

Statistical Analysis Plan for

Official Title of Study

**A RANDOMIZED, HEAD-TO-HEAD, SINGLE-BLINDED STUDY TO ASSESS  
CHANGES IN THE IMMUNE PROFILE IN RESPONSE TO TREATMENT WITH  
SUBCUTANEOUS ABATACEPT VERSUS SUBCUTANEOUS ADALIMUMAB, IN  
COMBINATION WITH METHOTREXATE IN ADULTS WITH EARLY RHEUMATOID  
ARTHRITIS**

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**STATISTICAL ANALYSIS PLAN  
FOR CLINICAL STUDY REPORT**

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ARTHRITIS**

**PROTOCOL(S) IM101-567**

**VERSION # 3.0**

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## 2 STUDY DESCRIPTION

### 2.1 Study Design

This is an exploratory, randomized, single-blinded assessment study in subjects with early RA defined as symptoms of RA for no more than 12 months prior to screening and satisfying the criteria for RA according to the ACR/EULAR 2010 classification at some point during the 12-month period. Eligible subjects must have been on methotrexate (MTX) for at least 12 weeks with a stable dose of MTX for at least 28 days prior to randomization and are naive to biologic DMARD. The study consists of a screening period of up to 28 days, followed by a 24-week single-blind treatment period with abatacept or adalimumab, followed by a 24-week open-label treatment period with abatacept, followed by an 85-day follow-up period.

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity and safety assessments. Randomization must occur within 28 days of signing the informed consent.

On Day 1, subjects will be randomized to one of two parallel treatment arms in a 1:1 ratio:

- abatacept SC (125mg) weekly
- adalimumab SC (40mg) once every two weeks

All subjects continuing in the open-label treatment period will receive abatacept 125mg SC, weekly. Those subjects randomized to adalimumab will switch to abatacept at Week 28 following a six week washout period. The dose of methotrexate must remain stable throughout the study and may only be lowered due to intolerance or adverse event. Subjects not wishing to continue on open-label abatacept have the option of discontinuing treatment at the end of the single-blind period and proceeding to the post-treatment follow-up period.

Subjects who discontinue treatment of study drug or complete the study will have one follow-up visit 85 days after the last dose of investigational product to perform safety assessments.

## 2.2 Treatment Assignment

At the time of enrollment, immediately after written informed consent is obtained and before any study-related procedures are performed, each subject will be assigned a unique, sequential five-digit number beginning with 00001, 00002, 00003 and so on, for identification throughout the study. This study number must not be reused for any other subject. The study physician or research coordinator must contact the Central Randomization System to enroll each subject into a centralized database at the time consent is obtained.

After completion of all screening evaluations and concomitant medication adjustment or stabilization, all eligible subjects will be randomized into the single-blind treatment phase of the study. Randomization schedules will be generated and kept by the Randomization Group within Drug Supply Management of Bristol-Myers Squibb. Each subject who qualifies for treatment will be assigned a unique randomization number. Randomization numbers will be assigned using a Central Randomization System in the order in which subjects qualify for treatment, not in the order of study enrollment. Subjects will be randomized on a 1:1 basis to either the abatacept treatment arm or the adalimumab treatment arm.

## 2.3 Blinding and Unblinding

Double blinding of study drug, adalimumab vis-à-vis abatacept, is not feasible due to logistical barriers around re-packaging adalimumab as well as the expected differences in injection site reactions. Both of these together make effective blinding of the patients to the randomized drug assignment impractical and unsustainable. The nature and frequency of adalimumab-associated injection site reactions makes blinding investigators responsible for clinical care unsustainable under usual practices. It is possible, however, to preserve the objectivity of clinical assessments with the following strategy that has been designed to establish and maintain a single-blinded assessor for clinical endpoints throughout the study. This will require a minimum of 3 individuals: a blinded clinical assessor, an unblinded Study Research Coordinator and an unblinded physician investigator/subinvestigator to complete/approve the CRF.

