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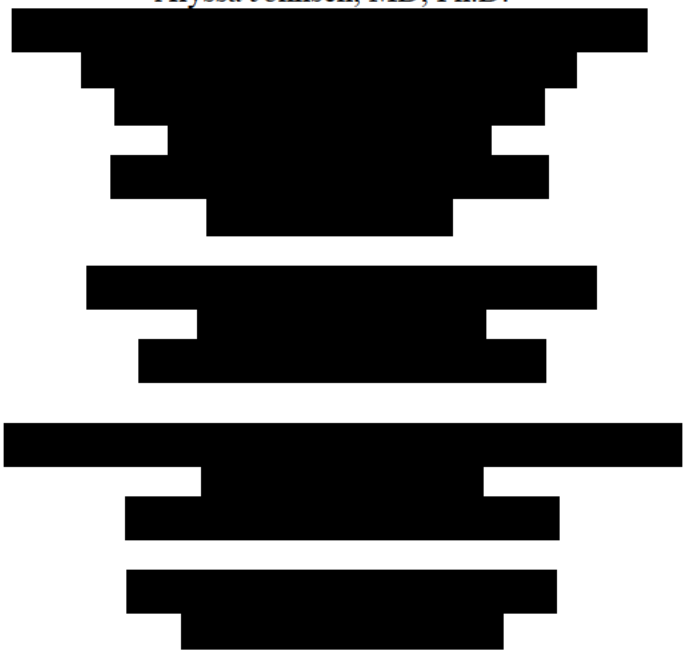
Clinical Protocol IM101332

A Phase 3 Randomized Placebo Controlled Study to Evaluate the Efficacy and Safety of Abatacept Subcutaneous Injection in Adults with Active Psoriatic Arthritis

Revised Protocol Number: 03
Incorporates amendment(s) 09

Study Director/Medical Monitor
Alyssa Johnsen, MD, Ph.D.



Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	19-Aug-2014	Incorporates Amendment 09
Amendment 09	19-Aug-2014	• Changed screening period from 7-42 to 7-56 days. • Added permission for rescreening. • Modified inclusion criteria for target lesion to be at screening and randomization/Day 1. • Changed exclusion criteria for subjects who have been exposed to more than 2 TNFi to specify subjects who have failed more than 2 TNFi due to inefficacy. • Changed drug stabilization time for prior use of TNFis. • Deleted exclusion of prior use of apremilast, ustekinumab, and briakinumab. • Added drug stabiliation time for prior use of apremilast, ustekinumab, and briakinumab. • Changed TB testing to allow use of a gamma release assay.
Revised Protocol 02	29-Oct-2013	Incorporate Amendment 05
Amendment 05	29-Oct-2013	• Modified definition of menopause to be 12 months amenorrhea rather than 6 months. • Added prior treatment of briakinumab as an exclusion criteria. • Indicated the Target Lesion should be assessed in addition to be identified at screening. • Added window the Day 1 radiograph to be - 3 days. [redacted] • Clarified that the clinical assessor for enthesitis, dactylitis, PASI, target lesion, and physician visual analog scales may be a different person from the joint assessor. • Added a window for the biopsy sample collection to be - 3 days on Days 1 and 169. • Clarified when pregnancy tests are required. [redacted]
Revised Protocol 01	22-Jul-2013	Incorporate Amendment 03
Amendment 03	22-Jul-2013	• Changed “entering” to “continue into” when describing how subjects can continue the one year long term extension (Section 3.1.4). • Added azathioprine as a medication which must be discontinued ≥ 28 days or five half lives prior to randomization.

Document	Date of Issue	Summary of Change
		• Deleted study from the breast cancer screening exclusion. • Added "prior to randomization (Day 1) to exclusions from Medical History Exclusion Criteria n, q, and v [Section 3.3.2, Subsection 2)]. • Added an exclusion for treatment with phototherapy within 28 days prior to randomization and hypersensitivity to investigational product excipients. • Added that the target lesion must not be in the axilla, genitals, groins, palms, or soles. • Changed dose reduction to dose limitation in the definition of intolerance for prior use of DMARDs. • Changed information on methods of contraception based on new language currently in discussion (protocol body and Appendix 2). • Clarified criteria for missed doses requiring discontinuation of treatment to be consistent throughout the protocol. • Added that subjects should avoid taking MTX within 48 hours of study drug administration to simplify determination of relatedness of adverse events to the study drug. • Added the hyaluronic acid is not permitted in the double-blind and open label periods. • Added storage conditions for investigational drug in the Study Treatment section. • Changed procedure guide to instructions to describe how subjects will be trained in the use of the safety syringe. • Changed caretaker to caregiver in Section 4.3 to be consistent with other language in the protocol. • [redacted] • Corrected description of DLQI in Table 5.1-2 and added subsection for Study Drug Administration. • Added note that the Physician and Subject Global Assessments if Disease Activity refers to arthritis as the disease (Table 5.1-2, Table 5.1-3, and Section 5.4.4.) • Added note that subjects should not apply emollients to the skin on the day of their office visits (Table 5.1-2, Table 5.1-3, and Section 5.4.4). • Changed description of OL-1 to correctly refer to "Same day as final day in the Double Blind Period. • Deleted urine pregnancy test in OL-1 since the testing is already done on the last day in the double blind period. • [redacted] • Added into table notes regarding provisioning of urine pregnancy

Document	Date of Issue	Summary of Change
		kits for WOCBP to be used during the monthly phone calls at OL-113 and OL-169 and that the results should be reported during those phone calls (Table 5.1-3). • Added table note to confirm the subject is giving the SC injections and recording the information on their diary cards (Tables 5.1-3 and 5.1.4. • Added visit windows to office visits in the long term extension. (Table 5.1-4). • Added dispensation of home use pregnancy kits to WOCBP at the monthly visits in the long term extension (Table 5.1-4). [redacted] • In Section 5.3.1 clarified that subjects who terminate the study early in the double-blind or open label period will have radiographs taken at the early termination visit. • Added statement that subjects should be discontinued from treatment if the investigator considers the subject has not achieved sufficient benefit from the treatment. • Added that the radiographs at Day 1 may be taken after dosing as long as they are performed on Day 1. • Specified the clinical assessor should complete the visual analog scales described as being completed by a physician. • Corrected spelling of plaque in Section 5.4.4.2. [redacted] [redacted] [redacted]
Original Protocol	11-Mar-2013	Not applicable

SYNOPSIS

Clinical Protocol IM101332

Protocol Title: A Phase 3 Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Abatacept Subcutaneous Injection in Adults with Active Psoriatic Arthritis

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

- Abatacept 125 mg weekly via SC injection
- Placebo to match the abatacept weekly via SC injection

Study Phase: Phase 3

Research Hypothesis:

Abatacept 125 mg when administered SC is more effective than placebo in achieving ACR20 response after 24 weeks (Day 169) of treatment in subjects with active Psoriatic Arthritis (PsA).

Objectives:

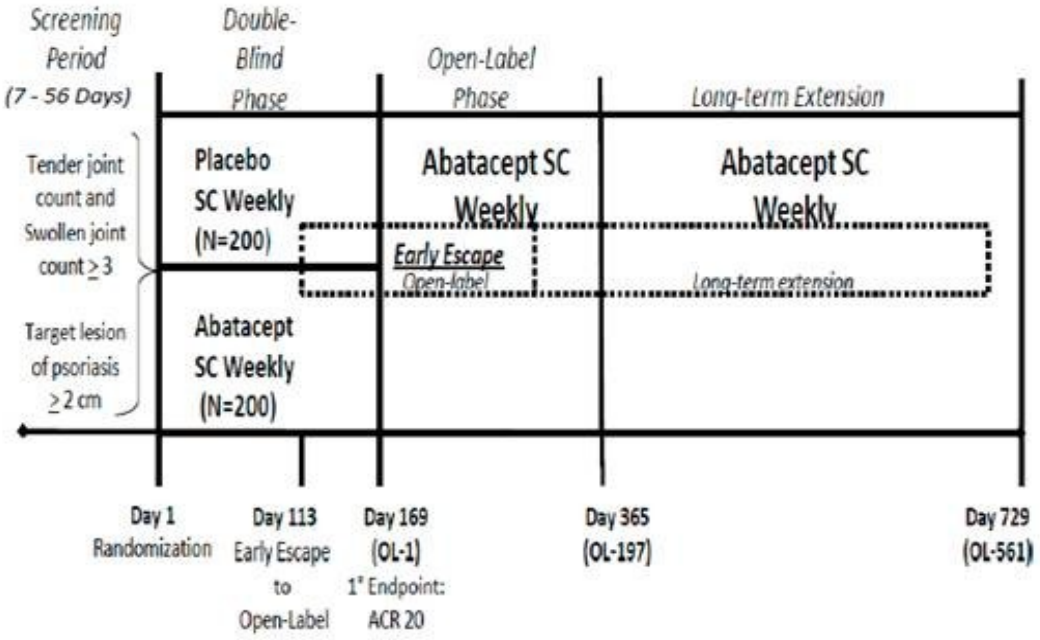
***Primary*:** To compare the efficacy of abatacept to placebo as assessed by the ACR20 response at Day 169.

