



Adalimumab  
M11-327 - Statistical Analysis Plan  
Version 3.0 – 07 July 2016

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**1.0                   Title Page**

**Statistical Analysis Plan – Amendment 2**

**STUDY M11-327**

**A Multicenter Open-Label Study of the Long-term  
Safety and Efficacy of the Human Anti-TNF  
Monoclonal Antibody Adalimumab in Subjects with  
Non-infectious Intermediate, Posterior, or Panuveitis**

**07 July 2016**

## Rationale for Changes

The changes to SAP Amendment 1 dated 09 March 2015 described in this amendment were necessary to include additional analyses.

## Summary of Changes

- Section 3.0: updated protocol amendment, changed notation for non-infectious intermediate, posterior and panuveitis and deleted IDMC section, since it was finished after second pivotal study terminated (Study M10-880)
- Section 4.1: changed notation for non-infectious intermediate, posterior and panuveitis
- Section 4.2: changed notation for non-infectious intermediate, posterior and panuveitis and changed study termination date
- Section 6.2: corrected First Rx Day column entry
- Section 6.3: added specification for interim analysis
- Section 7.1: changed labels for age variables
- Section 7.5: removed 'at baseline' next to IMMs and added abbreviation for corticosteroids
- Section 8.0: added additional category for interim analysis
- Section 10.1: added pooled analysis for efficacy variables
- Section 10.2: added new efficacy variables and additional analyses
- Section 10.4: added subgroups for some efficacy variables
- Section 11.1: added E/100PY for subgroup analysis of AEs and further subgroups
- Section 13.0: added new abbreviations

Full details of all changes are given in Section 15.0.

The amended Statistical Analysis Plan now reads as follows:

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### **3.0                   Introduction**

The SAP will provide details to further elaborate statistical methods as outlined in the protocol of Study M11-327, "A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate, Posterior, or Panuveitis" and will describe analysis conventions to guide the statistical programming work. The analysis plan is based on protocol amendment 10 dated as of 04 June 2015.

Analyses described in this SAP comprise the analyses that will be performed by AbbVie after the study (including the total set of subjects from Japan and non-Japan) has been terminated.

All analyses will be performed using SAS®.

### **4.0                   Study Objectives, Design and Procedures**

#### **4.1                   Objectives**

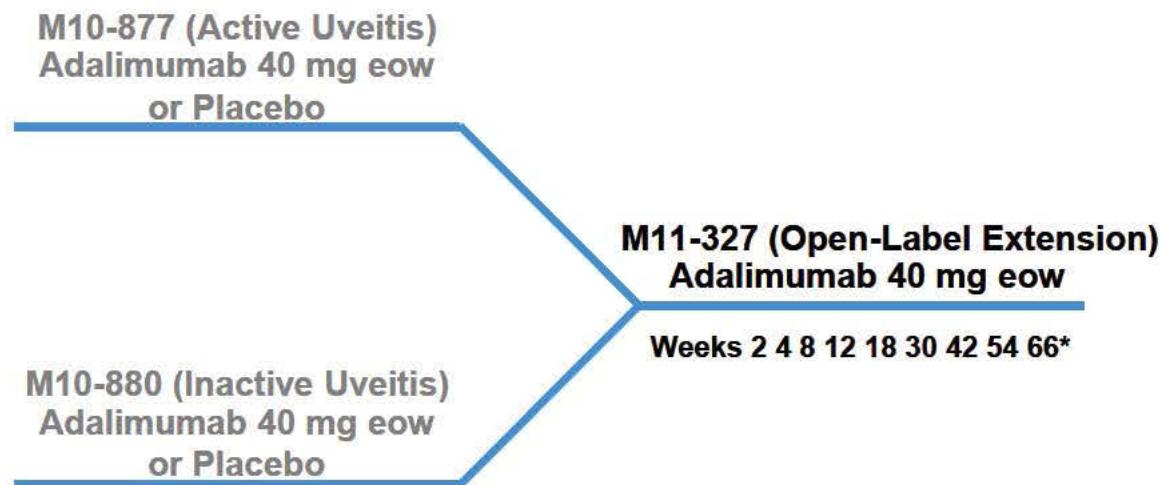
The primary objective of this study is to evaluate the long-term safety of adalimumab 40 mg given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate, posterior, or panuveitis who participated in Protocol M10-877 or Protocol M10-880. Long-term efficacy will also be assessed.

#### **4.2                   Design Diagram**

This study is a Phase 3, open-label multicenter study designed to evaluate long-term safety and efficacy of adalimumab in adult subjects with non-infectious intermediate, posterior, or panuveitis who have either discontinued from Study M10-877 or Study M10-880 for having met "Treatment Failure" criteria or have successfully completed Study M10-877 or Study M10-880. Subjects, who prematurely discontinued from Study M10-877 or Study M10-880 for reasons other than for Treatment Failure as defined in the parent protocol, will not be eligible for this study. Study visits will occur at Week 0, 2, 4, 8, 12, 18 and every 12 weeks thereafter. Visits will occur every 12 weeks

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following Week 66 until the end of the study. The entire study will be terminated in March 2018.



\* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2018).

## 5.0 Analysis Sets

The following analysis sets will be used for the analysis.

### 5.1 Definition for Analysis Sets

Safety analyses will be conducted in the safety set. The safety set includes all subjects who received at least one dose of study medication.

Efficacy analyses will be provided for the Intent-to-Treat (ITT) set. The ITT set includes all subjects who received at least one dose of study medication. In addition, the following subjects will be excluded from the ITT set:

- Subjects who developed Exclusion Criterion No. 5 ("Subject with proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy") during the study.

- Subjects undergoing a cataract surgery during the study.
- Subjects that had previous vitrectomy or are vitrectomized during the study.
- Subjects [REDACTED] from Investigator [REDACTED] ([REDACTED] France) will be excluded because of incomplete efficacy source data in studies M10-877 and M10-880.
- Subjects from Investigator [REDACTED] ([REDACTED] USA) will be excluded because of general compliance issues in studies M10-877 and M10-880.

Both, the ITT set and the safety set will include subjects recruited in and outside Japan.

## **6.0 Analysis Conventions**

### **6.1 Definition of Baseline and Final Observation**

Baseline of the parent study, Study M10-877/M10-880, is defined as the last non-missing observation made on or prior to the first dose of study drug in Study M10-877/M10-880.

Baseline of Study M11-327 is defined as the last non-missing observation made on or prior to the first dose of study drug in Study M11-327.

The final observation is defined as the last non-missing observation available prior to last dose plus 70 days.

### **6.2 Definition of Rx Days and Visit Windows**

Rx Days for efficacy analyses are calculated for each time point relative to the first adalimumab dose date in Study M11-327. Rx days are negative values when the time point of interest is prior to the first adalimumab dose day. Rx days are positive values when the time point of interest is after the first adalimumab dose day. The day of the first dose of adalimumab is defined as Rx Day 1, while the day prior to the first adalimumab dose is defined as Rx Day –1 (there is no Rx Day 0). Rx Days are calculated as:

## Rx Day

- = Date of the measurement – Day 1 + 1 if date of measurement  $\geq$  Day 1 date, or
- = Date of the measurement – Day 1 if date of measurement  $<$  Day 1 date.

All time points and corresponding time windows for efficacy analyses are defined based on Rx Days for efficacy analyses. If more than one assessment is included in a time window the assessment closest to the nominal day should be used. If there were two observations equally distant to the nominal day, the latest one will be used in analyses. If more than one assessment is included on the same day, then the last assessment on that day will be used in analyses.

The following visit windows will be used for efficacy analyses:

Visit Windows			
Week	Nominal Rx Day	First Rx Day	Last Rx Day
0	1	-	1
2	15	2	22
4	29	23	43
8	57	44	71
12	85	72	106
18	127	107	169
$18+i*12^a$	$127+i*84$	$170+(i-1)*84$	$169+i*84$

a     i = 1, 2, 3, 4 etc.

Rx Days for safety analyses are calculated for each time point relative to the first adalimumab dose date in Study M10-877, M10-880 or M11-327. Rx days are negative values when the time point of interest is prior to the first adalimumab dose day. Rx days are positive values when the time point of interest is after the first adalimumab dose day. The day of the first dose of adalimumab is defined as Rx Day 1, while the day prior to the first adalimumab dose is defined as Rx Day –1 (there is no Rx Day 0).