## 2.4 Protocol Amendments

The purpose of Amendment 1 (March 14, 2016) is to extend the treatment period of the study an additional 24 weeks. Subjects receiving abatacept will continue to receive abatacept for the additional 24 weeks. Subjects receiving adalimumab will switch to abatacept at Week 28 following a six week washout period and continue treatment with abatacept for the additional 24 weeks.

The purpose of Amendment 2 (June 8, 2016) is to modify some of the inclusion criteria to better align the characteristics of the targeted study population with patients with early Rheumatoid Arthritis seen in clinical practice.

The purpose of Amendment 6 (February 22, 2017) is to include the addition of blood sample collection for PBMC.



### **3 OBJECTIVES**

#### **3.1 Primary**

Not applicable

#### **3.2 Secondary**

Not applicable

[REDACTED]

### **4 ENDPOINTS**

No primary or secondary endpoints are defined for this protocol.

[REDACTED]

## **5 SAMPLE SIZE AND POWER**

In this study, 25 subjects will be randomized per treatment arm.

This is an exploratory study with only exploratory objectives. No formal sample size and power calculation was provided. It should be noted that with 25 subjects per arm the half width of the 95% CI for differences in proportion (e.g., proportion of seroconversion for anti-CCP2, ACPA) will range from 25 to 30%. This means that only if the treatment difference in proportion is larger than 25-30% the difference will be declared statistically significant at 5% significance level. For changes from baseline in continuous variables the minimum detectable effect size (treatment difference in changes divided by common standard deviation) to declare statistical significance (with 5% significance level) is 0.57.

During the study, the sample size was increased to get at least 30 subjects with additional collection of blood for With 40 (instead of 25) subjects per arm the half width of the 95% CI for differences in proportion (e.g., proportion of seroconversion for anti-CCP2, ACPA) will range from 17% to 21%. This means that only if the treatment difference in proportion is larger than 17-21% the difference will be declared statistically significant at 5% significance level. For changes from baseline in continuous variables the minimum detectable effect size (treatment difference in changes divided by common standard deviation) to declare statistical significance (with 5% significance level) is 0.44.

## **6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES**

### **6.1 Study Periods**

The following periods are defined for this statistical analysis plan:

- The pre-treatment period covers the time period prior to or on the first dose time of single-blind study medication.
- The single-blind treatment period starts at the time of the first dose of single-blind study medication and lasts until :
  - the time of the last dose of single-blind study medication for concomitant medication summaries
  - 56 days post last dose of single-blind study medication for subjects who do not enter OL. For those subjects who do enter OL, the single-blind treatment period lasts until first day of open-label for abatacept randomized subjects or until 10 days post last dose of single-blind treatment for adalimumab randomized subjects for safety analyses (AE and labs).
  - 21 days post last dose of single-blind study medication for subjects who do not enter OL. For those subject who do enter OL, the single-blind treatment period lasts until first day of open-label for abatacept randomized subjects or until 10 days post last dose of single-blind treatment for adalimumab randomized subjects for immunogenicity analyses

Note: To align the cut-off of the single-blind treatment period for abatacept and adalimumab and taking into account that for adalimumab there is a wash-out period of 6 weeks, 10 days is

used to cut the single-blind treatment period for adalimumab. Ten (10) is equal to the expected maximum number of days after last single-blind abatacept dose and prior to first open-label abatacept dose (7 days +/- 3 days).

- The open-label abatacept treatment period starts at the time of the first dose of open-label abatacept treatment and lasts until 56 days post last open-label abatacept dose (AE and labs), except for immunogenicity analyses for which the open-label period goes up to 21 days post last open-label abatacept dose.
- The cumulative abatacept period starts at the time of the first dose of abatacept (single-blind or open-label) and lasts until 56 days post last abatacept dose (single-blind or open-label), except for immunogenicity analyses for which the cumulative abatacept period goes up to 21 days post last abatacept dose.

## 6.2 Treatment Regimens

There are 2 single-blind treatment groups: abatacept 125mg SC weekly or adalimumab 40mg SC biweekly, both with concomitant MTX therapy.