Key Secondary:

- To compare the efficacy of abatacept to placebo as assessed by the Health Assessment Questionnaire (HAQ) response at Day 169.
- To compare the efficacy of abatacept to placebo in the subset of subjects who have never been exposed to Tumor Necrosis Factor α Inhibitor (TNFi) therapy, as assessed by the ACR20 response at Day 169.
- To compare the efficacy of abatacept to placebo in the subset of subjects who have previously taken TNFi therapy, as assessed by the ACR20 response at Day 169.
- To compare the efficacy of abatacept to placebo as assessed by the proportion of subjects who do not show progression by the PsA modified SHS (Sharp/van der Heidje score) of x-rays from baseline to Day 169.

Study Design: This is a 24 week (168 days), Phase 3, randomized, double-blind, placebo controlled, multicenter study, followed by a 28 week (196 days) open-label period in subjects with active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR). This study will include subjects who have had an inadequate response and/or intolerance to non-biologic DMARDs and may or may not been exposed to TNFi therapy. Subjects currently on biologic therapy cannot be enrolled. Approximately 400 subjects in total will be randomized in a 1:1 ratio to 125 mg SC weekly of abatacept and placebo (200 subjects per arm): approximately 248 subjects in the TNFi exposed subgroup and approximately 152 subjects in the TNFi naive subgroup. Randomization will be stratified globally by current MTX use, prior use of TNFi therapy and for psoriatic skin involvement ≥ 3% BSA. A maximum of approximately 40% of subjects with < 3% BSA psoriatic skin involvement will be randomized. On Day 113 subjects who do not achieve a ≥ 20% improvement from baseline in their swollen and tender joint counts will be labeled as treatment failures and removed from their blinded treatment arm and transitioned to the early escape arm, open label weekly SC abatacept 125 mg. At Day 169, all subjects will transition to the open-label phase and receive abatacept 125 mg SC weekly. At the end of the open label period, subjects have the option of entering a one year study extension.

Study Design:



Study Population: Subjects with active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR)

Key Inclusion Criteria:

- Subjects at least 18 years of age who have a diagnosis of PsA by Classification Criteria for Psoriatic Arthritis (CASPAR)
- Subjects have active PsA as shown by a minimum of ≥ 3 swollen joints and ≥ 3 tender joints (66/68 joint counts) at screening and randomization/Day 1 (prior to study drug administration). At least one of the swollen joints must be in the digit of the hand or foot.
- Subjects with at least one confirmed ≥ 2 cm target lesion of plaque psoriasis in a region of the body that can be evaluated at screening and randomization/Day 1.
- Subjects must have had an inadequate response or intolerance to at least one non-biologic disease-modifying anti-rheumatic drug (DMARD).
- If currently on a non-biologic DMARD (methotrexate, leflunomide, sulfasalazine, or hydroxychloroquine) the medication must have been used for at least 3 months with a stable dose for at least 28 days prior to randomization (Day 1).
- Subjects may have been exposed to TNFi therapy. Subjects may have discontinued for any reason (inadequate response, intolerance or other).
- If using oral corticosteroids (≤ 10 mg mg/day prednisone equivalent), dose must be stable ≥ 14 days prior to randomization (Day 1).
- Subjects may enroll on systemic retinoids (eg, acitretin) provided the medication has been used for at least 3 months with a stable dose for at least 28 days prior to randomization (Day 1).

Key Exclusion Criteria

- Subjects with guttate, pustular, or erythrodermic psoriasis
- Subjects who have had prior exposure to abatacept (CTLA 4Ig)
- Subjects who have been exposed to any investigational drug within 4 weeks or 5 half lives prior to randomization (Day 1), whichever is longer

- Female subjects who had a breast cancer screening procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations
- Subjects with a history of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to dosing. Subjects with carcinoma in situ, treated with definitive surgical intervention prior to study enrollment are allowed.
- Subjects with any bacterial infection within the last 60 days prior to screening (enrollment), unless treated and resolved with antibiotics, or any chronic bacterial infection (such as chronic pyelonephritis, osteomyelitis and bronchiectasis
- Subjects at risk for tuberculosis (TB). Specifically, subjects with:
    - Current clinical, radiographic or laboratory evidence of active TB
    - A history of active TB within the last 3 years even if it was treated
    - A history of active TB greater than 3 years ago unless there is documentation that the prior anti-TB treatment was appropriate in duration and type
    - Latent TB which was not successfully treated
    - Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless they have no evidence of current TB on chest x-ray at screening and they are actively being treated for TB with isoniazid (INH) or other therapy for latent TB given according to local health authority guidelines (eg, Center for Disease Control). Treatment must have been given for at least 4 weeks prior to randomization (Day 1). These subjects should complete treatment according to local health authority guidelines.
- Subjects with herpes zoster that resolved less than 2 months prior to enrollment
- Subjects with evidence (as measured by the investigator) of active or latent bacterial, active viral, or serious latent viral infections at the time of enrollment, including subjects with evidence of Immunodeficiency Virus (HIV) infection
- Subjects who are not currently treated with a non-biologic DMARD and have clinical or radiographic evidence of arthritis mutilans (eg, digital telescoping or "pencil-in-cup" radiographic changes)
- Subjects who have failed more than 2 TNFis due to inefficacy, with inefficacy defined as inadequate response after 3 months of treatment at a therapeutic dose: ***NOTE:*** There is no limit on the total number of TNFis to which the subject has been exposed.
- Subjects who have received TNFi therapy within 4 weeks for etanercept, 8 weeks for adalimumab, certolizumab, infliximab or golimumab prior to randomization (Day 1).
- Subjects who have received apremilast within 4 weeks, ustekinumab within 20 weeks, and briakinumab within 8 weeks prior to randomization (Day 1).
- Subjects who have discontinued a non-biologic DMARD or systemic retinoid within four weeks or five half-lives, whichever is longer, prior to randomization (Day 1)
- Use of any of the following within 28 days or five half lives whichever is longer prior to randomization (Day 1): azathioprine, cyclosporine A, oral tacrolimus, mycophenolate mofetil (MMF), hydroxyurea, fumaric acid esters, paclitaxel, 6-thioguanine, 6-mercatopurine, or tofacitinib

Study Assessments:

Efficacy will be assessed using the ACR response rate, the HAQ response rate, the radiographic non-progressor rate of the PsA-modified Sharp/van der Heidje score (SHS), and the Psoriasis Area and Severity Index (PASI) scores.

Statistical Considerations:

Sample Size: A hierarchical testing procedure will be applied for the primary endpoint (proportion of ACR20 responders at Day 169) and the 4 key secondary endpoints (proportion of HAQ responders, proportion of ACR20 responders in 2 subgroups and proportion of non-progressors in total SHS at Day 169) to ensure the preservation of the overall type I error. The sample size determination is calculated in such a way that the power is at least 80% for

each of the endpoints included in the hierarchical testing procedure and in addition, for the skin endpoint, PASI50. All estimates used for the sample size determination are based on the results of phase II study IM101158 for PsA, except for non-progressors using total PsA-modified Sharp/van der Heijde score (SHS) (x-ray). A 2-sided continuity corrected Chi-square test at alpha=0.05 is used. Based on the power calculations, a sample size of 400 randomized subjects (200 per arm) is required: 248 subjects in the TNFi exposed subgroup and 152 subjects in the TNFi naive subgroup.

Endpoints:

Primary endpoint: Proportion of ACR20 responders at Day 169

Key secondary endpoints:

- Proportion of HAQ responders (a reduction of at least 0.35 from baseline) at Day 169
- Proportion of ACR20 responders at Day 169 in the TNFi naive subpopulation
- Proportion of ACR20 responders at Day 169 in the TNFi exposed subpopulation
- Proportion of non-progressors in total PsA-modified SHS (defined as a change from baseline in total PsA-modified SHS ≤ 0) at Day 169

Other secondary endpoint:

- Proportion of subjects achieving a PASI50 (achieving at least 50% improvement from baseline in PASI) at Day 169 in subjects with baseline BSA ≥ 3%
- Proportion of ACR50 and ACR70 responders at Day 169
- Mean change from baseline in physical (PCS) and mental functions (MCS) of SF-36 at Day 169
- Proportions of subjects with positive immunogenicity response up to Day 169
- Safety (proportion of subjects with adverse events, deaths, SAEs, and AEs leading to discontinuation and proportion of subjects with marked laboratory abnormalities) up to Day 169

Analyses:

Efficacy Analysis:
All efficacy analyses will be for the intent-to-treat (ITT) analysis population. In general, no formal statistical testing will take place except for the primary, the key secondary efficacy endpoints and the proportion of subjects achieving PASI50 at Day 169. If the 2-sided test for the primary endpoint (proportion of ACR20 responders at Day 169) is statistically significant at alpha=5%, then a hierarchical approach for statistical testing will be used for the secondary endpoints. This procedure allows for preserving of the overall Type I error rate of 0.05 for the study. Hierarchical ordering of the secondary endpoints is as follows:

- Proportion of HAQ responders at Day 169
- Proportion of ACR20 responders at Day 169 in the TNFi naive subpopulation
- Proportion of ACR20 responders at Day 169 in the TNFi exposed subpopulation
- Proportion of non-progressors in total PsA-modified SHS (defined as a change from baseline in total PsA-modified SHS ≤ 0) at Day 169

P-values will be presented for each of these endpoints. However, no claim will be based on endpoints that have a rank lower than that endpoint whose null hypothesis was the first that could not be rejected. That is, no claim will be based on endpoints that have a rank lower than that endpoint whose test was the first to be non-statistically significant. A clear distinction will be made between p-values whereby claims can and cannot be made. All proportions mentioned above will be tested with a 2-sided Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by prior TNFi use (Yes, No), MTX use (Yes, No) and BSA (< 3%, ≥ 3%) at a 5% significance level.