## **6.3 Imputation of Missing Data**

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)
- Last Observation Carried Forward (LOCF)

In case of an interim analysis, NRI and LOCF will be used. Values will be imputed until that visit that the subject could have reached based on the cutoff date.

### **6.3.1 Non-Responder Imputation (NRI)**

The NRI approach is used for binary variables. These variables can take values of 'Response' or 'Non-Response' or can be missing for any reason including discontinuation from study. According to the NRI imputation approach, all missing values will be considered as non-response.

### **6.3.2 Last Observation Carried Forward (LOCF)**

For all continuous and rating variables (excluding time to event data), the following rules will be used for the LOCF approach:

- Baseline values will not be used to impute the missing post-baseline values for subjects with inactive uveitis.
- Week 8 values will not be used to impute the missing post-baseline values for subjects with active uveitis.
- Missing values after Rx Day 1 will be imputed using the latest non-missing value after Rx Day 1 and prior to the missing value.

### **6.3.3 Observed Case Analysis**

Missing values will not be used for the observed case analysis.

### **6.3.4                    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 1 for missing start month
- December 31 for missing end month

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

The subsequently described analyses will be provided by active uveitis (defined as having discontinued the parent study, Study M10-877/M10-880 due to Treatment Failure) versus inactive uveitis and overall in the ITT set.

All statistical analyses will be descriptive. Descriptive statistics will include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for continuous variables; and counts and percentages for discrete variables.

### **7.1                    Demographic and Baseline Characteristics**

Variables to be summarized at baseline of Study M11-327 will include:

- **Subject demographics**
  - Age (years)
  - Age categories 1 (< 40, 40 – 64, ≥ 65 years)
  - Age categories 2 (< 30, ≥ 30 to < 50, ≥ 50 years)
  - Gender (male/female)
  - Race (white, black, Asian, American Indian/Alaska native, native Hawaiian or other Pacific islander, other)
  - Ethnicity (Hispanic or Latino, no ethnicity)

- Asian race (Chinese, Japanese, Korean, Taiwanese, Singaporean, Malaysian, other) (only for subjects from Japan)
- **TB history/PPD test/QuantiFERON®-TB Gold test/TB prophylaxis**
  - BCG vaccination (yes, no)
  - Induration of Tuberculin PPD skin test (mm)
  - Tuberculin PPD skin test (negative, positive), positive defined as  $\geq 5\text{mm}$
  - QuantiFERON-TB Gold test (negative, positive, indeterminate)
  - Combined result of Tuberculin PPD skin test and QuantiFERON-TB Gold test
  - Enrollment under TB prophylaxis (yes, no)
- **Chest x-ray (only in subjects with positive TB test)**
  - Chest x-ray findings (normal, abnormal)
  - Calcified granulomas (absent, present)
  - Pleural scarring (absent, present)
  - Pleural thickening (absent, present)
  - Findings indicative of previous TB infection (yes, no)
- **Vital signs**
  - Systolic blood pressure (mmHg)
  - Diastolic blood pressure (mmHg)
  - Pulse (bpm)
  - Respiratory rate (rpm)
  - Temperature ( $^{\circ}\text{C}$ )
- **Patient reported outcomes**
  - Visual Functioning Questionnaire (VFQ-25): total score and subscale scores
  - EuroQol-5D Questionnaire (EQ-5D)
  - Work Productivity and Activity Impairment: Specific Health Problem Questionnaire (WPAI:SHP) and its components

The following **ophthalmologic variables** will be summarized separately for left and right eye at baseline of Study M11-327:

- Optical coherence tomography (OCT) evidence of macular edema (yes, no)
- Central retinal thickness (microns)
- Intraocular pressure (mmHg)
- Active chorioretinal lesions (yes, no) via dilated indirect ophthalmoscopy (DIO)
- Active retinal vascular lesions (yes, no) via DIO
- Anterior chamber (AC) cell grade (SUN criteria) (continuous and categorical)
- AREDS lens opacity grading (no statistical test):
  - nuclear opacity (grade < 1.0, 1.0, 1.5, 2.0, 2.5, 3.0, > 3.0)
  - cortical opacity (grade < 1.0, 1.0, 1.5, 2.0, 2.5, 3.0, > 3.0)
  - posterior subcapsular opacity (grade < 1.0, 1.0, 1.5, 2.0, 2.5, 3.0, > 3.0)
- Vitreous haze grades (NEI/SUN criteria) (continuous and categorical)
- LogMAR Best corrected visual acuity (BCVA) will be calculated as follows:
  - if  $\geq$  20 letters were read at 4 m OR if < 20 letters were read at 4 m but the test was not done at 1 m,  
$$\text{logMAR} = 1.7 - 0.02 * (\text{number of letters read at 4 m} + 30),$$
  - if < 20 letters were read at 4 m and the test was also done at 1 m,  
$$\text{logMAR} = 1.7 - 0.02 * (\text{number of letters read at 4 m} + \text{number of letters read at 1 m})$$
  - if 0 letters were read at 1 m, the following logMAR values will be calculated according to Holladay (1997):
    - in case of finger counting:  
$$\text{logMAR} = (-1) * \log_{10}(\text{distance in meters}/60)$$
    - in case of hand movements:  $\text{logMAR} = 3.0$
- Power of sphere (diopters)
- Power of cylinder (diopters)
- Axis of cylinder (degrees)

For analysis of central retinal thickness, the central retinal thickness measured by the investigator will be used. Central retinal thickness will be analyzed by OCT machine. Central retinal thickness and macular edema will be analyzed excluding patients with macular hole and/or rhegmatogenous retinal detachment affecting the macular. OCT evidence of macular edema will be defined as center point thickness  $\geq$  260 microns for Stratus,  $\geq$  320 microns for Cirrus,  $\geq$  340 microns for Spectralis.

## **7.2 Uveitis History**

Variables to be summarized will include:

- Duration of uveitis (months) at baseline of Study M11-327
- Type of uveitis (intermediate, posterior, intermediate + posterior, panuveitis) at baseline of the parent study, Study M10-877/M10-880
- Diagnosis (idiopathic, birdshot choroidopathy, multifocal choroiditis and panuveitis, Vogt Koyanagi Harada, sarcoid, Behcet's, Other) at baseline of the parent study, Study M10-877/M10-880

## **7.3 Medical History**

Medical history data at baseline of the parent study, Study M10-877/M10-880, 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.

## **7.4 Prior Medications**

Prior uveitis medications are defined as any uveitis-related medication discontinued prior to the first dose of study drug in the parent study, Study M10-877/M10-880. Prior uveitis medication will be summarized by generic drug name. In addition, the following

therapies discontinued prior to the first dose of study drug in the parent study, Study M10-877/M10-880 will be summarized by counts and percentages:

- Immunosuppressants
  - Azathioprine
  - Cyclosporine
  - Methotrexate (MTX)
  - Mycophenolate mofetil or equivalent drug (e.g., mycophenolic acid)
  - Tacrolimus
- Corticosteroids
  - Oral corticosteroids
  - Topical corticosteroids
  - Other corticosteroids

Previous medication is defined as any medication taken prior to the first dose of adalimumab in Study M11-327. The number and percentage of subjects who had taken previous medications will be summarized by generic drug name based on the World Health Organization (WHO) drug dictionary.

## **7.5 Concomitant Medications**

Medications with a start date prior to or on the first dose of adalimumab in Study M11-327 and a stop date on or after the first dose of adalimumab in Study M11-327 or a missing stop date will be considered as concomitant medications at baseline of Study M11-327. If the start date is missing and the stop date is on or after the baseline date in Study M11-327, or if start and stop dates are both missing, the medication will also be considered as concomitant at baseline in Study M11-327. The following therapies used by subjects at baseline in Study M11-327 will be summarized by counts and percentages:

- Immunosuppressants (IMMs)
  - Azathioprine

- Cyclosporine
- Methotrexate (MTX)
- Mycophenolate mofetil or equivalent drug (e.g. mycophenolic acid)
- Tacrolimus
- Corticosteroids (CSs)
  - Oral corticosteroids
  - Topical corticosteroids
  - Other corticosteroids

Concomitant medication is defined as any medication that started prior to the first dose of adalimumab in Study M11-327 and continued to be taken after the first dose of adalimumab in Study M11-327 or any medication that started after the first dose of adalimumab in Study M11-327, but not after the last dose of adalimumab in Study M11-327. The number and percentage of subjects who had taken concomitant medications will be summarized by generic drug name based on the World Health Organization (WHO) drug dictionary.