There is one open-label treatment group defined: abatacept 125mg SC weekly with concomitant MTX therapy.

## 6.3 Populations for Analyses

The as-treated analysis population will contain all randomized subjects who received at least one dose of single-blind study medication, and subjects will be grouped on an as-randomized basis unless the subject received the incorrect medication for the entire period of single-blind treatment. In that case, the subject will be analyzed in the treatment group associated with the incorrect medication they received. This population will be used for all analyses of the single blind period, including demography, baseline disease characteristics, biomarker, efficacy safety and immunogenicity analyses and for the Week 48 efficacy and biomarker analyses.

The open-label abatacept population will contain all subjects treated with open-label abatacept.

The cumulative abatacept population will contain all subjects treated with single-blind and/or open-label abatacept.

# 7 STATISTICAL ANALYSES

## 7.1 General Methods

All the analyses, with the exception of the analysis for efficacy responder rate, will be 'as-observed', ie. the available data will be used and there will be no imputation for missing values. For the efficacy responder rate analysis a non-responder imputation will be applied for missing data.

In [APPENDIX 1](#) the list of biomarkers is shown. The different biomarkers are classified into different biomarker categories (category 1 up to 12). The biomarker results (tables and plots) will be provided for each of these biomarker categories separately.

The focus of the exploration will be on Day 169 analysis. However, mean or median changes from baseline (with 95 % CI) over time from day 1 to day 169 of the single-blind period will be displayed for all biomarkers. These plots will be grouped by biomarker category (see [APPENDIX 1](#)).

All Day 337 analyses and analyses over time from day 1 to day 337 (efficacy and biomarkers) will be provided by original randomized treatment and grouped by biomarker category if applicable (see APPENDIX 1).

## **7.2 Study Conduct**

As this study includes only exploratory objectives, relevant protocol deviations will not be assessed.

## **7.3 Study Population**

Frequency distributions or summary statistics of data pertaining to subject disposition, demographics, baseline characteristics, and medical history will be tabulated and displayed by treatment group. No statistical test will be carried out for comparison of any baseline measures among treatment groups

### **7.3.1 Subject Disposition**

The number of subjects enrolled into the study at screening, the number of subjects randomized, the number of subjects who received at least 1 dose of single-blind study medication (abatacept or adalimumab), and the number of subjects who discontinued during the single-blind treatment period, together with reasons for discontinuation taken from the eCRF status page, will be summarized. The summary will also present the number of subjects treated in the OL period.

In addition, the number of subjects treated in open-label abatacept period, and the number of subjects who discontinued during the OL abatacept treatment period, together with reasons for discontinuation taken from the eCRF status page will be summarized.

### **7.3.2 Demography and Baseline Characteristics**

Demographic, baseline disease characteristics and biomarkers at baseline of all randomized subjects who received at least one dose of study medication will be summarized. For continuous variables, they will be summarized using means, standard deviations, median, quartiles and ranges. The distribution of categorical variables will be summarized by treatment group using frequencies and percentages.

Baseline demographic characteristics include the following:

- age in years
- weight in kg
- gender
- race
- geographic region

Baseline disease characteristics include:

- duration of disease in months
- number of tender joints (28)
- number of swollen joints (28)
- number of tender joints (68)
- number of swollen joints (66)
- pain
- HAQ-DI
- subject assessment of disease activity
- physician assessment of disease activity
- CRP
- Rheumatoid factor status
- DAS28-CRP
- SDAI
- CDAI

In addition, all the biomarkers will be summarized at baseline.

### **7.3.3 Medical History and Prior Medication**

Medical history and prior anti-rheumatic medication information will be summarized by treatment group using frequencies for all subjects in the as-treated analysis population.

## **7.4 Extent of Exposure**

### **7.4.1 Study Therapy**

Extent of exposure to single-blind study drug (abatacept and adalimumab) in the as-treated analysis population will be summarized in two ways; first, by the number of study drug doses, summarizing frequency distribution of number of study drug doses by treatment group, and second, by the number of days the subject is known to be on study drug, ignoring any dosing interruptions.