Safety Analysis:

The evaluation of drug safety is primarily based on clinical adverse events and laboratory abnormalities reported during the study.

Frequency distributions and listings of all adverse events, deaths, serious adverse events, adverse events leading to discontinuation and adverse events of special interests will be generated. Laboratory marked abnormalities, using pre-defined abnormality criteria, will also be descriptively summarized. There will be no statistical testing of treatment group differences with respect to the frequency of adverse events or laboratory marked abnormalities.

The following safety analysis time points will be defined:

- Safety from Day 1 up to Day 169. This analysis will be on the as-treated analysis population. The summaries will be presented by treatment group.

[redacted]

TABLE OF CONTENTS

[redacted]

1 INTRODUCTION [redacted]

[redacted]

1.3 Objectives(s)

1.3.1 Primary Objective

- To compare the efficacy of abatacept to placebo as assessed by the ACR20 response at Day 169

1.3.2 Secondary Objectives

1.3.2.1 Key Secondary Objectives

- To compare the efficacy of abatacept to placebo as assessed by the Health Assessment Questionnaire (HAQ) response at Day 169
- To compare the efficacy of abatacept to placebo in the subset of subjects who have never been exposed to TNFi therapy, as assessed by the ACR20 response at Day 169
- To compare the efficacy of abatacept to placebo in the subset of subjects who have previously taken TNFi therapy, as assessed by the ACR20 response at Day 169
- To compare the efficacy of abatacept to placebo as assessed by the proportion of subjects who do not show progression of x-rays [using the PsA modified Sharp/van der Heidje score (SHS)] from baseline to Day 169

1.3.2.2 Other Secondary Objectives

- To compare the proportion of subjects achieving at least 50% improvement from baseline in psoriasis, as assessed by the Psoriasis Area and Severity Index Arthritis (PASI) skin score between the two treatment groups at Day 169
- To assess the efficacy of abatacept to placebo as measured by the proportion of subjects achieving ACR50 and ACR70 response at Day 169
- To determine the improvement in the physical and mental function subscales of the Short Form-36 (SF-36), at Day 169
- To determine the proportion of subjects with at least one positive immunogenicity response up to Day 169
- To assess safety by the proportion of subjects with adverse events (all AEs, deaths, SAEs, and AEs leading to discontinuation) and the proportion of subjects with laboratory marked abnormalities up to Day 169

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to Bristol-Myers Squibb (BMS) immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

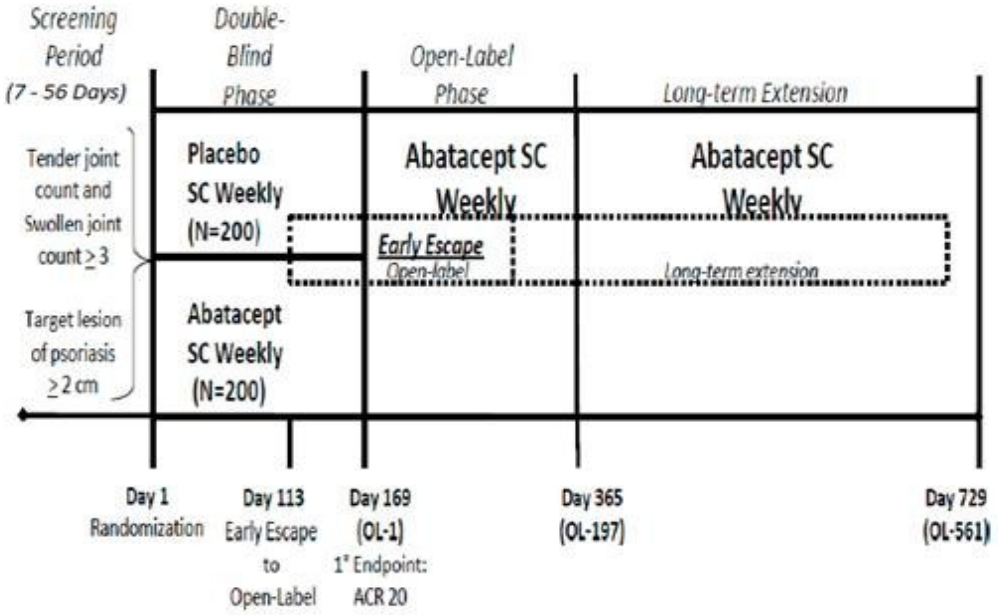
3.1 Study Design and Duration

This is a 24 week (168 days), Phase 3, randomized, double-blind, placebo controlled, multicenter study, followed by a 28 week (196 days) open-label period in subjects with active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR) (Appendix 1). This study will include subjects who have had an inadequate response or intolerant response to non-biologic DMARDs and may or may not have had been exposed to TNFi therapy. Subjects currently on biologic therapy cannot be enrolled.

Approximately 400 subjects in total will be randomized in a 1:1 ratio to 125 mg SC weekly of abatacept and placebo (200 subjects per arm), approximately 248 subjects (124 subjects per arm) in the TNFi exposed subgroup and approximately 152 subjects (76 subjects per arm) in the TNFi naïve subgroup. Randomization will be stratified globally by current MTX use, prior use of TNFi therapy and for psoriatic skin involvement ≥ 3% BSA. An approximate maximum of 40% of subjects with < 3% BSA psoriatic skin involvement will be randomized. Once enrollment maximums for TNFi exposure and % BSA subgroups have been reached, randomization of additional subjects in these subgroups may be closed.

On Day 113 subjects who do not achieve a ≥ 20% improvement from baseline (Day 1) in their swollen and tender joint counts will be labeled as treatment failures and removed from their blinded treatment arm and transitioned to the early escape arm, open label weekly SC abatacept 125 mg. At Day 169, all subjects will transition to the open-label period and receive abatacept 125 mg SC weekly. At the end of open label period, subjects have the option of entering a one year long term extension.

Figure 3.1-1: Study Design Schematic



3.1.1 Screening

Eligibility will be based on specified Inclusion/Exclusion Criteria. Information on medical history and concomitant medications will be determined and safety assessments will be performed. Randomization must occur within 28 days of the qualifying screening visit. An optional Screening Visit 2 will be performed if >28 days (but ≤ 56 days) has elapsed since Screening Visit 1 prior to randomization. For example, if a subject qualified for the study but requires additional time to stabilize on existing therapies or the site has not received results from all the relevant laboratory testing within the 28 day window, the subject could be rescreened. A rescreened subject must be randomized within 28 days.

3.1.2 Double-Blind Period

Following screening, eligible subjects will be randomized to either abatacept 125 mg SC weekly or placebo.

No change of psoriasis or PsA therapeutic regimen is allowed during the double period except for intolerance based on investigator judgment (other than rescue therapy in Section 3.1.2.1).

3.1.2.1 Rescue Therapy (Day 1 Baseline to Day 169)

At any time from baseline to Day 169 except for the 28 days prior to Day 113 or Day 169, rescue therapy may be considered for exacerbation of psoriatic arthritis disease activity.

For psoriatic arthritis, only one instance of rescue therapy may be given during the double-blind period. This may occur at a regularly scheduled study visit or between study visits. Permitted therapy for psoriatic arthritis is as follows:

- A single oral tapering dose of glucocorticosteroid (no greater than 40 mg of prednisone [or prednisone equivalent]) per day, not to exceed 2 weeks
- An intra-articular dose of glucocorticoids (no greater than 40 mg methylprednisolone or 40 mg of triamcinolone [or methylprednisolone or triamcinolone equivalent] into one joint or divided into two joints
- A single intramuscular dose of glucocorticoids (no greater than 40 mg methylprednisolone or 40 mg of triamcinolone [or methylprednisolone or triamcinolone equivalent])
- An entheseal injection with glucocorticosteroid (no greater than 40 mg methylprednisolone or 40 mg of triamcinolone [or methylprednisolone or triamcinolone equivalent]) into one entheseal site or divided into two entheseal sites

For the treatment of psoriasis in subjects not currently using low potency topical corticosteroids, low potency topical corticosteroids [potency group VI (eg, desonide 0.5%, or equivalent) or potency group VII (eg, hydrocortisone 1%, or equivalent) for palms, soles, face, and intertriginous areas (where two skin areas rub together) may be initiated.

