergent adverse events is from the day of the first injection of Study M06-807 study drug to the last non-missing injection date + 70 days.

Definition of Missing Data Imputation

Baseline Value is Missing: Subjects will be excluded from analysis of change and percent change from baseline if baseline evaluation (Baseline of Study M06-806) is missing.

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

When an endpoint in the study is analyzed as observed (this is denoted as Observed Case [OC]), no imputation of the missing values will be performed.

In the subgroup analysis of efficacy variables, Last Observation Carried Forward (LOCF) analysis will also be carried out as sensitivity analysis. The following rules will be used for the LOCF approach:

1. Baseline (the Week 52 visit of Study M06-806) 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.

Rule for PCDAI and CDAI Calculation

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 PCDAI or CDAI score will be missing.

Partial Study Dates: If the day and/or month are missing, the following conventions will be used to impute the missing visit (or assessment) dates other than the dosing dates:

- 01 for missing start day,
- End of month for missing end day,
- January 1st will be used for a missing start month,

- December 31st for missing end month.

In case of partially missing AE start and stop dates, the dates will be imputed by comparing to first dose date of study medication so that the corresponding AEs will be made treatment-emergent whenever possible. If the start date of an AE is partially missing and the month is the same as the start date of a new therapy, the AE will be made treatment-emergent to the new therapy.

In case of missing or partially missing study drug dosing dates, the dates will not be imputed. Subjects will be treated as not receiving dose on that date.

Rounding

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

The mean and median will be rounded for presentation to 1 decimal more than the data were entered into the database. For example, mean systolic blood pressure will be presented to 1 decimal place (125.2 mmHg) when it is recorded to integer level in the database (110 mmHg). The standard deviation will be rounded to 2 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 1 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

All demographic variables and baseline characteristics will be summarized descriptively based on baseline values from double-blind Study M06-806. Categorical data will be described by frequency and percentage, whereas continuous data will be presented by mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum, and the number of non-missing values. The following demographic variables and baseline characteristics will be summarized for the ITT population.

- Sex [Male, Female],
- Race [White, Black, American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, Asian, Other],
- Race categories [White, Non-white],
- Ethnicity [Hispanic, Non-Hispanic],
- Age [years],
- Age categories [< 13 years, ≥ 13 years],
- Body weight [kg],
- Body weight categories [< 40 kg, ≥ 40 kg],
- Height [cm],
- BMI [kg/m^2],
- Location of Crohn's disease [Anal/Perianal, Rectum, Gastroduodenum, Colon, Jejunum, Ileum, Other],
- Tobacco/nicotine use at Baseline [User, Ex-user, Non-user, unknown],
- Alcohol use at Baseline [Drinker, Ex-drinker, Non-drinker, unknown],
- Prior infliximab use [No, Yes],
- Initial response to infliximab [No, Yes],
- Loss of response to infliximab [No, Yes],
- Demonstrated a reaction to infliximab [No, Yes],

- Reaction to infliximab [Acute, Delayed],
- Draining cutaneous fistula counts,
- Erythrocyte sedimentation rate (ESR),
- C-reactive protein (CRP) [mg/dL],
- CRP categories [< 1.0, ≥ 1.0 mg/dL],
- Immunosuppressant use at Baseline [No, Yes],
- Corticosteroid use at Baseline [No, Yes],
- Baseline PCDAI,
- Baseline CDAI (for subjects ≥ 13 years of age),
- Baseline IMPACT III (for subjects greater or equal to 10 years old at Baseline),
- Baseline WPAI.

7.2 Medical History

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

7.3 Previous Treatment and Concomitant Medications

Previous medications and concomitant medications will be coded by WHO DRUG dictionary. The number and percentage of subjects who had taken medications will be summarized by generic drug name for the ITT population. Previous medications taken prior to the first dose of the previous Study M06-806 will be summarized. Concomitant medications taken during Study M06-807 will be summarized.

Concomitant immunomodulator use at Study M06-806 baseline is defined as the use of immunomodulators [6-mercaptopurine (6-MP), azathioprine (AZA), and methotrexate

(MTX)] if the medication start date was before or equal to adalimumab first dose date and the medication end date was after or equal to adalimumab first dose date. The study required that subjects stayed on concomitant immunomodulators at least through Week 26 in Study M06-806 if they were using those immunomodulators at Study M06-806 baseline. After Week 8, decreases in the dose or discontinuation of Crohn's related concomitant treatments were allowed according to the investigators' medical judgment. Subjects who were in flare or who flared after they had reduced or completely tapered their dose of corticosteroid could have their corticosteroid dose increased or restarted at the discretion of the investigator.