For subjects who are not treated in the open-label period, exposure to single-blind study drug in days is calculated as:

- $\text{exposure} = (\text{date of last single-blind study medication} - \text{date of first single-blind study medication} + 1) + 56.$

The offset of 56 days represents approximately four times the half-life of abatacept in humans.

For subjects who receive single-blind abatacept study drug and enter the open-label period within 56 days of the last dose of single-blind study medication, exposure to single-blind study drug in days is calculated as:

- $\text{exposure} = (\text{date of first open-label study medication} - \text{date of first single-blind study medication}).$

For subjects who receive single-blind adalimumab study drug, exposure to single-blind study drug in days is calculated as:

- $\text{exposure} = (\text{date of last single-blind study medication} + 10 - \text{date of first single-blind study medication}).$

To align the exposure of adalimumab with the exposure of abatacept and taking into account that for adalimumab there is a wash-out period of 6 weeks, 10 days is used to adjust the exposure for adalimumab. Ten (10) is equal to the expected maximum number of days after last single-blind abatacept dose and prior to the first open-label abatacept dose (7 days +/- 3 days).

Extent of exposure to abatacept (single blind and open-label) during the cumulative abatacept period will be summarized in two ways; first, by the number of abatacept injections, and second, by the number of days the subject is known to be on abatacept, ignoring any dosing interruptions.

$$\text{exposure} = (\text{date of last abatacept dose} - \text{date of first abatacept dose} + 1) + 56.$$

The offset of 56 days represents approximately four times the half-life of abatacept in humans.

Abatacept includes single-blind abatacept and open-label abatacept. Exposure will be summarized for cumulative abatacept population and presented for all subjects in this population combined

Extent of exposure to abatacept during the open-label abatacept period will be summarized in two ways; first, by the number of abatacept injections, and second, by the number of days the subject is known to be on abatacept, ignoring any dosing interruptions.

- $\text{exposure} = (\text{date of last OL abatacept dose} - \text{date of first OL abatacept dose} + 1) + 56.$

The offset of 56 days represents approximately four times the half-life of abatacept in humans.

Exposure will be summarized for the open-label population by the original randomized treatment groups and for all OL treated subjects combined.

#### **7.4.2 Discontinuation of Study Therapy**

See [Section 7.3.1](#).

The number of subjects who missed study doses during the single-blind (excluding missed study doses due to premature discontinuation from the study) will be summarized by treatment and number of study doses missed. A corresponding listing of subjects with missed doses during the single-blind period will be provided.

In addition, the number of subjects who missed study doses during the cumulative abatacept period (excluding missed study doses due to premature discontinuation from the study) will be summarized for the cumulative abatacept population. A corresponding listing of subjects with missed doses during cumulative abatacept period will be provided.

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## 7.7 Safety

Analysis of all safety data will follow the BMS standard safety data conventions<sup>2,3</sup> and supplements to the standard conventions for the abatacept programs<sup>4</sup>.

The evaluation of drug safety is based primarily on clinical AEs, vital signs and laboratory abnormalities reported during the single-blind treatment period. All safety presentations for the Week 24 analyses will be based on the as-treated analysis population by treatment group.

All safety presentations for the cumulative abatacept period will be based on the cumulative abatacept population and the presentation will be for all abatacept treated subjects (single-blind and/or open-label) combined into one group.

Frequency distribution and individual listings of all AEs will be generated. Changes in clinical laboratory test results from baseline will be summarized. Laboratory marked abnormalities using pre-defined abnormality criteria will also be descriptively summarized. There will be no statistical testing of group difference with respect to frequencies of AEs or laboratory marked abnormalities.

### 7.7.1 Adverse Events

All AEs are coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the latest approved version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of database lock. Listings and summaries will be based on the resulting SOC and PTs.

All reported AEs during the single-blind treatment period and all reported AEs reported during the cumulative abatacept period will be listed, indicating the subjects id, age, gender, the date of onset, the day of onset relative to the start of treatment, investigator's assessment of severity and relationship to study drug.