3.1.2.2 Early Escape (Day 113)

On Day 113, subjects who do not achieve a ≥ 20% improvement from baseline in their swollen and tender joint counts will be labeled as treatment failures and removed from their blinded treatment arm and transitioned to "Early Escape" treatment with open label weekly SC abatacept 125 mg. In addition to all Day 113 procedures, these subjects will perform the additional procedures of the Early Escape Visit.

3.1.3 Open Label [Day 169 (Open Label Day1) to Day 365 (Open Label Day 197)]

Subjects will remain on open-label abatacept 125 mg SC until Day 365. Permitted changes in treatment are described in the following sections (Section 3.1.3.1 and 3.1.3.2).

3.1.3.1 Increases in Medication to Manage Increased Disease Activity in the Open Label Period

Psoriatic Arthritis

For increased arthritis disease activity that in the opinion of the investigator requires additional treatment, the following hierarchy of treatments should be followed.

1. NSAIDs may be added or the dose thereof may be increased according to labeling guidelines as determined by patient tolerance.
2. The dose of currently prescribed concomitant non-biologic DMARD therapy should be increased according to labeling guidelines as determined by patient tolerance.
3. Short-courses of therapy with glucocorticosteroids may be used up to two times during the open-label period as follows:
   a. An oral tapering dose of glucocorticosteroid (no greater than 40 mg of prednisone [or prednisone equivalent]) per day, not to exceed 2 weeks
   b. An intra-articular dose of glucocorticoids (no greater than 40 mg methylprednisolone or 40 mg of triamcinolone [or methylprednisolone or triamcinolone equivalent] into one joint or divided into two joints
   c. A single intramuscular dose of glucocorticoids (no greater than 40 mg methylprednisolone or 40 mg of triamcinolone [or methylprednisolone or triamcinolone equivalent])
   d. An entheseal injection with glucocorticosteroid (no greater than 40 mg methylprednisolone or 40 mg of triamcinolone [or methylprednisolone or triamcinolone equivalent]) into one entheseal site or divided into two entheseal sites

   NOTE: Daily doses of glucocorticosteroids should not be increased and not exceed 10 mg prednisone (or equivalent) during the open label period.
4. After maximizing NSAIDs and current non-biologic DMARD therapy and utilizing options for glucocorticosteroid therapy, permitted non-biologic DMARD may be initiated per investigator judgment according to labeling guidelines.

Psoriasis

For increased psoriasis disease activity that in the opinion of the investigator requires additional treatment, the addition or change of topical therapies including all potencies of topical corticosteroids but excluding topical calcineurin inhibitors (tacrolimus and pimecrolimus) are allowed. If topical therapies are not sufficient for the control of psoriasis, the addition of permitted non-biologic DMARDs and systemic retinoid are allowed. If topical therapies and non-biologic DMARDs are insufficient to control psoriasis disease activity, phototherapy may be used at the discretion of the investigator.

[redacted]

3.1.4 Long Term Extension

Subjects have the option of continuing into a one year long term extension during which abatacept will be provided. Subjects will complete quarterly safety visits.

For WOCBP, monthly telephone calls will be performed to collect the results of pregnancy tests.

Adverse event and concomitant medication will be recorded quarterly. Any occurring between office visits must be reported immediately to BMS (see Section 6.1).

Concomitant therapies for the treatment of psoriatic arthritis and psoriasis that are not specifically prohibited (Section 3.4.1.1) may be used according to product labeling instructions at the discretion of the investigator.

3.1.5 Early Termination

Subjects who terminate early should complete the procedures specified in the Early Termination Visits as defined by study period.

3.1.6 Post Dose Follow-up Period

During the 6-month post dose follow-up period (28, 84, and 168 days post treatment) when subjects are no longer receiving study medication, safety and immunogenicity assessments will be performed.

[redacted]

[redacted]

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to supply study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subject is willing to participate in the study and signed the informed consent

2) Target Population

a) Subjects have a diagnosis of PsA by Classification Criteria for Psoriatic Arthritis (CASPAR) (Appendix 1)

b) Subjects have at least one confirmed ≥ 2 cm target lesion of plaque psoriasis in a region of the body that can be evaluated excluding the axilla, genitals, groin, palms, and soles at screening and randomization/Day 1.

c) Subjects must have had an inadequate response or intolerance to at least one non-biologic disease-modifying anti-rheumatic drug (DMARD)

> **NOTE**: Inadequate response to a non-biologic DMARD is defined as prior treatment with MTX, leflunomide, or sulfsalazine at a therapeutic dose for at least 3 months (For MTX, therapeutic dose is define as at least 15 mg weekly), that was discontinued for lack of efficacy or was associated with ongoing active disease.
>
> Intolerance to a non-biologic DMARD is defined as discontinuation or dose limitation due to an adverse event.

d) Subjects may have been exposed to TNFi therapy. Subjects may have discontinued for any reason (inadequate response, intolerance or other).

> **NOTE**: Inadequate response to TNFi therapy is defined as prior treatment with a TNFi at an approved dose for at least 3 months, which was discontinued for lack of efficacy or was associated with ongoing active disease.
>
> Intolerance to a TNFi is defined as discontinuation or dose limitation due to an adverse event.

e) Subjects have active disease as shown by a minimum of ≥ 3 swollen joints and ≥ 3 tender joints (66/68 joint counts) at screening and randomization/Day 1 (prior to study drug administration). At least one of the swollen joints must be in the digit of the hand or foot.

f) If currently on a non-biologic DMARDs [methotrexate (maximum of 25 mg weekly), leflunomide, sulfasalazine, or hydroxychloroquine], the medication must have been used for at least 3 months with a stable dose for at least 28 days prior to randomization (Day 1).

g) NSAIDs doses must be stable for at least 14 days before randomization (Day 1) and consistent with labeling recommendations.

h) If using oral corticosteroids (≤ 10 mg/day prednisone equivalent), dose must be stable ≥ 14 days before randomization (Day 1).

i) Subjects may enroll on systemic retinoids (eg, acitretin) provided the subject has used the medication for at least 3 months with a stable dose at least 4 weeks prior to randomization (Day 1).

j) Concurrent topical therapy for plaque psoriasis must have been stable for ≥ 14 days prior to randomization (Day 1).

k) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie subject has not been randomized). If re-enrolled, the subject must be re-consented.

3) Age and Reproductive Status

See Section 3.3.3 for the definition of WOCBP.

a) Men and women, at least 18 years of age.

b) Women of childbearing potential (WOCBP) must use method(s) of contraception based on guidelines described in Appendix 2. The individual methods of contraception and duration should be determined in consultation with the investigator.

c) Women must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

d) Women must not be breastfeeding

e) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) do not require contraception

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with active systemic inflammatory condition other than PsA (eg, systemic lupus erythematosus).

2) Medical History and Concurrent Diseases

a) Subjects who are impaired, incapacitated, or incapable of completing study related assessments

b) Current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, neurological, or cerebral disease including severe and uncontrolled infections, such as sepsis and opportunistic infections. Concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

c) Female subjects who had a breast cancer screening procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations

d) Subjects with a history of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to dosing. Subjects with carcinoma in situ, treated with definitive surgical intervention prior to study enrollment are allowed.

e) Subjects with a history of (within 12 months of signing informed consent), or known current problems with drug or alcohol abuse history or known cirrhosis including alcoholic cirrhosis

f) Subjects with any bacterial infection within the last 60 days prior to screening (enrollment), unless treated and resolved with antibiotics, or any chronic bacterial infection (such as chronic pyelonephritis, osteomyelitis and bronchiectasis).

g) Subjects at risk for tuberculosis (TB). Specifically, subjects with:

   i) Current clinical, radiographic or laboratory evidence of active TB

   ii) A history of active TB within the last 3 years even if it was treated

   iii) A history of active TB greater than 3 years ago unless there is documentation that the prior anti-TB treatment was appropriate in duration and type

   iv) Latent TB which was not successfully treated

   v) Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless they have no evidence of current TB on chest x-ray at screening and they are actively being treated for TB with isoniazid (INH) or other therapy for latent TB given according to local health authority guidelines (eg, Center for Disease Control). Treatment must have been given for at least 4 weeks prior to randomization (Day 1). These subjects should complete treatment according to local health authority guidelines.

h) Subjects with herpes zoster that resolved less than 2 months prior to enrollment

i) Subjects with evidence (as measured by the investigator) of active or latent bacterial, active viral, or serious latent viral infections at the time of enrollment, including subjects with evidence of Immunodeficiency Virus (HIV) infection

j) Subjects with guttate, pustular, or erythrodermic psoriasis

k) Subjects who have a history of systemic fungal infections (such as histoplasmosis, blastoplasmosis, or coccidioides)

l) Subjects who fulfill ACR Functional Class 4 (Appendix 3)

m) Subjects who have had prior exposure to abatacept (CTLA4-Ig) or other CTLA4 therapies.