8.0 Patient Disposition

Number of subjects included in each analysis population/analysis set will be summarized. The number and percentage of subjects contributed by each investigator will be summarized for ITT population. Number of subjects who needed a dose increase because of increased weight will be summarized for ITT population. Number of subjects who dose escalated from eow to ew dosing because of flare and number of subjects who dose de-escalated will be summarized as well. The number and percentage of subjects prematurely discontinuing study drug for each reason will be summarized. Subjects may have multiple reasons for prematurely discontinuing study drug, but will be counted only once for the primary reason.

9.0 Study Drug Exposure and Compliance

Study drug exposure (defined below) and the number of injections will be summarized for the ITT population. The number of subjects who dose escalated from eow to weekly administration of study drug will be summarized by visit with frequencies and percentages.

Study drug exposure: Exposure to study treatment in days (d) during Study M06-807 will be defined as follows:

Treatment exposure [d] = the date of last ADA injection in Study M06-807 – date of first ADA injection in Study M06-807 + 14 days.

Treatment Compliance (%), defined as the number of injections received divided by the number of injections planned or expected (in accordance with the study design), during the subject's participation in Study M06-807 and multiplied by 100 (rounded to 0.1%). Treatment Compliance will also be summarized using descriptive statistics.

10.0 Safety Analysis

10.1 General Considerations

Safety analysis will be performed on Safety Analysis Set as defined in Section 5.1.

Adverse events, laboratory data and vital signs are the primary safety parameters, and these will be assessed throughout the study. Safety data will be summarized using descriptive statistics. No statistical tests will be performed.

10.2 Analysis of Adverse Events

Adverse events will be coded using version 19.1 of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs). 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. The following two types of tables are planned:

1. Crude incidence rate, i.e., the number and percent of subjects with treatment-emergent AEs will be tabulated.
2. Events per 100 patient years of observation: The number of AEs per 100 patient-years of observation will be tabulated.

Treatment-emergent adverse events are defined as new events that begin either on or after the first dose of the study medication in Study M06-806 and within 70 days after the last dose of the study medication in Study M06-807. The treatment-emergent adverse events listed below are of special interest:

- Any adverse event (AE),
- Any serious AE,
- Any AE leading to discontinuation,
- Any severe event,
- Any at least possibly drug-related AE,
- Any at least possibly drug-related serious AE,
- Any AE leading to death,
- 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,
- 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 adalimumab administration related medication error,
- Any injection site reaction.

Adverse events that are reported more than 70 days after last study injection will be excluded from the summaries; however, all reported adverse events will be included in the adverse event data listings.

Adverse events with missing or unknown severity will be categorized as severe. Adverse events with missing or unknown relationship to study drug will be categorized as at least possibly drug-related. A subject who reports more than one adverse event 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 adverse event 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). An overview of planned adverse event tables is provided below.

Treatment-emergent adverse events will be summarized as follows:

- Grouped by System Organ Class and Preferred Term.
- Grouped by System Organ Class, Preferred Term and Severity.
- Grouped by System Organ Class, Preferred Term and Relation to Study Drug.
- Grouped by System Organ Class and Preferred Term with subject numbers.

Treatment-emergent serious adverse events will be summarized as follows:

- Grouped by System Organ Class and Preferred Term.
- Grouped by System Organ Class, Preferred Term and Relation to Study Drug.
- A by-subject listing will be provided.

Treatment-emergent adverse events leading to death or premature discontinuation of study drug will be summarized separately as follows:

- Grouped by System Organ Class and Preferred Term
- A by-subject listing will be provided.

Treatment-emergent adverse events of special interest (listed above) will be summarized as follows:

- Grouped by System Organ Class and Preferred Term.
- A by-subject listing will be provided.

Treatment-emergent AEs (TEAEs) will be listed if less than five subjects had AE data in the dose de-escalation set. Otherwise, the number and percentage of subjects with TEAEs and TEAEs per 100 patient-years will be summarized for the dose de-escalation set. The collection periods for the dose de-escalation set are defined as any event with onset on or after the first dose of ADA treatment in Study M06-806 and up to 70 days after the last study drug injection.