## **8.0                   Subject Disposition**

The number of subjects in each of the following categories will be summarized. The subsequently described analyses will be provided by country as well as by investigator and overall. Additionally, tables will be stratified by the parent study, Study M10-877/M10-880:

- Subjects who received at least one dose of study medication (safety set)
- Subjects who received at least one dose of study medication (ITT set)
- Subjects who completed (safety set)
- Subjects who prematurely discontinued (safety set)
- Subjects who are ongoing (safety set, in case of an interim analysis)

The number and percentages of subjects by parent study, Study M10-877/M10-880, and treatment in the parent study will be presented overall for the safety set.

The number and percentage of subjects who prematurely discontinued study drug during the study will be summarized by reason overall for the safety set.

The number and percentage of subjects with protocol deviations will be presented overall for the safety set.

The number and percentage of subjects per visit will be presented overall for the safety set.

## **9.0 Study Drug Exposure and Compliance**

Exposure to adalimumab in days (d) will be defined as follows:

Treatment exposure (days)

- = date of last dose of adalimumab in Study M11-327
- date of first dose of adalimumab in Study M11-327
- + 14 (days)

In addition, the total amount of exposure from first adalimumab dose in Study M10-877/M10-880 will be calculated as follows:

Treatment exposure (days)

- = date of last dose of adalimumab in Study M11-327
- date of first dose of adalimumab in Study M10-877/M10-880 or Study M11-327
- + 14 (days)

Exposure will be presented in weeks.

Exposure will be summarized by number of subjects, mean, standard deviation, minimum, first quartile, median, third quartile and maximum in the safety set. In addition, exposure

will be categorized and counts will be given for the number of subjects in the respective interval.

Treatment compliance (%) is defined as the number of adalimumab injections received divided by the number of injections planned in Study M11-327. Tabulations for treatment compliance will display the number of observations, mean, standard deviation, minimum, median and maximum.

## **10.0 Efficacy Analysis**

### **10.1 General Considerations**

The subsequently described analyses will be provided in the ITT set. All statistical analyses will be descriptive. Results will be stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had inactive and subjects who had active uveitis when they entered the study, the efficacy analyses will start at Baseline of Study M11-327. Results will also be provided overall except for efficacy variables defined differently for subjects entering Study M11-327 with active and inactive uveitis.

### **10.2 Efficacy Variables**

The following efficacy variables will be analyzed:

- Proportion of subjects with no active lesions in both eyes at each study time point.
- Proportion of subjects at each study time point with no new active, inflammatory chorioretinal or inflammatory retinal vascular lesion in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- AC cell grade left/right eye and mean of both eyes at each study time point.
- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in AC cells in both eyes on Slit Lamp Exam, according to SUN criteria.

- VH grades left/right eye and mean of both eyes at each study time point.
- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in vitreous haze in both eyes on indirect ophthalmoscopy, according to NEI/SUN criteria.
- Proportion of subjects at each study time point with VH  $\leq 0.5$  and AC  $\leq 0.5$ .
- Proportion of subjects at each study time point with new lesions, AC  $\geq 2$  or VH  $\geq 2$ .
- Proportion of subjects at each study time point in quiescence defined as no active lesions, AC  $\leq 0.5$  and VH  $\leq 0.5$ .
- Proportion of subjects who experienced a uveitis flare (defined as no quiescence) during the study and who did or did not discontinue from the study due to the flare.
- LogMAR Best corrected visual acuity (BCVA) left/right eye and mean of both eyes at each study time point.
- Proportion of subjects at each study time point without a worsening of BCVA by  $\geq 15$  letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Proportion of subjects who started IMMs in Study M11-327.
- Proportion of subjects on/off IMMs at each study time point only in subjects on IMMs at baseline of Study M11-327.
- Proportion of subjects at each study time point achieving a  $\geq 50\%$  reduction in immunosuppression load relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Change in dose of IMM at each study time point relative to baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study only in subjects on IMMs at baseline/Week 8 of Study M11-327.
- Proportion of subjects who started systemic CS in Study M11-327.
- Systemic CS dose at each study time point.
- Proportion of subjects at each study time point with

- Systemic CS dose = 0 mg/day
- Systemic CS dose > 0 to  $\leq$  5 mg/day
- Systemic CS dose > 5 to  $\leq$  7.5 mg/day
- Systemic CS dose > 7.5 to  $\leq$  10 mg/day
- Systemic CS dose > 10 to  $\leq$  20 mg/day
- Systemic CS dose > 20 mg/day
- Percent change in systemic CS dose at each study time point relative to baseline only in subjects on CS at baseline.
- Proportion of subjects in steroid-free quiescence at each study time point.
- Proportion of subjects in quiescence and for subjects without quiescence the proportion of subjects
  - with/without a change in concomitant medication (topical/systemic corticosteroids, immunosuppressants) within 5 days after non-quiescence and with/without quiescence at the next visit (at least 8 Weeks after non-quiescence)
  - with premature discontinuation
- OCT evidence of macular edema in at least one eye at each study time point.
- Central retinal thickness left/right eye and mean of both eyes at each study time point by OCT machine.
- Percent change in central retinal thickness (1 mm subfield) in each eye at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Change in NEI Visual Functioning Questionnaire (VFQ-25) score at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.

For analysis of central retinal thickness, the central retinal thickness measured by the investigator will be used. Changes and percent changes in central retinal thickness may only be calculated for measurements from the same machine. Central retinal thickness

will be analyzed excluding patients with macular hole and/or rhegmatogenous retinal detachment affecting the macular.

Immunosuppression load will be assessed according to the article by Nussenblatt et al. (2005). The below grading scheme will be used to accommodate the simultaneous use of multiple agents and provide a combined, single numeric score for the total immunosuppression load per unit body weight per day at each visit. For patients receiving multiple medications, the sum of the grading scores for each drug will be used to calculate a total immunosuppression score at each visit.

Medication	Immunosuppression Grade Based on Dose in mg/kg/day (or per Week if Dosed Weekly)							
	0	1	2	3	4	5	6	7
Prednisone	0	< 0.15	0.15 – 0.30	0.31 – 0.45	0.46 – 0.60	0.61 – 0.75	0.76 – 0.90	0.91 – 1.05
Cyclosporine	0	< 0.75	0.75 – 1.50	1.51 – 2.25	2.26 – 3.00	3.01 – 3.75	3.76 – 4.50	4.51 – 5.25
Azathioprine	0	< 0.25	0.25 – 0.50	0.51 – 0.75	0.76 – 1.00	1.01 – 1.25	1.26 – 1.50	1.51 – 1.75
Mycophenolate	0	< 10	10 – 20	21 – 30	31 – 40	41 – 50	51 – 60	> 60
Methotrexate	0	< 0.05	0.05 – 0.10	0.11 – 0.15	0.16 – 0.20	0.21 – 0.25	0.26 – 0.30	0.31 – 0.35
Cyclophosphamide	0	< 0.25	0.25 – 0.50	0.51 – 0.75	0.76 – 1.00	1.01 – 1.25	1.26 – 1.50	1.51 – 1.75
Chlorambucil	0	< 0.025	0.025 – 0.050	0.051 – 0.075	0.076 – 0.100	0.101 – 0.125	0.126 – 0.150	0.151 – 0.175

Note: Dose ranges are for the average in mg/kg/day, except for weekly doses of methotrexate, which are measured as mg/kg/week

The efficacy variables will be analyzed as follows.

Descriptive statistics for quantitative variables will include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for values at each visit, changes from Baseline/Week 8 to each visit thereafter and change from Baseline/Week 8 to Final/Early Termination Visit for continuous variables. In addition, for central retinal thickness percent change from Baseline/Week 8 to each visit thereafter and percent change from Baseline/Week 8 to Final/Early Termination Visit will be analyzed. For central retinal thickness, values at each visit and changes will be analyzed by OCT machine, percent changes will be analyzed overall. 95% confidence intervals for means will be provided. Data will be analyzed by Last Observation Carried Forward (LOCF) and as observed. For as observed analyses, graphs will be generated for subjects with active vs. inactive uveitis at entry of Study M11-327 for:

- LogMAR Best corrected visual acuity (BCVA) (mean of both eyes) at each study time point.
- Systemic CS dose at each study time point.
- Central retinal thickness (mean of both eyes) at each study time point by OCT machine.