n) Subjects who have been exposed to any investigational drug within 4 weeks or 5 half-lives prior to randomization (Day 1), whichever is longer

o) Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines. (In view of the long half-life of abatacept, study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication).

p) Subjects who are not currently treated with a non-biologic DMARD and have clinical or radiographic evidence of arthritis mutilans (eg, digital telescoping or "pencil-in-cup" radiographic changes).

q) Subjects who have discontinued a non-biologic DMARD or systemic retinoid within four weeks or five half-lives prior to randomization (Day 1) whichever is longer.

r) Subjects who have discontinued oral corticosteroids within 14 days prior to randomization (Day 1).

s) Subjects who have received an IM, IV or IA administration of a corticosteroid ≤ 28 days prior to randomization (Day 1)

t) Subjects who have discontinued oral NSAIDs within 14 days prior to randomization (Day 1).

u) Subjects who have failed more than 2 TNFis due to inefficacy with inefficacy defined as inadequate response after 3 months of treatment at a therapeutic dose. NOTE: There is no limit on the total number of TNFi to which the subject has been exposed.

v) Subjects who have received TNFi therapy within 4 weeks for etanercept or within 8 weeks for adalimumab, certolizumab, infliximab, or golimumab prior to randomization (Day 1).

w) Prior use of rituximab ≤ 6 months ago; if after > 6 months has elapsed since use, must have documented reconstitution of total peripheral B cell counts to a level within normal laboratory range.

x) Subjects who have been treated with apremilast within 4 weeks, ustekinumab within 20 weeks, or briakinumab within 8 weeks prior to randomization(Day 1).

y) Use of any of the following within 28 days or five half lives whichever is longer prior to randomization (Day 1): azathioprine, cyclosporine A, oral tacrolimus, mycophenolate mofetil (MMF), hydroxyurea, fumaric acid esters, paclitaxel, 6-thioguanine, 6-mercatopurine, or tofacitinib

z) Treatment with the following topical therapies within 14 days prior to randomization (Day 1): calcineurin inhibitors (tacrolimus and pimecrolimus), topical vitamin D analogs (eg, calcipotriene, calcitriol, tacalcitol), topical retinoids (eg, tazorotene), shampoo containing corticosteroids, topical tar and salicylic acid (except on the scalp), or medium to high potency corticosteroids (potency great than or equal to triamcinolone 0.1%).

aa) Treatment with phototherapy within 28 days prior to randomization.

3) Physical and Laboratory Test Findings

a) Hepatitis B surface antigen-positive subjects with detectable hepatitis B viral DNA or Hepatitis B core antibody positive subjects and with detectable hepatitis B viral DNA

b) Hepatitis C antibody-with detectable hepatitis C viral RNA

c) Hemoglobin (Hgb) < 8.5 g/dl

d) White Blood Count (WBC) < 3,000/mm^3 (3 x 10^9/L)

e) Platelets < 100,000/mm^3 (100 x 10^9/L)

f) Any laboratory test results that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study

4) Allergies and Adverse Drug Reaction

a) Hypersensitivity to one of the investigational product excipients.

5) Sex and Reproductive Status

a) Women who are breast-feeding.

6) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

c) Subjects who are illiterate

d) Subjects with a history or suspicion of unreliability, poor cooperation, or non-compliance with medical treatment.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, women under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/ml to confirm menopause.

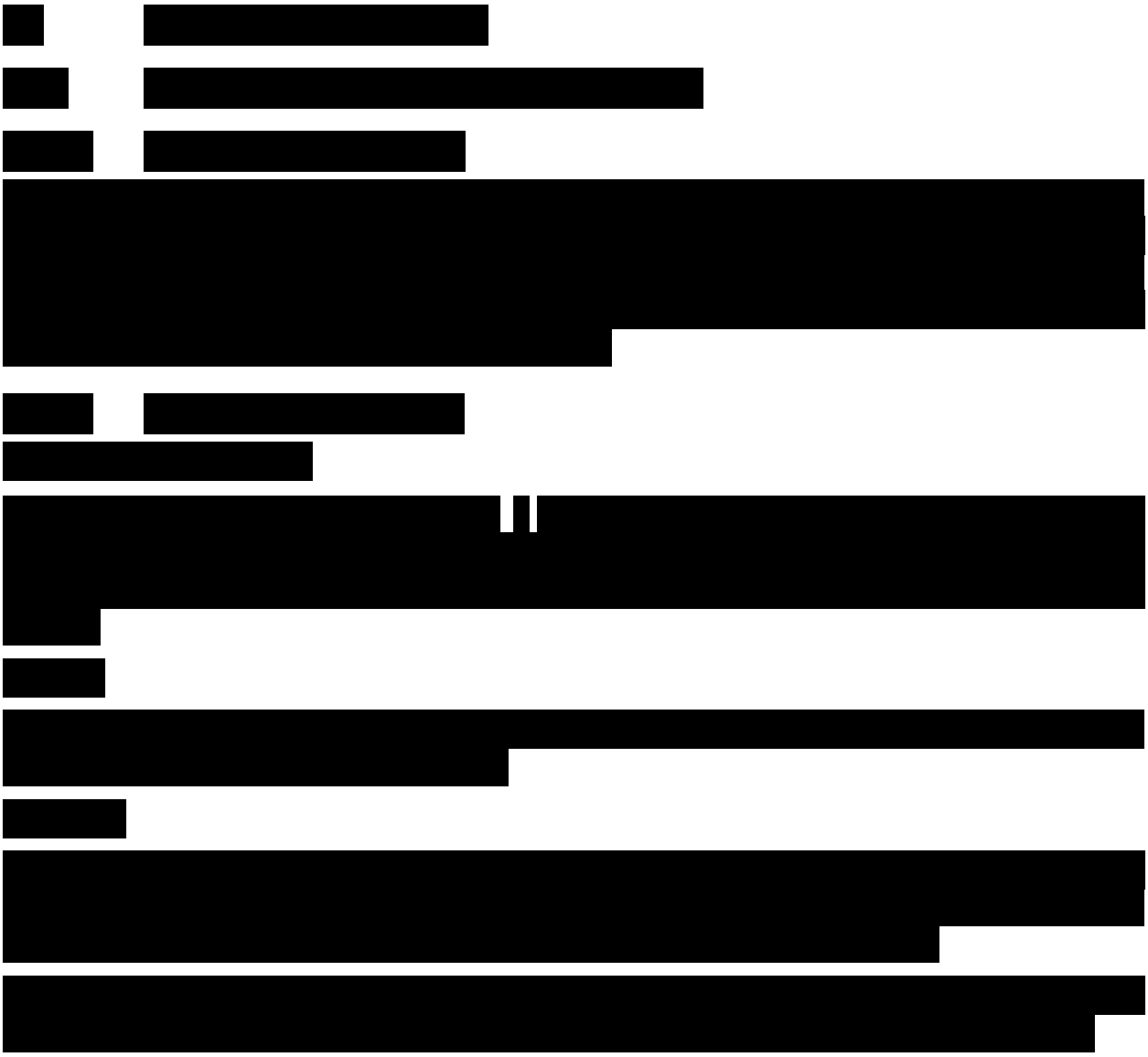
Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used: The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

1 week minimum for vaginal hormonal products, (rings, creams, gels)

4 week minimum for transdermal products

8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.



[redacted]

[redacted]

3.5 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and noninvestigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), abnormal laboratory test results or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding a subject for any reason (emergency or non-emergency)
- Use of any prohibited medication (See Section 3.4.1)
- Use of any investigational drug therapy excluding study medication

- Significant non-compliance with protocol (ie, procedures, assessments, medication, etc). The investigator should discuss such issues with the BMS Medical Monitor.
- Missed doses
    - During the double-blind period, any subject who misses greater than four consecutive doses must be withdrawn from the study.
    - During the open-label period, any subject who misses greater than six consecutive doses must be withdrawn from the study.

If in the opinion of the investigator continued participation in the study is not in the best interest of the subject due to lack of sufficient benefit, the investigator should advise the subject to discontinue study treatment.

All subjects who discontinue should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow-up

Subjects who discontinue study treatment may continue to be followed.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter.

All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

Study drugs include both Non-investigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

For all study sites, Bristol-Myers Squibb Research and Development will supply the following Investigational Product(s).

4.1 Study Treatments

Double-Blind and Open Label Period: Abatacept (or matching placebo) will be administered subcutaneously (SC) once per week. Subjects will be trained by the investigational staff in self-administration and then proceed with independent self-administration.