10.3 Analysis of Laboratory Data

A summary of all analyses (shift tables and change from Baseline) for clinical laboratory parameters is presented in Table 5. A listing of all subjects with any clinical laboratory determinations meeting Common Toxicity Criteria (CTC) Version 3.0 of Grade ≥ 3 will be provided.

Table 5. Summary of Clinical Laboratory Analyses

Parameter	Clinical Laboratory Analysis
Hematology Results	Mean change from Baseline to minimum, maximum, and final Shift table from Baseline to worst CTC toxicity grade Identify subjects with CTC toxicity grade 3 or worse
Clinical Chemistry Results	Mean change from Baseline to minimum, maximum, and final Shift table from Baseline to worst CTC toxicity grade Identify subjects with CTC toxicity grade 3 or worse
Urinalysis Results	Mean change from Baseline to minimum, maximum

Changes from baseline in continuous laboratory parameters will be summarized over all treated subjects by n, mean, standard deviation and median values.

Cross (Shift) tables from baseline to the final value (i.e., the last non-missing value available) according to the normal range will be provided for each hematology, clinical chemistry parameter and urinalysis parameters.

For selected laboratory parameters with CTC grades, a listing of all subjects with any laboratory determinations meeting Grade > 3 will be provided. For each of these subjects, the whole course of the parameter will be listed. For subjects with laboratory values with Grade > 3, all of the laboratory parameters for those subjects will be listed.

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 (ULN is the upper normal limit):

1. $< 1.5 \times$ ULN,
2. $\geq 1.5 \times$ ULN TO $< 3 \times$ ULN,
3. $\geq 3 \times$ ULN TO $< 5 \times$ ULN,
4. $\geq 5 \times$ ULN TO $< 8 \times$ ULN, and
5. $\geq 8 \times$ ULN.

Shift tables showing shift will be presented using the 5 categories listed above.

For liver specific laboratory tests, a listing of all observations collected will be generated for subjects that had at least one post-baseline observation meeting the pre-defined criteria for a potentially clinically significant (PCS) value. The number and percentage of subjects in each treatment group who have at least one post-baseline observation meeting the pre-defined criteria for PCS values will be provided for each variable.

Pre-defined criteria for PCS laboratory values are given in Table 6 below:

Table 6. Potentially Clinically Significant Criteria for Laboratory Values

		Definition of Potentially Clinically Significant	
Chemistry Variables	**Units**	**Very Low**	**Very High**
Total Bilirubin	mcmol/L		> 1.5 × ULN
Serum glutamic-oxaloacetic transaminase (SGOT/AST) (Aspartate transaminase)	U/L		> 2.5 × ULN
Serum glutamic-pyruvic transaminase (SGPT/ALT) (Alanine aminotransferase)	U/L		> 2.5 × ULN
Alkaline phosphatase	U/L		> 2.5 × ULN

10.4 Analysis of Vital Signs and Weight

The following vital sign parameters will be obtained at each visit and summarized:

- Sitting systolic blood pressure [mmHg],
- Sitting diastolic blood pressure [mmHg],
- Pulse [bpm],
- Weight [kg],
- Height [cm],
- Respiratory rate [breaths per minute],
- Body temperature [°C].

Vital sign will be summarized following a similar procedure as described above for laboratory values. For continuous vital sign parameters, mean change from Baseline to minimum (smallest) value, maximum (largest) value, and final value will be summarized. Subjects with potentially clinically significant results will be identified according to the criteria in Table 7, and shift tables will be provided.

Table 7. Criteria for Potentially Clinically Significant Vital Sign Results

Vital Sign	Criterion	Definition of Potentially Clinically Significant
Systolic blood pressure	Low	Value ≤ 70 mmHg and decreased ≥ 20 mmHg from initial value
	High	Value ≥ 160 mmHg and increased ≥ 20 mmHg from initial value
Diastolic blood pressure	Low	Value ≤ 50 mmHg and decreased ≥ 15 mmHg from initial value
	High	Value ≥ 105 mmHg and increased ≥ 15 mmHg from initial value
Pulse	Low	Value ≤ 50 bpm and decreased ≥ 30 bpm from initial value
	High	Value ≥ 120 bpm and increased ≥ 30 bpm from initial value

10.5 Safety Subgroup Analysis

Concomitant immunomodulator use at Study M06-806 baseline defined in Section 7.3 and concomitant corticosteroid use will be used in subgroup analysis for incidence of treatment-emergent serious infections. The incidence of treatment-emergent serious infections and rates of serious infections per patient years for subjects who received adalimumab monotherapy compared with subjects who received adalimumab plus immunomodulators will be summarized. In addition to the analysis of serious infections, the two subgroups (adalimumab monotherapy and adalimumab plus immunomodulators) are further stratified by concomitant corticosteroid use.