Categorical variables will be summarized by counts and percentages at each visit. 95% confidence intervals for proportions will be provided. Data will be analyzed by Non Responder Imputation (NRI) and as observed. For as observed analyses, graphs will be generated for subjects with active vs. inactive uveitis at entry of Study M11-327 for:

- Proportion of subjects with no active lesions in both eyes at each study time point.
- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in AC cells in both eyes on Slit Lamp Exam, according to SUN criteria.
- Proportion of subjects at each study time point with Grade  $\leq 0.5+$  in vitreous haze in both eyes on indirect ophthalmoscopy, according to NEI/SUN criteria.

- Proportion of subjects at each study time point in quiescence defined as no active lesions,  $AC \leq 0.5$  and  $VH \leq 0.5$ .
- Proportion of subjects with steroid-free quiescence at each study time point.
- OCT evidence of macular edema in at least one eye at each study time point.

### **10.3 Other Efficacy Variables**

The following other efficacy variables will be analyzed:

- Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI:SHP) and its components
- EuroQol Questionnaire (EQ-5D)
- Health Resource Utilization Questionnaire (HRU)

These other efficacy variables will be analyzed as follows.

For WPAI: SHP and EQ-5D, descriptive statistics will include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for values at each visit, changes from Baseline/Week 8 to each visit thereafter and change from Baseline/Week 8 to Final/Early Termination Visit for continuous variables. Data will be analyzed by Last Observation Carried Forward (LOCF) and as observed.

For HRU data, the individual cumulative number of utilizations per time under observation in Study M11-327 will be calculated in each category (i.e., unscheduled uveitis-related health care professional visits, emergency room visits, hospital admissions and the total number of days in hospital) as follows:

- Time under observation for a subject will be defined as "date of last visit with non-missing HRU – date of Baseline/Week 8 for subjects with inactive/active uveitis."
- The number of utilizations (documented starting at Week 2/Week 12 for subjects with inactive/active uveitis) will be summed up for each subject.

For cumulative HRU data, the ratio of the total number of utilizations (i.e., separately over all subjects with inactive and active uveitis) and the total time under observation (i.e., separately over all subjects with inactive and active uveitis) will be calculated across all subjects. HRU will be analyzed as observed only.

## 10.4 Efficacy Subgroup Analyses

The following efficacy variables will be analyzed as described in Section 10.2 by pooling subjects with active and inactive uveitis at start of Study M11-327

- Proportion of subjects with no active lesions in both eyes at each study time point.
- AC cell grade (mean of both eyes) at each study time point.
- Proportion of subjects with a Grade  $\leq 0.5+$  in AC cells in both eyes on Slit Lamp Exam, according to SUN criteria at each study time point.
- VH grades (mean of both eyes) at each study time point.
- Proportion of subjects at each study time point with Grade  $\leq 0.5+$  in vitreous haze in both eyes on indirect ophthalmoscopy, according to NEI/SUN criteria.
- Proportion of subjects at each study time point in quiescence defined as no active lesions, AC  $\leq 0.5$  and VH  $\leq 0.5$ .
- LogMAR Best corrected visual acuity (BCVA) (mean of both eyes) at each study time point.
- Proportion of subjects who started IMMs in Study M11-327.
- Systemic CS dose at each study time point.
- Proportion of subjects with steroid-free quiescence at each study time point.
- OCT evidence of macular edema in at least one eye at each study time point.
- Central retinal thickness (mean of both eyes) at each study time point by OCT machine.

in the following subgroups:

- Gender (male/female)

- Duration of uveitis (< 1,  $\geq$  1 years)
- Type of uveitis (intermediate versus posterior versus panuveitis)
- Diagnosis (idiopathic/other versus birdshot choroidopathy versus multifocal choroiditis and panuveitis versus Vogt Koyanagi Harada versus sarcoid versus Behcet's)
- IMM usage at Baseline of Study M11-327 (yes, no)

In addition, the efficacy variable "Proportion of subjects at each study time point without a worsening of BCVA by  $\geq$  15 letters on the ETDRS in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study" will be analyzed as described in Section 10.2 in the following subgroups:

- Subjects with/without AE "posterior capsule opacification/rupture"

## **11.0 Safety Analysis**

The subsequently described analyses will be provided overall in the safety set.

### **11.1 Treatment-Emergent Adverse Events**

Treatment-emergent adverse events (AEs) are defined as any event with an onset date that is on or after the first dose of adalimumab in Study M11-327 and no more than 70 days after the last dose of study drug administration.

If an incomplete onset date was collected for an AE, the event will be assumed to be treatment emergent unless there is other evidence that confirms that the event was not treatment emergent (e.g., the event end date was prior to the study drug start date). In case of increasing severity of an existing AE, the worsening will be considered as a new AE with a new onset date.

AE data will be summarized using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the most current implemented version of the MedDRA

coding dictionary. The SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC. For AEs with an incidence rate  $\geq 5\%$  in the adalimumab group and SAEs, the PTs will also be presented in decreasing frequency.

### **Adverse Event Overview**

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized for the following AE categories.

- AEs
- AEs rated at least possibly related to study drug by the investigator (Probably Related or Possibly Related)
- Severe AEs
- SAEs
- SAEs rated at least possibly related to study drug by the investigator (Probably Related or Possibly Related)
- AEs leading to discontinuation of study drug
- AEs leading to death
- Uveitis-related AEs (see below)
- AEs of special interest (see below)

Uveitis-related AEs will be:

- Loss of transparency of the cornea
- Band keratopathy
- Synechiae
- Cataracts
- Glaucoma/increased intraocular pressure
- Vitreous hemorrhage
- Macular edema
- Retinal detachment
- Epiretinal membrane

- Vitreo-macular traction
- Retinal ischemia
- Vision loss
- Hypotony

The current list of AEs of special interest for treatment with adalimumab is:

**Infection**

- All Infections
- Serious Infection
- Legionella Infection
- Diverticulitis
- Opportunistic Infection Excluding Oral Candidiasis and TB
- Oral Candidiasis
- Tuberculosis<sup>a</sup>
  - Active Tuberculosis<sup>a</sup>
  - Latent Tuberculosis<sup>a</sup>
- Parasitic Infections
- Reactivation of Hepatitis B
- Progressive Multifocal Leukoencephalopathy (PML)

**Malignancies**

- Malignancies
- Lymphoma
- Hepatosplenic T-Cell Lymphomas (HSTCL)
- Non-Melanoma Skin Cancer (NMSC)
- Melanoma
- Leukaemia
- Other Malignancies Except Lymphoma, HSTCL, Leukemia, NMSC, and Melanoma

**Immune Reactions**

- Allergic Reactions Including Angioedema, Anaphylaxis
- Lupus-Like Reactions and Systemic Lupus Erythematosus (SLE)
- Vasculitis<sup>a</sup>
  - Cutaneous Vasculitis<sup>a</sup>
  - Non-Cutaneous Vasculitis<sup>a</sup>
- Sarcoidosis
- Autoimmune Hepatitis

**Cardiovascular/Vascular**

- Myocardial Infarction
- Cerebrovascular Accident
- Congestive Heart Failure
- Pulmonary Embolism

**Respiratory**

Interstitial Lung Disease

**Gastrointestinal Events**

Intestinal Perforation

Pancreatitis

**Skin and Subcutaneous Tissue Disorders**

Steven's Johnson Syndrome

Erythema Multiforme

Worsening and New Onset of Psoriasis

**Nervous System Disorder**

Demyelinating Disorders Including Multiple Sclerosis, Guillain-Barré Syndrome, and Optic Neuritis and Others

Amyotrophic Lateral Sclerosis

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

**Hematologic Events**

Hematologic Disorders Including Pancytopenia

**Hepatic Events**

Liver Failure and Other Liver Events (Except Gallbladder-Related Events)

**Other**

Humira Administration-related Medication Errors

Injection Site Reactions

- a. An additional column will be included in the spreadsheet to indicate the subcategories: active or non-active tuberculosis, cutaneous or non-cutaneous vasculitis.

This list might be modified at time of analysis to comply with any future version.

**Adverse Events by System Organ Class and Preferred Term**

The number and percentage of subjects experiencing AEs will be tabulated according to the primary MedDRA SOC and PT for each treatment group. Subjects reporting more than one AE for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one type of AE within a SOC will be counted only once for that SOC. Subjects reporting more than one type of AE will be counted only once in the overall total.