Table 4.1-1: Investigational Products				
PRODUCT	**ROUTE OF ADMINISTRATION**	**POTENCY**	**APPEARANCE**	**STORAGE CONDITIONS**
Abatacept Injection	Subcutaneous	125 mg/syringe (125 mg/mL)	Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated, 2-8 ° C (36-46 ° F); protect from light; protect from freezing
Placebo for Abatacept Injection	Subcutaneous	To match 125 mg/syringe	Clear to slightly opalescent, colorless to pale yellow solution, essentially free of particulate matter on visual inspection	Store refrigerated, 2-8 ° C (36-46 ° F); protect from light; protect from freezing

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are:

- Abatacept for subcutaneous injection, 125 mg/ml
- Placebo to match Abatacept for subcutaneous injection, 125 mg/ml

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

In this protocol, noninvestigational product(s) is/are not applicable for this study.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

4.2 Method of Assigning Subject Identification

At the time of enrollment, immediately after written informed consent is obtained and before performing any study-related procedures, each subject will be assigned a unique sequential subject number beginning with 001, 002, 003, etc, for identification throughout the study. Any subject number must not be reused for any other participant. The physician/coordinator must contact the Central Randomization System to enroll each subject into a centralized database at the time of signing consent.

After completion of all screening evaluations and concomitant adjustment or stabilization, all eligible subjects will enter the 24-week double-blind, Treatment Period. Subjects completing the double-blind period and fulfilling the necessary criteria may enter the 28-week open-label period during which all subjects receive abatacept 125 mg/ml subcutaneous injection.

Randomization schedules will be generated and kept by the Randomization Group within Drug Supply Management of Bristol-Myers Squibb. Each subject who is qualified 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 to abatacept SC or abatacept SC placebo in a 1:1 ratio. Randomization will be stratified globally by current MTX use, prior exposure to TNFi and whether plaque psoriasis involves $\geq 3\%$ BSA. Enrollment will be limited to approximately 38% TNFi naïve subjects and approximately 40% subjects with $< 3\%$ BSA involvement with plaque psoriasis.

Specific instructions for randomization into the Central Randomization System will be provided in a separate manual.

4.3 Selection and Timing of Dose for Each Subject

Subjects will be trained to self-administer their weekly SC injection of study medication.

Training should be performed by investigational site personnel that are considered qualified trainers by the Investigator. Subjects will be trained using instructions that will be provided by

BMS. The subject should be able to self-administer the SC injection between office visits. If the subject is unable to self-administer the SC injection, a caregiver may administer the injection for the subject. Under these circumstances, the caregiver should be trained by the investigational staff and be present when the subject returns to the office.

If a subject administers another SC medication (eg, SC MTX), then the study drug should be administered to a site on the left side of the body and the other SC medication to a site on the right side of the body.

On "Office Visit" days, SC injections should occur AFTER all assessments, including blood draws for assessment of immunogenicity and drug concentrations. To ensure compliance and to monitor technique "office visit" SC injections should be conducted in the presence of a qualified investigational staff.

4.3.1 Dose Modifications

4.3.1.1 Dose Modifications in the Absence of Adverse Events.

All Study Medications (Abatacept SC and matching placebo): Every effort should be made to give all medications within ±3 days of the target date in the double-blind and open label treatment periods. The last dose before each office visit should be administered at least 4 days before the scheduled visit date. If study medication is not received within the dosing window, this dose should be skipped and the next dose must then be administered on the next scheduled target administration day.

In the long term extension period, the office visits may be modified to be ±7 days of the target dosing administration day for a significant reason (including an adverse event).

During the double-blind period, any subject who misses greater than four consecutive doses should be discontinued from the study.

During the open-label period, any subject who misses greater than six consecutive doses should be discontinued from the study.

4.3.1.2 Dose Modifications Due to Adverse Events

If abnormal laboratory test results or clinical adverse events indicate toxicity that, in the judgment of the investigator, could place the subject at risk, study drug administration should be interrupted and the investigator should notify the BMS medical monitor. Subjects may receive further study medication treatment only if full resolution of the adverse event or abnormal laboratory finding is documented.

If a dose is skipped, the next SC injection should be administered on the subsequent targeted administration day.

4.4 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the

investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

For this study, the method of unblinding for emergency purposes is the IVRS. For information on how to unblind in an emergency, consult the IVRS material.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

The BMS Bioanalytical Science Department or its designee will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of PK and immunogenicity samples from the placebo group of subjects. Other members will remain blinded.

4.5 Treatment Compliance

Monthly study drug administration compliance will be performed at the investigational site office by reviewing the diary cards.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.

- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (IM101-332)

Procedure	Screening Visit 1	Screening Visit 2[a]	Notes
Contact IVRS to enroll subject	X		Contact IVRs for subject number. If subject does not meet eligibility criteria, contact IVRS to screen fail/enroll fail the subject
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
[redacted]	[redacted]	[redacted]	[redacted]
Medical History	X		
Safety Assessments			
Complete Physical Examination	X		
Targeted (Brief) Physical Examination		X	
Chest X-ray	X		Chest x-ray is required if not performed within 6 months of Screening visit, documentation must be on file.
Vital Signs	X	X	Seated blood pressure, heart rate, and temperature
Height and Weight	X		
Serious Adverse Events Assessment	X	X	

Table 5.1-1: Screening Procedural Outline (IM101-332)			
Procedure	**Screening Visit 1**	**Screening Visit 2[a]**	**Notes**
Laboratory Tests			
TB Screening	X		TB screening should be performed during screening period & all testing be completed prior to randomization.
Hepatitis B surface antigen (HbsAg)	X		If positive, obtain HBV DNA
Hepatitis B core antibody	X		If positive, obtain HBV DNA.
Hepatitis C antibody	X		If positive, obtain HCV RNA.
Hematology	X	X	CBC with platelets
Chemistry Panel	X	X	
HIV Testing	X		HIV testing will performed in countries that require the testing.
Urinalysis	X		
Urine/serum Pregnancy Test	X	X	WOCBP only
Rheumatoid Factor	X		
Efficacy Assessments			
Tender Joint Count (68)	X	X	
Swollen Joint Count (66)	X	X	
Identify and Assess Target Lesion	X	X	
% Body Surface Area of Psoriasis Involvement	X	X	
ACR Functional Status Assessment	X		

[a] An optional screening visit (Screening Visit 2) must be performed if >28 days has elapsed since Screening Visit 1 was performed. The Screening Visit 2 may be used if a subject qualified for the study but required additional time to stabilize on existing medication or additional time is required to receive all pertinent laboratory results.

Table 5.1-2: Flow Chart for Protocol IM101332 - Double-Blind Treatment Period

Procedure	Day 1 Randomization	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Early Termination	Early Escape[a]	Notes
Contact IVRS	X							X	X	X	At Day 169 or at Escape update IVRS regarding the subject's status
Safety Assessments											
Targeted Physical (Brief) Exam	X	X	X	X	X	X	X	X	X		
% Body Surface Area of Psoriasis Involvement	X										
Weight	X							X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X		Seated blood pressure, heart rate, temperature
Adverse Events Assessment	X	X	X	X	X	X	X	X	X		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Laboratory Assessments											
Hematology	X			X		X		X	X		CBC with platelets
Chemistry panel	X			X		X		X	X		
Fasting lipid panel	X							X	X	X	Subjects should be fasting at least 8 hours.
Highly sensitive (hs) CRP	X	X	X	X	X	X	X	X	X		
Urine/serum pregnancy test	X		X	X	X	X	X	X	X		WOCBP only, results confirmed prior to administration of study drug.
[redacted]	[redacted]		[redacted]					[redacted]	[redacted]	[redacted]	

Table 5.1-2: Flow Chart for Protocol IM101332 - Double-Blind Treatment Period

Procedure	Day 1 Randomization	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Early Termination	Early Escape[a]	Notes
RNA	X		X					X	X	X	
DNA	X										
[redacted]	[redacted]				[redacted]			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]			[redacted]	[redacted]	[redacted]	
Efficacy Assessments											
Tender Joint Count (68)	X	X	X	X	X	X	X	X	X		
Swollen Joint Count (66)	X	X	X	X	X	X	X	X	X		
Physician's Global Assessment of Disease Activity VAS	X	X	X	X	X	X	X	X	X		Physicians should only consider arthritis disease activity when performing this assessment.