In addition, all reported AEs during the washout-out period (beyond 20 days past last single blind dose of adalimumab up to first dose of open-label abatacept) will be in a separate listing. This listing will only include adalimumab patients who are treated with OL abatacept. The threshold of 20 days is chosen for this listing, because AEs up to 20 days past last single-blind dose of adalimumab are included in the AE summaries of the single-blind period. It should be noted that for the single-blind analysis a threshold of 20 days (post-hoc) was used instead of 10 days defined in version 1.0 of SAP.

AEs will be summarized for the single-blind treatment period and the cumulative abatacept period. This period is defined in [Section 6.1](#). These AE summaries will be based on proportions, which represent the number of subjects experiencing the AEs divided by the number of subjects who received at least 1 dose of single-blind study medication for the Week 24 analysis and by the number of subjects treated with abatacept for the cumulative abatacept period analysis.

Any AEs irrespectively of when they occur, but will appear on the above mentioned comprehensive listing.

Summary information (the number and percent of subjects by treatment) will be tabulated for the following AEs:

- all AEs including clinical and laboratory AEs
  - most common AEs (reported in 10% of subjects or more in any treatment group)
  - categorized by severity
- related events
  - most common (reported in 5% of subjects or more in any treatment group)
  - categorized by severity
- serious adverse events (SAEs)
- discontinuations due to SAEs/AEs

## **7.7.2 Adverse Events of Interest**

### **7.7.2.1 Infections**

All reported infections and infestations within the SOC: *Infections and infestations* occurring during the single-blind treatment period will be summarized by preferred term and treatment group and also provided in a separate listing. The events will also be summarized by severity.

Similar summaries and listings will be done for the cumulative abatacept period .

### **7.7.2.2 Malignancy**

All events in the MedDRA Maintenance and Support Services Organization (MSSO) malignancies Structured MedDRA Query (SMQ) list occurring during the single-blind treatment period will be captured and reported. These events will be summarized by preferred term and treatment group and will also be listed.

Similar summaries and listings will be done for the cumulative abatacept period .

### **7.7.2.3 Autoimmune Disorders**

The frequency of pre-specified autoimmune disorders, defined using a BMS customized SMQ, occurring during the single-blind treatment period will be provided. Autoimmune disorders occurring during the single-blind treatment period will be summarized by severity. All reported autoimmune disorders occurring during the single-blind treatment period will be listed.

Similar summaries and listings will be done for the cumulative abatacept period.

#### **7.7.2.4 Injection Adverse Events**

A. Systemic Injection Reactions (pre-specified, defined using a BMS customized SMQ) are defined as systemic AEs (such as hypersensitivity reactions) occurring during the first 24 hours after abatacept/adalimumab SC administration.

B. Local Injection Site Reactions (pre-specified, defined using a BMS customized SMQ) are defined as those AEs that occur at the site of SC injection.

The pre-specified systemic injection reactions and local injection site reactions occurring during the single-blind treatment period will be summarized by severity. These AEs will also be listed.

In addition, a pre-specified local injection site reaction event of interest, defined as the AEs with the following PT that occur at the site of SC injection: *Erythema, Pain, Pruritus, Haematoma, and Swelling* will be summarized by severity.

Similar summaries and listings will be done for the cumulative abatacept period.

#### **7.7.3 Deaths**

All AEs with the outcome of death reported during the single-blind treatment period will be listed by treatment group, together with a clinical narrative relating to the death of the subjects.

A similar listing will be done for the cumulative abatacept period.

#### **7.7.4 Other Serious Adverse Events**

SAEs are captured on a CRF page. All SAEs occurring during the single-blind treatment period will be summarized by treatment group and listed.

Similar summaries and listings will be done for the cumulative abatacept period.