11.0 Efficacy Analysis

11.1 General Considerations

For the analysis, the efficacy for the ITT population will be evaluated by number and percent of subjects with clinical remission, response (as per CDAI and PCDAI), corticosteroid-free remission (per PCDAI and CDAI), concomitant corticosteroid-free remission (per PCDAI and CDAI), and summary of the CDAI and PCDAI over time.

No inferential analysis will be performed for this open-label study. Analysis will be only descriptive summaries, and will be presented for the ITT population. Results will be presented for all subjects as one group. In general, CDAI and PCDAI will be summarized by the mean, standard deviation, minimum, median, and maximum; and clinical

remission/response and corticosteroid-free remission will be summarized by number and percent of subjects in remission and response over time.

Efficacy summaries will be presented based on the derived visits discussed in Section 6.0.

11.2 Efficacy Analysis

For subjects with corticosteroid use at Study M06-806 Baseline, the number and percent of them with corticosteroid-free remission and concomitant corticosteroid-free remission (per PCDAI and CDAI, as defined in Section 4.5) over time will be summarized.

Change from Baseline in total IMPACT III over time for patients at least 10 years old at Baseline, change from Baseline in WPAI scores over time, change from Baseline in "z" scores for height over time and change from Baseline in BMI over time will be summarized.

In addition, change from Baseline in hsCRP levels over time will be summarized. Due to a technical issue a number of blood samples were affected by an under-recovery of hsCRP. All hsCRP values will be kept in the database as initially reported and will be analyzed as such in the primary analysis. Additional sensitivity analyses will be performed to account for hsCRP values of affected samples as follows:

- all affected values will be considered as missing values in an observed case analysis.
- all affected values will be imputed using LOCF rule.

For Health Care Resource Utilization (HCRU), cumulative HCRU including number of physician visits; number of emergency room visits; number of hospital admissions; total number of days in hospital will be summarized for the ITT population. And the ratio of the total number of utilizations and the total time under observation will be calculated across all subjects. HCRU will be analyzed as observed only.

11.3 Handling of Multiplicity

There will be no adjustment for multiple comparisons since no statistical testing will be performed.

11.4 Efficacy Subgroup Analysis

The subgroups listed below will be used in subgroup analysis for number and percentage of subjects in PCDAI remission/response over time. Both LOCF and OC analyses will be performed.

- Baseline Age (< 13 years, ≥ 13 years)
- Baseline Weight (< 40 kg, ≥ 40 kg)
- Prior Infliximab Use (yes, no)
- Baseline Corticosteroid Use (yes, no)
- Baseline IMM Use (yes, no)

12.0 Summary of Change

This is the final version of the SAP.

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

Protocol (Amendment 7) Section 8.1.2.1 read:

Summary statistics for the demographic and baseline characteristics will be computed based on the Week 52 values (from double-blind Study M06-806).

SAP Version 4 Section 7.1 read:

All demographics variables and baseline characteristics will be summarized descriptively based on baseline values from double-blind Study M06-806.

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

This is the final version of the SAP. The study Activity table reflects the latest version of protocol.

13.0 List of Abbreviations

AE	Adverse Event
ANA	Antinuclear Antibodies
AZA	Azathioprine
BMI	Body Mass Index
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CRP	C-reactive protein
ESR	Erythrocyte Sedimentation Rate
EOW	Every Other Week
EW	Every Week
FDA	Food and Drug Administration
HCRU	Health Care Resource Utilization
hsCRP	High Sensitivity C-reactive protein
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
OC	Observed Case
PCDAI	Pediatric Crohn's Disease Activity Index
PTs	Preferred Terms
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TNF	Tumor Necrosis Factor
WPAI	Work Productivity and Activity Impairment
WHO	World Health Organization
6-MP	6-mercaptopurine

Document Approval

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