Table 5.1-2: Flow Chart for Protocol IM101332 - Double-Blind Treatment Period

Procedure	Day 1 Randomization	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Early Termination	Early Escape[a]	Notes
Subject Global Assessment of Disease Activity VAS	X	X	X	X	X	X	X	X	X		Subjects must be instructed to only consider arthritis disease activity when performing this assessment.
Subject Global Assessment of Pain VAS	X	X	X	X	X	X	X	X	X		
Subject's Assessment of Physical Function (HAQ)	X	X	X	X	X	X	X	X	X		
X-rays of the hands and feet	X							X	X	X	The allowed window for performance of the X-ray for Day 1 is -3 days. For Day 169 the window is ± 14 days and Day 113 is + 14 days.
SF 36	X			X		X		X	X		
Target Lesion Score	X	X	X	X	X	X	X	X	X		
PASI	X	X	X	X	X	X	X	X	X		Subjects should not apply emollients to their skin on the day of their study visit until after their visit has been completed.
[redacted]	[redacted]			[redacted]		[redacted]		[redacted]	[redacted]		
[redacted]	[redacted]			[redacted]		[redacted]		[redacted]	[redacted]		

Table 5.1-2: Flow Chart for Protocol IM101332 - Double-Blind Treatment Period

Procedure	Day 1 Randomization	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Early Termination	Early Escape[a]	Notes
[redacted]	[redacted]			[redacted]		[redacted]		[redacted]	[redacted]		
[redacted]	[redacted]			[redacted]		[redacted]		[redacted]	[redacted]		
[redacted]	[redacted]			[redacted]		[redacted]		[redacted]	[redacted]		
[redacted]	[redacted]										
Physician Global Assessment of Psoriasis and Arthritis Disease Activity	X			X		X		X	X		
Subject Global Assessment of Psoriasis and Arthritis Disease Activity	X			X		X		X	X		
Study Drug Administration											
Train subjects on how to self-inject and how to fill out the diary cards	X										
Dispense diary cards	X		X	X	X	X	X				
Collect diary cards			X	X	X	X	X	X	X		
Dosing Injectable Study Med	X	X	X	X	X	X	X				

[a] If a subject qualifies for early escape, all of the Day 113 assessments and the early escape assessments need to be completed.

Table 5.1-3: Flow Chart for Protocol IM101332 – Open Label Treatment Period											
Procedure	**OL-1 (Same day as final day in the Double Blind Period)**	**OL -15**	**OL -29**	**OL -57**	**OL -85**	**Day 113 - Phone Call**	**OL -141**	**Day 169 - Phone Call**	**OL -197**	**Early Termination**	**Notes**
Call IVRS	X								X	X	
Safety Assessments											
Targeted Physical Examination		X	X	X	X		X		X	X	
Weight									X	X	
Vital Signs		X	X	X	X		X		X	X	Seated blood pressure/heart rate/temperature
Adverse Events Assessment		X	X	X	X	X	X	X	X	X	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests											
Hematology		X	X	X	X		X		X	X	CBC with differential, platelets
Chemistry panel		X	X	X	X		X		X	X	
Fasting lipid panel									X	X	Subject should be fasting at least 8 hours.

Table 5.1-3: Flow Chart for Protocol IM101332 – Open Label Treatment Period											
Procedure	**OL-1 (Same day as final day in the Double Blind Period)**	**OL -15**	**OL -29**	**OL -57**	**OL -85**	**Day 113 - Phone Call**	**OL -141**	**Day 169 - Phone Call**	**OL -197**	**Early Termination**	**Notes**
Urine /serum pregnancy test			X	X	X	X	X	X	X	X	WOCBP only, results confirmed prior to administration of study drug, Pregnancy testing is required every 4 weeks. The subject will be provided with urine pregnancy kits to be used at Day 113 and Day 169 at home.
[redacted]				[redacted]					[redacted]	[redacted]	
[redacted]				[redacted]					[redacted]	[redacted]	
Highly sensitive (hs) CRP		X	X	X	X		X		X	X	
Efficacy Assessments											
Tender Joint Count (68)		X	X	X	X		X		X	X	
Swollen Join Count (66)		X	X	X	X		X		X	X	
X-rays of hand and feet				X					X	X	Only subjects who have entered the open label after early escape will have a Day 57 X-ray performed. The allowed window for performance of the X-rays is ± 14 days.

Table 5.1-3: Flow Chart for Protocol IM101332 – Open Label Treatment Period											
Procedure	**OL-1 (Same day as final day in the Double Blind Period)**	**OL -15**	**OL -29**	**OL -57**	**OL -85**	**Day 113 - Phone Call**	**OL -141**	**Day 169 - Phone Call**	**OL -197**	**Early Termination**	**Notes**
Subject's Assessment of Physical Function (HAQ)		X	X	X	X		X		X	X	

Table 5.1-3: Flow Chart for Protocol IM101332 – Open Label Treatment Period

Procedure	OL-1 (Same day as final day in the Double Blind Period)	OL -15	OL -29	OL -57	OL -85	Day 113 - Phone Call	OL -141	Day 169 - Phone Call	OL -197	Early Termination	Notes
Physician's Global Assessment of Disease Activity VAS		X	X	X	X		X		X	X	Physicians should only consider arthritis disease activity when performing this assessment.
Subject Global Assessment of Disease Activity VAS		X	X	X	X		X		X	X	Subjects must be instructed to only consider arthritis disease activity when performing this assessment.
Subject Global Assessment of Pain VAS		X	X	X	X		X		X	X	
Target Lesion Score		X	X	X	X		X		X	X	
PASI		X	X	X	X		X		X	X	Subjects should not apply emollients to their skin on the day of their study visit until after their visit has been completed.
SF 36					X				X	X	
[redacted]					[redacted]				[redacted]	[redacted]	
[redacted]					[redacted]				[redacted]	[redacted]	
[redacted]					[redacted]				[redacted]	[redacted]	

Table 5.1-3: Flow Chart for Protocol IM101332 – Open Label Treatment Period											
Procedure	**OL-1 (Same day as final day in the Double Blind Period)**	**OL -15**	**OL -29**	**OL -57**	**OL -85**	**Day 113 - Phone Call**	**OL -141**	**Day 169 - Phone Call**	**OL -197**	**Early Termination**	**Notes**
[redacted]					[redacted]				[redacted]	[redacted]	
[redacted]					[redacted]				[redacted]	[redacted]	
[redacted]					[redacted]				[redacted]	[redacted]	
Physician Global Assessment of Psoriasis Activity and Arthritis Disease					X				X	X	
Subject Global Assessment of Psoriasis and Arthritis Disease Activity					X				X	X	
Study Drug Administration											
Dispense diary cards	X		X	X	X		X				
Dispense urine pregnancy kits for WOCBP for home use at Day 113 and Day 169					X		X				
Collect diary cards			X	X	X		X		X	X	

Table 5.1-3: Flow Chart for Protocol IM101332 – Open Label Treatment Period											
Procedure	**OL-1 (Same day as final day in the Double Blind Period)**	**OL -15**	**OL -29**	**OL -57**	**OL -85**	**Day 113 - Phone Call**	**OL -141**	**Day 169 - Phone Call**	**OL -197**	**Early Termination**	**Notes**
Dosing Injectable Study Medication	X	X	X	X	X[1]	X	X[1]	X	X[2]		Confirm the subject is giving the SC injections and recording the information on their diary cards. [1] One urine pregnancy kit and an 8 week supply of prefilled syringes will be dispensed to the subjects at this office visit along with two diary cards to capture injections. [2] If a subject continues into the long term extension, two pregnancy kits and a 12-week supply of pre-filled syringes will be dispensed to the subjects at this office visits along with a diary card to capture injections.

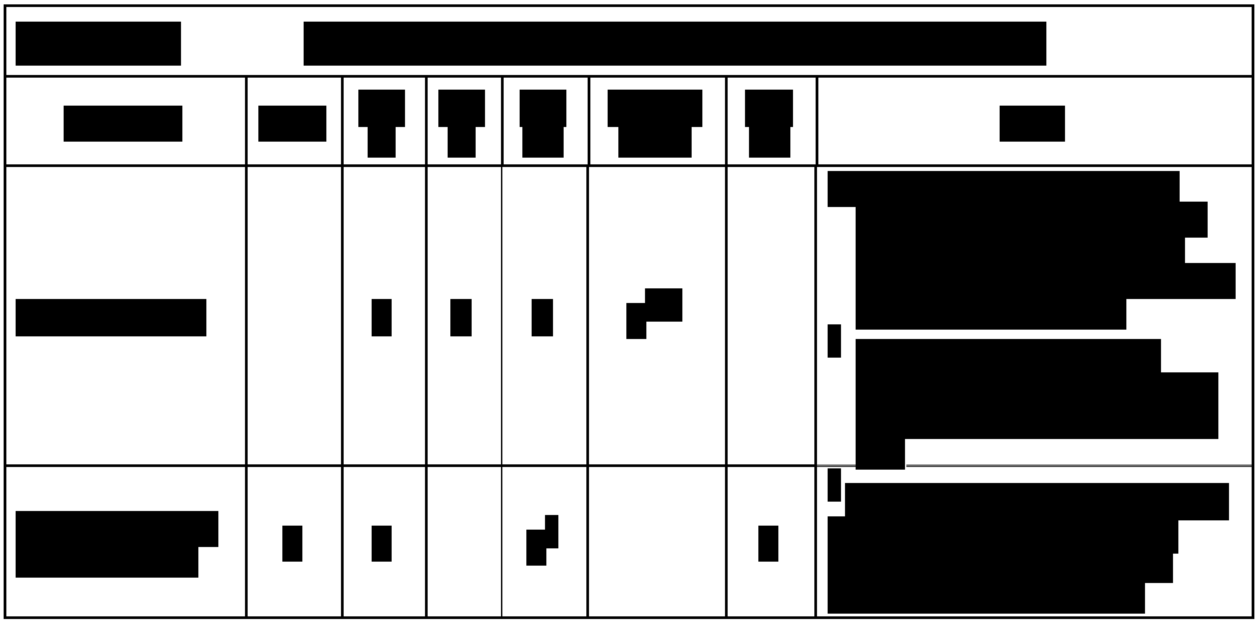
Table 5.1-4: Flow Chart for Protocol IM101332 – Long Term Extension