#### **7.7.5 Adverse Events Leading to Discontinuation of Study Therapy**

AEs leading to discontinuation of study drug are identified as those AEs with an action code of 5 on the eCRF page (5 = discontinued study drug). All such AEs occurring during the single-blind treatment period will be listed and summarized by SOC, PT and treatment group. In addition, a listing of subjects with SAEs leading to discontinuation will be provided.

Similar summaries and listings will be done for the cumulative abatacept period.

#### **7.7.6 Multiple Adverse Events**

Several descriptive summaries of adverse events that takes into account the number of occurrences that an AE was reported by individual patients will be provided. In order to prepare these summaries, the CRF data will be processed according to standard BMS algorithms to categorize each line of patient data as a new occurrence or a continuation of an existing event. This

determination will be based upon onset and resolution dates. Each line of patient data will represent the maximum severity observed as well as the last known assessed relationship to study medication by the investigator.

This data will be presented as the rate per 100 years of patient exposure. Exposure to study medication will be calculated according to approved standard BMS algorithms as well.

As an example, if 5 patients report 7 unique episodes of headache and had a combined cumulative exposure of 20 years to study medication, the incidence rate is reported as  $7 / 20 * (100)$  or 35 cases per 100 patient years of exposure.

The following summary tables will be provided:

- A table showing the total number and rate (exposure adjusted) of occurrences for all AEs occurring in at least 10% of the subjects treated will be presented for the single-blind period.
- Listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event have been collapses.

Similar summaries and listings will be done for the cumulative abatacept period.

### **7.7.7 Summaries of Laboratory Data**

Safety summaries based on laboratory test results include evaluation of laboratory abnormalities and change in laboratory test values from baseline. The baseline value on a per analyte basis is the last non-missing value prior to the start of single-blind study drug

Laboratory abnormalities are identified using a pre-defined set of marked abnormality criteria. The criteria will be listed in the CSR. The frequencies of laboratory abnormalities will be presented by laboratory test and treatment group during the single-blind treatment period and by laboratory test and all abatacept subject combined into one group for the cumulative abatacept period. The single-blind treatment period and the cumulative abatacept period for the laboratory analyses are defined in [Section 6.1](#).

Evaluation of change from baseline during the single-blind treatment period and during the cumulative abatacept period will be carried out for all laboratory parameters whose regular collection is indicated in the protocol. Summary statistics will be presented for baseline, post-baseline laboratory values and the change from baseline. Subject who have laboratory measures at baseline and corresponding measure on at least 1 scheduled visit during the single-blind treatment period or on at least 1 scheduled visit during the cumulative abatacept period will be included in the laboratory analyte assessment. Note that not all subjects have laboratory determinations for all analytes at all visits, and therefore the sample size may vary from analyte to analyte. Some laboratory samples may be inadvertently analyzed multiple times for the same test, producing multiple laboratory results for the same collection date and time for the same subjects. The average of a subject's multiple laboratory results will be taken as the final lab result on that date and time for this subject if assessments are tested at the same laboratory center.

[illegible]

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[REDACTED]

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#### **7.7.7.2 Vital Signs**

On each visit day, vital signs are monitored. Body temperature, seated blood pressure and heart rate will be summarized using mean, standard deviation, median and range at each visit measured during the single-blind treatment period.

Similar summaries will be done for the cumulative abatacept period.

## **8 CONVENTIONS**

### **8.1 Calculations of Key Measures**

#### **8.1.1 Evaluation of Joint Counts**

Joints may have been surgically replaced/fused due to worsening RA during the study. Joint status is adjusted for surgical replacement and intra-articular injections according to the following rules:

- If a joint is replaced/fused on or before the start of single-blind study drug, then for this joint both tenderness and swelling will be imputed as ‘not done’ for all visits.
- If a joint is replaced/fused due to RA involvement and occurs after the start of study drug, then for this joint both tenderness and swelling will be considered as ‘present’ for all visits on or after the replacement procedure date.
- If a joint is replaced for reason other than RA involvement and occurs after the start of study drug, then for this joint both tenderness and swelling will be considered as ‘not done’ for all visits on or after the replacement procedure date.
- If an intra-articular injection occurs, then for that joint both tenderness and swelling will be considered as ‘present’ at that particular visit and all subsequent visits.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The ACR20, ACR 50, or ACR 70 definition of improvement is a 20%, 50%, or 70% improvement, respectively, over baseline in tender and swollen joint counts (#1 and #2) and 50%, or 70% improvement, respectively in 3 of the 5 remaining core data set measures (components #3 to #7).