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

- AEs
- AEs rated at least possibly related to study drug by the investigator
- AEs by highest relationship
- AEs by maximum severity
- SAEs
- AEs leading to discontinuation of study drug
- AEs leading to death
- AEs of special interest

A listing of subject numbers associated with AEs by SOC and PT will be provided.

By-subject listings will be provided for AEs at least possibly related to study drug, severe AEs, SAEs, AEs leading to discontinuation, AEs leading to death, and AEs of special interest. In addition, SAEs with onset after informed consent but before the first dose of adalimumab was administered will be considered as pre-treatment SAEs and will be listed separately.

### **Adverse Events by Maximum Severity**

Adverse events will also be summarized by maximum severity. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

### **Adverse Events by Maximum Relationship**

Adverse events will also be summarized by maximum relationship to study, as assessed by the investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has

another occurrence of the same 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 "Probably Related" or "Possibly Related." In this case, the subject will be counted under the "Probably Related" or "Possibly Related" category, respectively.

### **Adverse Event Rates per 100 Subject-Years of Study Drug Exposure**

The analysis of AEs per 100 subject-years will be presented for the AE overview, for AEs by SOC and PT, and for SAEs by SOC and PT.

The treatment-emergent AE rate per 100 subject-years of exposure to study drug (ADA) will be calculated. For this calculation, one year will be considered to be 365.25 days. The numerator of the rate will be the total number of AEs reported that a subject can be counted more than once overall. The denominator of the rates will be the total number of days exposed to study drug summed across all treated subjects divided by 365.25. The AE rate per 100 subject-years of exposure will be calculated as  $[(\text{numerator}/\text{denominator})]*100$ . The number of AEs reported (numerator), the total number of years of study drug exposure (denominator), and the AE rate per 100 subject-years will be presented overall.

### **Subgroup Analyses of Adverse Events**

Analyses of AEs per subgroup will be presented for the AE overview. The number and percentage of subjects experiencing AEs as well as E/100PYs will be tabulated overall.

Subgroups used for the analyses are:

- Concomitant use of corticosteroids (yes, no)
- Baseline immunosuppressant usage (yes, no)
- Baseline azathioprine usage
- Baseline cyclosporine usage
- Baseline methotrexate usage

- Baseline mycophenolate mofetil or an equivalent drug (e.g., mycophenolic acid) usage
- Baseline tacrolimus usage

An AE overview (with number and percentage of subjects experiencing treatment-emergent AEs as well as E/100PYs) will also be presented separately for

- treatment periods with/without concomitant use of corticosteroids
- treatment periods with corticosteroid dose  $> 0$  to  $\leq 15$  mg/day
- treatment periods with corticosteroid dose  $> 15$  mg/day
- treatment periods with/without concomitant use of immunosuppressant
- treatment periods
  - without concomitant use of corticosteroids and immunosuppressant
  - with concomitant use of corticosteroids only
  - with concomitant use of immunosuppressant only
  - with concomitant use of corticosteroids and immunosuppressant

## **11.2 Analysis of Laboratory Data**

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC), white blood cell (WBC), WBC differentials (neutrophils, lymphocytes, monocytes, basophils, eosinophils), and platelet count.

Clinical chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, cholesterol, total protein, glucose, triglycerides, and albumin.

Urinalysis variables include: specific gravity, pH.

For quantitative laboratory parameters, mean changes from baseline in Study M11-327 to the minimum value, maximum value, and final value in the laboratory variables will be

summarized with the baseline mean, min/max/final mean, change from baseline mean, standard deviation, and median.

Laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. Shift tables from baseline in Study M11-327 to final values will be created. The shift tables cross tabulate the frequency of subjects with baseline values below/within/above the normal range versus final values below/within/above the normal range.

### **11.3                   Analysis of Potentially Clinically Significant Laboratory Values**

For selected laboratory parameters (hematology: Hemoglobin, Lymphocytes, Neutrophils, Platelet Count, WBC; clinical chemistry: Albumin, Alkaline Phosphatase, ALT, AST, Total Bilirubin, Calcium, Cholesterol, Creatinine, Glucose, Inorganic Phosphorus, Potassium, Sodium, Triglycerides) with Common Toxicity Criteria (CTC) criteria, Potentially Clinically Significant Laboratory Findings (Common Toxicity Criteria CTC Grades 3 and 4) will be assessed.

For definition of CTC V3.0 criteria, see <http://ctep.cancer.gov/reporting/ctc.html>.

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

Laboratory Parameter	CTC Grade 1	CTC Grade 2	CTC Grade 3	CTC Grade 4
Hemoglobin	< LLN – 100 g/L	< 100 – 80 g/L	< 80 – 65 g/L	< 65 g/L
Lymphocytes	< LLN – 0.8 × 10 <sup>9</sup> /L	< 0.8 – 0.5 × 10 <sup>9</sup> /L	< 0.5 – 0.2 × 10 <sup>9</sup> /L	< 0.2 × 10 <sup>9</sup> /L
Neutrophils	< LLN – 1.5 × 10 <sup>9</sup> /L	< 1.5 – 1.0 × 10 <sup>9</sup> /L	< 1.0 – 0.5 × 10 <sup>9</sup> /L	< 0.5 × 10 <sup>9</sup> /L
Platelet count	< LLN – 75.0 × 10 <sup>9</sup> /L	< 75.0 – 50.0 × 10 <sup>9</sup> /L	< 50.0 – 25.0 × 10 <sup>9</sup> /L	< 25.0 × 10 <sup>9</sup> /L
WBC	< LLN – 3.0 × 10 <sup>9</sup> /L	< 3.0 – 2.0 × 10 <sup>9</sup> /L	< 2.0 – 1.0 × 10 <sup>9</sup> /L	< 1.0 × 10 <sup>9</sup> /L
Albumin	< LLN – 30 g/L	< 30 g/L – 20 g/L	< 20 g/L	—
Alkaline Phosphatase	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
ALT	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
AST	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
Total Bilirubin	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Calcium	> ULN – 2.9 mmol/L < LLN – 2.0 mmol/L	> 2.9 – 3.1 mmol/L < 2.0 – 1.75 mmol/L	> 3.1 – 3.4 mmol/L < 1.75 – 1.5 mmol/L	> 3.4 mmol/L < 1.5 mmol/L
Cholesterol	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN
Glucose	> ULN – 8.9 mmol/L < LLN – 3.0 mmol/L	> 8.9 – 13.9 mmol/L < 3.0 – 2.2 mmol/L	> 13.9 – 27.8 mmol/L < 2.2 – 1.7 mmol/L	> 27.8 mmol/L < 1.7 mmol/L
Inorganic Phosphorus	< LLN – 0.8 mmol/L	< 0.8 – 0.6 mmol/L	< 0.6 – 0.3 mmol/L	< 0.3 mmol/L
Potassium	> ULN – 5.5 mmol/L < LLN – 3.0 mmol/L	> 5.5 – 6.0 mmol/L —	> 6.0 – 7.0 mmol/L < 3.0 – 2.5 mmol/L	> 7.0 mmol/L < 2.5 mmol/L
Sodium	> ULN – 150 mmol/L < LLN – 130 mmol/L	> 150 – 155 mmol/L —	> 155 – 160 mmol/L < 130 – 120 mmol/L	> 160 mmol/L < 120 mmol/L
Triglycerides	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 10 × ULN	> 10 × ULN

LLN = lower limit of normal range; ULN = upper limit of normal range

Shift tables from baseline value in Study M11-327 to worst value will be created. The shift tables cross tabulate the frequency of subjects with baseline values with CTC<3/CTC≥3 versus worst values with CTC<3/CTC≥3. Furthermore, for subjects with laboratory values with CTC ≥ 3, the whole course of the parameter will be listed.

## 11.4 Analysis of Liver Specific Laboratory Tests

The liver specific laboratory tests include ALT/SGPT, AST/SGOT, alkaline phosphatase and total bilirubin. Each of these laboratory values will be categorized as follows:

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

where ULN is the upper normal limit.

For each variable, shift tables will be generated that cross tabulate the number of subjects with baseline values in Study M11-327 in these 5 categories versus the min/max/final value in these 5 categories.

A listing of potentially clinically significant liver function laboratory values will be provided. The listing will include all subjects who meet any of the following 4 criteria:

1.  $\text{ALT} \geq 2.5 \times \text{ULN}$ , or
2.  $\text{AST} \geq 2.5 \times \text{ULN}$ , or
3. Alkaline phosphatase  $\geq 2.5 \times \text{ULN}$ , or
4. Total bilirubin  $\geq 1.5 \times \text{ULN}$ .