### **8.1.6 Evaluation of CDAI**

CDAI is a simple linear sum of the following four components:

- Tender joint counts out of 28 joints
- Swollen joint counts out of 28 joints
- Subject global assessment of disease activity (0-10cm)
- Physicians global assessment of disease activity (0-10cm)

## **8.2 Baseline Measures**

For all outcome measures, the baseline value is the last assessment taken prior to first dose of single-blind study medication. In general, this is the assessment taken on study Day 1 before the administration of study medication. For some variables that are also measured during screening, if Day 1 assessments are unavailable then the last assessment prior to Day 1 from screening assessments will be used as baseline value. When there is a missing baseline assessment in joint counts, it will not be imputed. Thus, subjects are excluded from any change from baseline analysis for which they have a missing baseline value.

## **8.3 Missing Measurements**

For listings of efficacy measures or biomarkers, missing values will be represented as missing. For analyses involving efficacy or biomarkers, missing values will not be imputed.

## **8.4 Missing, Unknown or Partial Dates**

The BMS safety guidelines<sup>2,3,4</sup> for conventions relating to the handling of missing or partial dates and the determination of appropriate default values in such cases (in particular, for concomitant medication dose start dates and end dates and AE onset dates) will be utilized.

## **8.5 Day Ranges for Analysis of Time Points**

Single -blind period

Subjects do not always adhere strictly to the visit schedule timing in the protocol. Therefore, the designation of visits during the single-blind period of the study will be based on the day of evaluation relative to the trial (day of first single-blind study medication = study Day 1) rather than the nominal visit recorded in the CRF. Mutually exclusive relative day windows are defined below to provide derived visits that correspond to the post-baseline time points. If a visit falls outside the pre-specified visit windows, then the data collected at that visit will not be assigned a derived visit but will remain in the derived data sets. Determination of baseline values is addressed in



**Section 8.2.** The day ranges for assessments during the single-blind treatment period are presented in Table 8.5-1.

**Table 8.5-1: Day Ranges for Assessments during Single-Blind Treatment Period**

Visit	Target Day	Assessments
Screening	< 1	< 1
Day 1 (Baseline)	1	1*
Week 4	29	8 - 43
Week 8	57	44 - 85
Week 16	113	86 - 141
Week 24	169	142 - 211

\* Note: See [Section 8.3](#) for baseline measures.

For subjects who receive single-blind abatacept and continue into the open-label treatment period, the upper limit of Week 24 window is first dose day of the open-label period. For subjects who receive single-blind adalimumab and continue into the open-label treatment period, the upper limit of this window is the last dose of single-blind study medication + 10 days.



Open-label period

The day ranges for assessments during the open-label period are presented in Table 8.5-2.

**Table 8.5-2: Day Ranges for Assessments during Open-label Period**

Visit	Target Day	Assessments
Week 28	197	Day 2 OL - 211
Week 32	225	212 - 253
Week 40	281	254 - 309
Week 48	337	310 - 365

Efficacy and biomarker assessments performed beyond 42 days after the last dose are excluded.

Lab assessment performed beyond 56 days after the last dose are excluded.

If a subject has more than 1 visit where a measurement is recorded within a window, the measurement closest to the target day will be used. In case of 2 visits being equidistant from the target, the later measurement will be used in analyses.

## **9 CONTENT OF REPORTS**

At the time of the first lock when the last randomized subject completes the 24 week single-blind treatment period, the analyses described in this SAP, with the exceptions of the analyses for the biomarker categories 2, 3 and 5 in [APPENDIX 1](#), will be performed. The results of these analyses will be presented in a standard BMS Clinical Study Report (CSR).