## **11.5 Analysis of Vital Signs**

Vital signs include: Blood Pressure (Systolic/Diastolic) (mmHg), Pulse (bpm), Respiratory Rate (rpm), Temperature (°C).

Mean changes from baseline in Study M11-327 to the minimum value, maximum value, and final value in the vital signs variables will be summarized with the baseline mean, min/max/final mean, change from baseline mean, standard deviation, and median.

## **11.6 Analysis of Other Safety Variables**

Other safety variables are:

- Intraocular pressure (0–9, 10–21, 22–25, 26–30, > 30 mmHg)
- Nuclear opacity (grade < 1.0, 1.0, 1.5, 2.0, 2.5, 3.0, > 3.0)
- Cortical lens opacity (grade < 1.0, 1.0, 1.5, 2.0, 2.5, 3.0, > 3.0)
- Posterior subcapsular opacity (grade < 1.0, 1.0, 1.5, 2.0, 2.5, 3.0, > 3.0)
- 2-step increase in lens opacity (defined as change from grade < 1.0 to 2.5 or higher, from 1.0 to 3.0 or higher, or from 1.5 to > 3.0) in at least one eye in at least one of the three opacity variables

For each variable, shift tables will be generated that cross tabulate the number of subjects with baseline values in Study M11-327 in the above categories versus the worst observations (i.e., largest values) in these categories.

## **12.0 List of Tables, Figures and Data Listings that Are to be Programmed**

Will be provided in a separate document.

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## 13.0 List of Abbreviations

AC	Anterior Chamber
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
CS	Corticosteroid
CTC	Common Toxicity Criteria
DIO	Dilated Indirect Ophthalmoscopy
eow	Every Other Week
EQ-5D	EuroQol Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
HRU	Health Resource Utilization Questionnaire
IDMC	Independent Data Monitoring Committee
IMM	Immunosuppressant
ITT	Intent-to-Treat
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NEI	National Eye Institute
NMSC	Non-Melanoma Skin Cancer
NRI	Non-Responder Imputation
OCT	Optical Coherence Tomography
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOC	System Organ Class
SUN	Standardization of Uveitis Nomenclature

ULN	Upper Limit Normal
VH	Vitreous Haze
VFQ	Visual Functioning Questionnaire
WBC	White Blood Cell
WHO	World Health Organization
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire

## **14.0 References**

1. Nussenblatt RB, Peterson JS, Foster CS, Rao NA, See RF, Letko E, et al. Initial evaluation of subcutaneous daclizumab treatments for noninfectious uveitis. *Ophthalmology*. 2005;112:764-70.
2. Holladay JT. Proper method for calculating average visual acuity. *J Refract Surg*. 1997;13(4):388-91.

## **15.0                   Summary of Changes**

### **Details of changes in Amendment 2 to the Statistical Analysis Plan:**

#### **Section 3.0**

##### **Section previously read:**

The SAP will provide details to further elaborate statistical methods as outlined in the protocol of Study M11-327, "A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate-, Posterior-, or Pan-uveitis" and will describe analysis conventions to guide the statistical programming work. The analysis plan is based on protocol amendment 9 dated as of 26 June 2013.

The Independent Data Monitoring Committee is established for the study to independently monitor and assess data from the study. At each safety review meeting, the IDMC will undertake a comprehensive review and assessment of the safety data. Details on analyses prepared for the IDMC meetings are to be found in a separate SAP.

Analyses described in this SAP comprise the analyses that will be performed by AbbVie after the study (including the total set of subjects from Japan and non-Japan) has been terminated.

All analyses will be performed using SAS®.

##### **Has been changed to read:**

The SAP will provide details to further elaborate statistical methods as outlined in the protocol of Study M11-327, "A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate, Posterior, or Panuveitis" and will describe analysis

conventions to guide the statistical programming work. The analysis plan is based on protocol amendment 10 dated as of 04 June 2015.

Analyses described in this SAP comprise the analyses that will be performed by AbbVie after the study (including the total set of subjects from Japan and non-Japan) has been terminated.

All analyses will be performed using SAS®.

#### **Section 4.1**

##### **Section previously read:**

The primary objective of this study is to evaluate the long-term safety of adalimumab 40 mg given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate-, posterior-, or pan-uveitis who participated in Protocol M10-877 or Protocol M10-880. Long-term efficacy will also be assessed.

##### **Has been changed to read:**

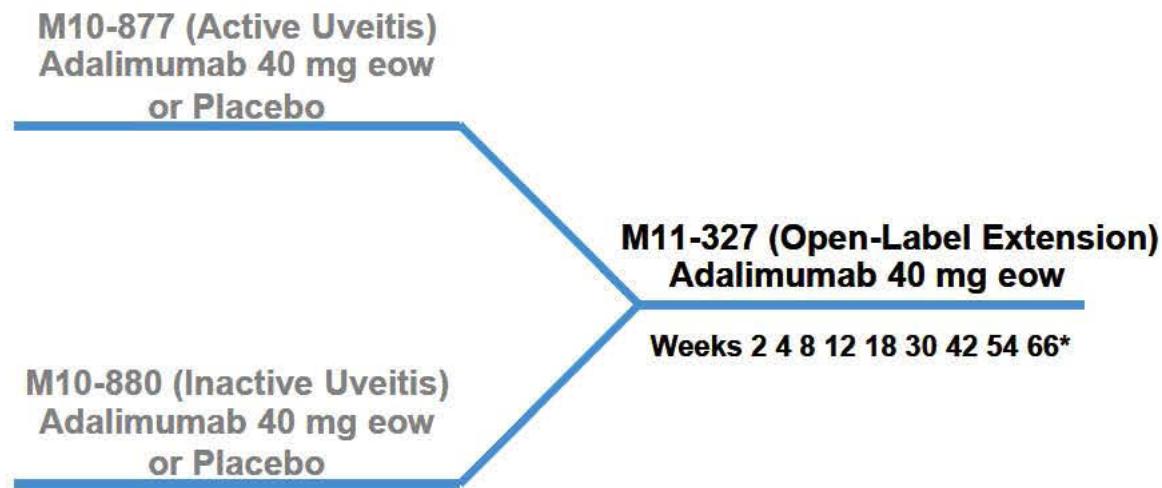
The primary objective of this study is to evaluate the long-term safety of adalimumab 40 mg given every other week (eow) subcutaneously (SC) in subjects with non-infectious intermediate, posterior, or panuveitis who participated in Protocol M10-877 or Protocol M10-880. Long-term efficacy will also be assessed.

#### **Section 4.2**

##### **Section previously read:**

This study is a Phase 3, open-label multicenter study designed to evaluate long-term safety and efficacy of adalimumab in adult subjects with non-infectious intermediate-, posterior-, or pan-uveitis who have either discontinued from Study M10-877 or Study M10-880 for having met "Treatment Failure" criteria or have successfully completed Study M10-877 or Study M10-880. Subjects who prematurely discontinued

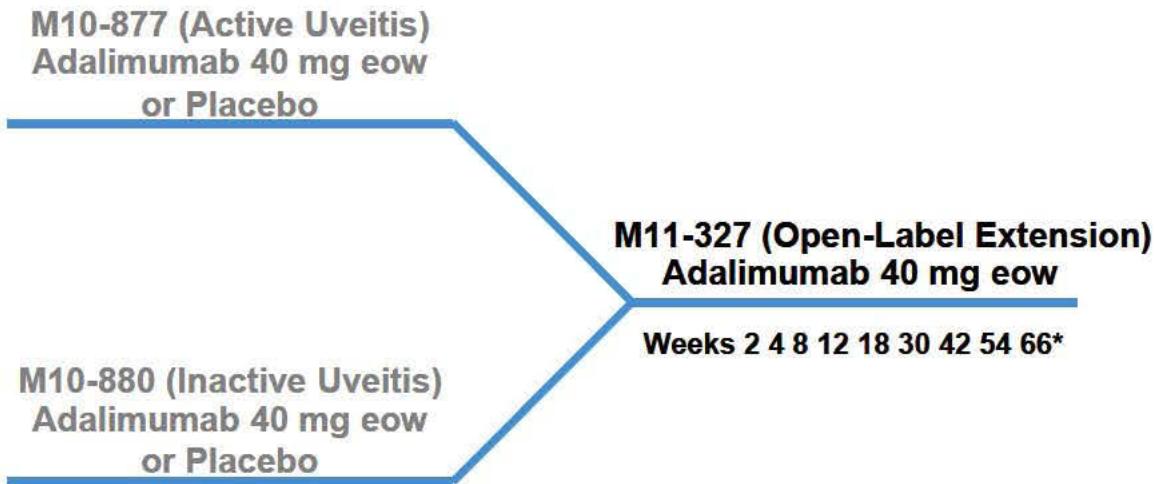
from Study M10-877 or Study M10-880 for reasons other than for Treatment Failure as defined in the parent protocol, will not be eligible for this study. Study visits will occur at Week 0, 2, 4, 8, 12, 18 and every 12 weeks thereafter. Visits will occur every 12 weeks following Week 66 until the end of the study. The entire study will be terminated in March 2016.



\* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2016).

#### **Has been changed to read:**

This study is a Phase 3, open-label multicenter study designed to evaluate long-term safety and efficacy of adalimumab in adult subjects with non-infectious intermediate, posterior, or panuveitis who have either discontinued from Study M10-877 or Study M10-880 for having met "Treatment Failure" criteria or have successfully completed Study M10-877 or Study M10-880. Subjects, who prematurely discontinued from Study M10-877 or Study M10-880 for reasons other than for Treatment Failure as defined in the parent protocol, will not be eligible for this study. Study visits will occur at Week 0, 2, 4, 8, 12, 18 and every 12 weeks thereafter. Visits will occur every 12 weeks following Week 66 until the end of the study. The entire study will be terminated in March 2018.



\* Visits will occur every 12 weeks following Week 66 until the end of the study (not to exceed 15 March 2018).

## Section 6.2

**Third paragraph previously read:**

The following visit windows will be used for efficacy analyses:

Visit Windows			
Week	Nominal Rx Day	First Rx Day	Last Rx Day
0	1	-	1
2	15	2	22
4	29	23	43
8	57	44	71
12	85	72	106
18	127	107	169
18+i*12 <sup>a</sup>	127+i*84	107+i*84	169+i*84

a i = 1, 2, 3, 4 etc.

**Has been changed to read:**

The following visit windows will be used for efficacy analyses:

Visit Windows			
Week	Nominal Rx Day	First Rx Day	Last Rx Day
0	1	-	1
2	15	2	22
4	29	23	43
8	57	44	71
12	85	72	106
18	127	107	169
18+i*12 <sup>a</sup>	127+i*84	170+(i-1)*84	169+i*84

a i = 1, 2, 3, 4 etc.

**Section 6.3****Section previously read:**

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)
- Last Observation Carried Forward (LOCF)

**Has been changed to read:**

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)
- Last Observation Carried Forward (LOCF)

In case of an interim analysis, NRI and LOCF will be used. Values will be imputed until that visit that the subject could have reached based on the cutoff date.

## **Section 7.1**

### **First bullet previously read:**

- **Subject demographics**
  - Age (years)
  - Age categories (< 40, 40 – 64, ≥ 65 years)
  - Age (< 30, ≥ 30 to < 50, ≥ 50 years)
  - Gender (male/female)
  - Race (white, black, Asian, American Indian/Alaska native, native Hawaiian or other Pacific islander, other)
  - Ethnicity (Hispanic or Latino, no ethnicity)
  - Asian race (Chinese, Japanese, Korean, Taiwanese, Singaporean, Malaysian, other) (only for subjects from Japan)

### **Has been changed to read:**

- **Subject demographics**
  - Age (years)
  - Age categories 1 (< 40, 40 – 64, ≥ 65 years)
  - Age categories 2 (< 30, ≥ 30 to < 50, ≥ 50 years)
  - Gender (male/female)
  - Race (white, black, Asian, American Indian/Alaska native, native Hawaiian or other Pacific islander, other)
  - Ethnicity (Hispanic or Latino, no ethnicity)
  - Asian race (Chinese, Japanese, Korean, Taiwanese, Singaporean, Malaysian, other) (only for subjects from Japan)

## Section 7.5

### First and second bullet previously read:

- Immunosuppressants (IMMs) at baseline
  - Azathioprine
  - Cyclosporine
  - Methotrexate (MTX)
  - Mycophenolate mofetil or equivalent drug (e.g. mycophenolic acid)
  - Tacrolimus
- Corticosteroids
  - Oral corticosteroids
  - Topical corticosteroids
  - Other corticosteroids

### Has been changed to read:

- Immunosuppressants (IMMs)
  - Azathioprine
  - Cyclosporine
  - Methotrexate (MTX)
  - Mycophenolate mofetil or equivalent drug (e.g. mycophenolic acid)
  - Tacrolimus
- Corticosteroids (CS)
  - Oral corticosteroids
  - Topical corticosteroids
  - Other corticosteroids

## Section 8.0

### First paragraph previously read:

The number of subjects in each of the following categories will be summarized. The subsequently described analyses will be provided by country as well as by investigator and overall. Additionally, tables will be stratified by the parent study,

Study M10-877/M10-880:

- Subjects who received at least one dose of study medication (safety set)
- Subjects who received at least one dose of study medication (ITT set)
- Subjects who completed (safety set)
- Subjects who prematurely discontinued (safety set)

### Has been changed to read:

The number of subjects in each of the following categories will be summarized. The subsequently described analyses will be provided by country as well as by investigator and overall. Additionally, tables will be stratified by the parent study,

Study M10-877/M10-880:

- Subjects who received at least one dose of study medication (safety set)
- Subjects who received at least one dose of study medication (ITT set)
- Subjects who completed (safety set)
- Subjects who prematurely discontinued (safety set)
- Subjects who are ongoing (safety set, in case of an interim analysis)

## **Section 10.1**

### **Section previously read:**

The subsequently described analyses will be provided in the ITT set. All statistical analyses will be descriptive. Results will be stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had active uveitis when they entered the study, the efficacy analyses will start at Week 8 of Study M11-327. For subjects who had inactive uveitis when they entered the study, the efficacy analyses will start at Baseline of Study M11-327.

### **Has been changed to read:**

The subsequently described analyses will be provided in the ITT set. All statistical analyses will be descriptive. Results will be stratified between subjects who entered into the study with active versus inactive uveitis. For subjects who had inactive and subjects who had active uveitis when they entered the study, the efficacy analyses will start at Baseline of Study M11-327. Results will also be provided overall except for efficacy variables defined differently for subjects entering Study M11-327 with active and inactive uveitis.

## **Section 10.2**

### **First paragraph previously read:**

The following efficacy variables will be analyzed:

- Proportion of subjects at each study time point with no new active, inflammatory chorioretinal or inflammatory retinal vascular lesion in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.

- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in AC cells in both eyes on Slit Lamp Exam, according to SUN criteria.
- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in vitreous haze in both eyes on indirect ophthalmoscopy, according to NEI/SUN criteria.
- Proportion of subjects at each study time point without a worsening of BCVA by  $\geq 15$  letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Percent change in central retinal thickness (1 mm subfield) in each eye at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Change in NEI Visual Functioning Questionnaire (VFQ-25) score at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Proportion of subjects at each study time point achieving a  $\geq 50\%$  reduction in immunosuppression load relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.

**Has been changed to read:**

The following efficacy variables will be analyzed:

- Proportion of subjects with no active lesions in both eyes at each study time point.
- Proportion of subjects at each study time point with no new active, inflammatory chorioretinal or inflammatory retinal vascular lesion in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.

- AC cell grade left/right eye and mean of both eyes at each study time point.
- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in AC cells in both eyes on Slit Lamp Exam, according to SUN criteria.
- VH grades left/right eye and mean of both eyes at each study time point.
- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in vitreous haze in both eyes on indirect ophthalmoscopy, according to NEI/SUN criteria.
- Proportion of subjects at each study time point with VH  $\leq 0.5$  and AC  $\leq 0.5$ .
- Proportion of subjects at each study time point with new lesions, AC  $\geq 2$  or VH  $\geq 2$ .
- Proportion of subjects at each study time point in quiescence defined as no active lesions, AC  $\leq 0.5$  and VH  $\leq 0.5$ .
- Proportion of subjects who experienced a uveitis flare (defined as no quiescence) during the study and who did or did not discontinue from the study due to the flare.
- LogMAR Best corrected visual acuity (BCVA) left/right eye and mean of both eyes at each study time point.
- Proportion of subjects at each study time point without a worsening of BCVA by  $\geq 15$  letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) in both eyes relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Proportion of subjects who started IMMs in Study M11-327.
- Proportion of subjects on/off IMMs at each study time point only in subjects on IMMs at baseline of Study M11-327.
- Proportion of subjects at each study time point achieving a  $\geq 50\%$  reduction in immunosuppression load relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Change in dose of IMM at each study time point relative to baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study only in subjects on IMMs at baseline/Week 8 of Study M11-327.

- Proportion of subjects who started systemic CS in Study M11-327.
- Systemic CS dose at each study time point.
- Proportion of subjects at each study time point with
  - Systemic CS dose = 0 mg/day
  - Systemic CS dose > 0 to  $\leq$  5 mg/day
  - Systemic CS dose > 5 to  $\leq$  7.5 mg/day
  - Systemic CS dose > 7.5 to  $\leq$  10 mg/day
  - Systemic CS dose > 10 to  $\leq$  20 mg/day
  - Systemic CS dose > 20 mg/day
- Percent change in systemic CS dose at each study time point relative to baseline only in subjects on CS at baseline.
- Proportion of subjects in steroid-free quiescence at each study time point.
- Proportion of subjects in quiescence and for subjects without quiescence the proportion of subjects
  - with/without a change in concomitant medication (topical/systemic corticosteroids, immunosuppressants) within 5 days after non-quiescence and with/without quiescence at the next visit (at least 8 Weeks after non-quiescence)
  - with premature discontinuation
- OCT evidence of macular edema in at least one eye at each study time point.
- Central retinal thickness left/right eye and mean of both eyes at each study time point by OCT machine.
- Percent change in central retinal thickness (1 mm subfield) in each eye at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.
- Change in NEI Visual Functioning Questionnaire (VFQ-25) score at each study time point relative to Baseline for subjects who had inactive uveitis when they entered the study and to Week 8 for subjects who had active uveitis when they entered the study.

**Last paragraph previously read:**

The efficacy variables will be analyzed as follows.

Descriptive statistics for quantitative variables will include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for values at each visit, changes from Baseline/Week 8 to each visit thereafter and change from Baseline/Week 8 to Final/Early Termination Visit for continuous variables. In addition, for central retinal thickness percent change from Baseline/Week 8 to each visit thereafter and percent change from Baseline/Week 8 to Final/Early Termination Visit will be analyzed. For central retinal thickness, values at each visit and changes will be analyzed by OCT machine, percent changes will be analyzed overall. Data will be analyzed by Last Observation Carried Forward (LOCF) and as observed. Categorical variables will be summarized by counts and percentages at each visit. Data will be analyzed by Non Responder Imputation (NRI) and as observed.

**Has been changed to read:**

The efficacy variables will be analyzed as follows.

Descriptive statistics for quantitative variables will include the number of observations, mean, standard deviation, minimum, first quartile, median, third quartile, and maximum for values at each visit, changes from Baseline/Week 8 to each visit thereafter and change from Baseline/Week 8 to Final/Early Termination Visit for continuous variables. In addition, for central retinal thickness percent change from Baseline/Week 8 to each visit thereafter and percent change from Baseline/Week 8 to Final/Early Termination Visit will be analyzed. For central retinal thickness, values at each visit and changes will be analyzed by OCT machine, percent changes will be analyzed overall. 95% confidence intervals for means will be provided. Data will be analyzed by Last Observation Carried Forward (LOCF) and as observed. For as observed analyses, graphs will be generated for subjects with active vs. inactive uveitis at entry of Study M11-327 for:

- LogMAR Best corrected visual acuity (BCVA) (mean of both eyes) at each study time point.
- Systemic CS dose at each study time point.
- Central retinal thickness (mean of both eyes) at each study time point by OCT machine.

Categorical variables will be summarized by counts and percentages at each visit.

95% confidence intervals for proportions will be provided. Data will be analyzed by Non Responder Imputation (NRI) and as observed. For as observed analyses, graphs will be generated for subjects with active vs. inactive uveitis at entry of Study M11-327 for:

- Proportion of subjects with no active lesions in both eyes at each study time point.
- Proportion of subjects at each study time point with a Grade  $\leq 0.5+$  in AC cells in both eyes on Slit Lamp Exam, according to SUN criteria.
- Proportion of subjects at each study time point with Grade  $\leq 0.5+$  in vitreous haze in both eyes on indirect ophthalmoscopy, according to NEI/SUN criteria.
- Proportion of subjects at each study time point in quiescence defined as no active lesions, AC  $\leq 0.5$  and VH  $\leq 0.5$ .
- Proportion of subjects with steroid-free quiescence at each study time point.
- OCT evidence of macular edema in at least one eye at each study time point.

## Section 10.4

### First paragraph previously read:

The efficacy variables from Section 10.2 will be analyzed as described in Section 10.2 in the following subgroups:

- IMM usage at Baseline of Study M11-327 (yes, no)

**Has been changed to read:**

The following efficacy variables will be analyzed as described in Section 10.2 by pooling subjects with active and inactive uveitis at start of Study M11-327

- Proportion of subjects with no active lesions in both eyes at each study time point.
- AC cell grade (mean of both eyes) at each study time point.
- Proportion of subjects with a Grade  $\leq 0.5+$  in AC cells in both eyes on Slit Lamp Exam, according to SUN criteria at each study time point.
- VH grades (mean of both eyes) at each study time point.
- Proportion of subjects at each study time point with Grade  $\leq 0.5+$  in vitreous haze in both eyes on indirect ophthalmoscopy, according to NEI/SUN criteria.
- Proportion of subjects at each study time point in quiescence defined as no active lesions, AC  $\leq 0.5$  and VH  $\leq 0.5$ .
- LogMAR Best corrected visual acuity (BCVA) (mean of both eyes) at each study time point.
- Proportion of subjects who started IMMs in Study M11-327.
- Systemic CS dose at each study time point.
- Proportion of subjects with steroid-free quiescence at each study time point.
- OCT evidence of macular edema in at least one eye at each study time point.
- Central retinal thickness (mean of both eyes) at each study time point by OCT machine.

in the following subgroups:

- Gender (male/female)
- Duration of uveitis ( $< 1$ ,  $\geq 1$  years)
- Type of uveitis (intermediate versus posterior versus panuveitis)
- Diagnosis (idiopathic/other versus birdshot choroidopathy versus multifocal choroiditis and panuveitis versus Vogt Koyanagi Harada versus sarcoid versus Behcet's)

- IMM usage at Baseline of Study M11-327 (yes, no)

## **Section 11.1**

### **Last paragraph previously read:**

Analyses of AEs per subgroup will be presented for the AE overview. The number and percentage of subjects experiencing AEs will be tabulated overall.

Subgroups used for the analyses are:

- Concomitant use of corticosteroids (yes, no)
- Baseline immunosuppressant usage (yes, no)
- Baseline azathioprine usage
- Baseline cyclosporine usage
- Baseline methotrexate usage
- Baseline mycophenolate mofetil or an equivalent drug (e.g., mycophenolic acid) usage
- Baseline tacrolimus usage

### **Has been changed to read:**

Analyses of AEs per subgroup will be presented for the AE overview. The number and percentage of subjects experiencing AEs as well as E/100PYs will be tabulated overall.

Subgroups used for the analyses are:

- Concomitant use of corticosteroids (yes, no)
- Baseline immunosuppressant usage (yes, no)
- Baseline azathioprine usage
- Baseline cyclosporine usage
- Baseline methotrexate usage

- Baseline mycophenolate mofetil or an equivalent drug (e.g., mycophenolic acid) usage
- Baseline tacrolimus usage

An AE overview (with number and percentage of subjects experiencing treatment-emergent AEs as well as E/100PYs) will also be presented separately for

- treatment periods with/without concomitant use of corticosteroids
- treatment periods with corticosteroid dose  $> 0$  to  $\leq 15$  mg/day
- treatment periods with corticosteroid dose  $> 15$  mg/day
- treatment periods with/without concomitant use of immunosuppressant
- treatment periods
  - without concomitant use of corticosteroids and immunosuppressant
  - with concomitant use of corticosteroids only
  - with concomitant use of immunosuppressant only
  - with concomitant use of corticosteroids and immunosuppressant

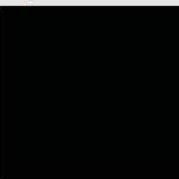
## Document Approval

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