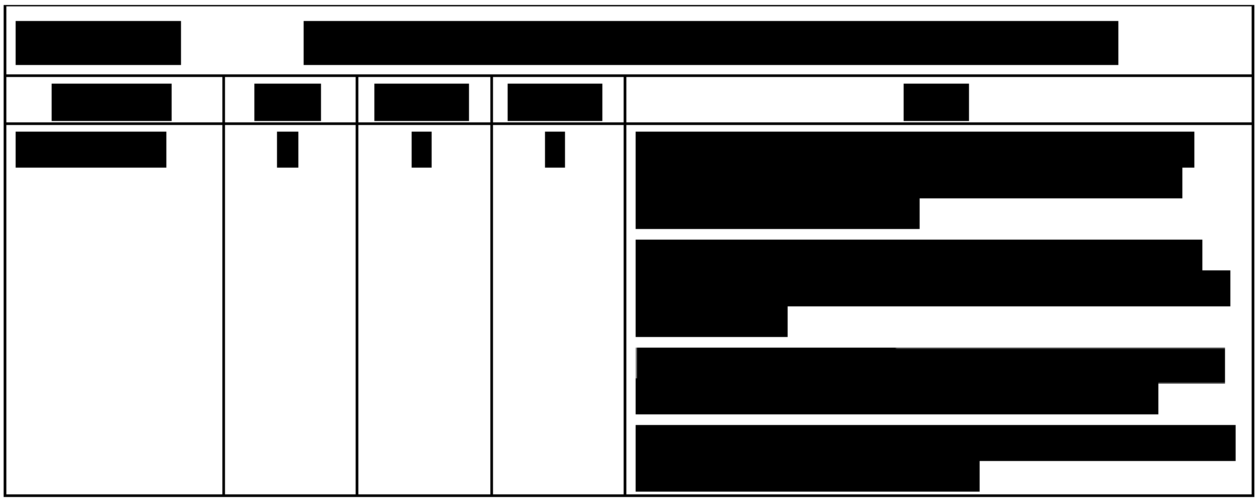
Procedure	Phone Call OL-225	Phone Call OL-253	OL-281 (± 7 days)	Phone Call OL-309	Phone Call OL-337	OL-365 (± 7 days)	Phone Call OL-393	Phone Call OL-421	OL-449 (± 7 days)	Phone Call OL-477	Phone Call OL-505	Phone Call OL-533	OL-561 (± 7 days)	Early Termination	Notes
Targeted Physical Examination			X			X			X				X	X	
Vital Signs			X			X			X				X	X	
Adverse Events Assessment			X			X			X				X	X	
[redacted]			[redacted]			[redacted]			[redacted]				[redacted]	[redacted]	
Hematology			X			X			X				X	X	
Chemistry panel			X			X			X				X	X	
Urine /serum pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense diary cards and home use urine pregnancy kits for WOCBP			X			X			X						
Collect diary cards			X			X			X				X	X	

Table 5.1-4: Flow Chart for Protocol IM101332 – Long Term Extension															
Procedure	**Phone Call OL-225**	**Phone Call OL-253**	**OL-281 (± 7 days)**	**Phone Call OL-309**	**Phone Call OL-337**	**OL-365 (± 7 days)**	**Phone Call OL-393**	**Phone Call OL-421**	**OL-449 (± 7 days)**	**Phone Call OL-477**	**Phone Call OL-505**	**Phone Call OL-533**	**OL-561 (± 7 days)**	**Early Termination**	**Notes**
Dosing Injectable Study Med	X	X	X[1]	X	X	X[1]	X	X	X[1]	X	X	X	X		Confirm the subject is administering the SC injections weekly and recording the information on the diary cards. [1]- A 12-week supply of pre-filled syringes will be dispensed to the subjects at the first three quarterly office visits along with a diary card to capture injection date, time and location and results of pregnancy testing for WCBP subjects. At the

Table 5.1-4: Flow Chart for Protocol IM101332 – Long Term Extension															
Procedure	**Phone Call OL-225**	**Phone Call OL-253**	**OL-281 (± 7 days)**	**Phone Call OL-309**	**Phone Call OL-337**	**OL-365 (± 7 days)**	**Phone Call OL-393**	**Phone Call OL-421**	**OL-449 (± 7 days)**	**Phone Call OL-477**	**Phone Call OL-505**	**Phone Call OL-533**	**OL-561 (± 7 days)**	**Early Termination**	**Notes**
															beginning of the fourth quarter of the year, a 16-week supply of prefilled syringes will be dispensed to the subject.

Table 5.1-5: Flow Chart for Protocol IM101332 - Follow-up Visits (FUV)				
Procedure	**28 days after last dose**	**84 days after last dose**	**168 days after last dose**	**Notes**
Safety Assessments				
Vital Signs	X	X	X	Seated blood pressure, heart rate, temperature
Adverse Events Assessment	X	X	X	
[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Assessments				
Urine/serum pregnancy test (WOCBP only)	X	X		
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	





5.2 Study Materials

- Diary cards
- eCRF instructions
- Serious Adverse Event pages
- Pregnancy Surveillance Forms
- Source documents for the Joint Count Assessments
- Source documents for the Enthesitis Index
- Source documents for the Dactylitis Index
- Source documents for the Outcomes Research questionnaires
- Drug Inventory binder
- Interactive Voice Response System (IVRS) worksheets
- Laboratory test kits for all required laboratory testing
- Cooler bags and gel packs will be provided to assist subjects in transporting study drug
- Sharps containers will be provided to assist subjects in disposing of used SC syringes
- Dactylometer
- A 10 cm ruler for measurement of Visual Analog Scale Source Document
- For WOCBP pregnancy kits will be provided to be used monthly by subjects during the open label and long term extension periods.

5.3 Safety Assessments

On Day 1, the results of all assessments must be reviewed to assure that eligibility requirements are met before contacting the Central Randomization System for the subject's randomization assignment.

Subjects who terminate early from the double blind treatment period, the open label period or the long term extension should complete the appropriate Early Termination Visit and the Post Drug Follow-up Visits. The Early Termination Visit should be as soon as possible after the last dose of study medication.

All assessments should be performed or administered prior to study drug administration unless otherwise indicated.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from BMS.

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handling by the Study Investigator as per standard medical/clinical judgment.

Plain radiographs of the hands and feet will be taken at baseline (Day 1, -3 days), Day 169 (± 14 days) [and Day 113 (+14 days) and Open Label Day 57 (± 14 days) for subjects who qualify for the Early Escape], and Day 365 (Open Label 197) (± 14 days). Subjects who terminate the study early in the double-blind period or open label period will have radiographs taken at the Early Termination visit.

Radiographs of the hands and feet may be taken after dosing on Day 1 as long as they are performed on Day 1.

Radiography of the hands and feet will be standardized to ensure sufficient image quality for the evaluation of radiographic progression. Radiology facilities and personnel will be qualified for participation in the study based on the technical capabilities of the equipment and experience and the licensing of the x-ray technologists. Radiographic technique will be harmonized through the use of written radiographic procedure manual and training of x-ray technologists. In addition the film-screen system will be standardized to ensure sufficient resolution for the evaluation of erosions and joint space narrowing.

Radiographs collected for the study will be sent to a central reading facility for quality control and central evaluation (in a blinded manner) by a radiologist trained and experienced in the scoring of PsA by the Sharp-van der Heijde Modified Scoring Method (SHS) for psoriatic arthritis.[41,42]

Details of the standardization and evaluation of the radiographs will be covered in a separate Charter for the independent review of radiographs.

5.3.2 Physical Examination

Complete and/or targeted (brief) physical examinations may be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician's Assistant (PA), or Nurse Practitioner (NP).

While the brief interim physical exam may not be as comprehensive as the initial full examination, key aspects of the brief interim examination should evaluate important body systems as clinically indicated. The brief physical examination should include examination of the heart, lungs and abdomen, and may include other relevant body systems such as the lymph nodes, liver, spleen and breasts, at the discretion of the examiner. A brief interim physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

5.3.3 Chest X-ray

A posterior-anterior and lateral chest x-ray, performed during screening, is required for all subjects unless performed within 6 months prior to obtaining written informed consent and documentation of the earlier x-ray is on file. All subjects must have a chest x-ray that does not show any cardiac or pulmonary disease in order to be eligible for this study. The chest x-ray result will be recorded on the appropriate page of the eCRF.

5.3.4 Physical Measurements

Weight and height is to be recorded at screening. Weight is to be recorded at the beginning and end of the double-blind and open label periods.

5.3.5 Vital Signs

Vital signs (seated blood pressure, heart rate, and temperature) will be recorded during the screening visit, during every visit, and at study discharge or as soon as possible after the last dose for subjects who terminate early, and at the post study drug follow-up visits. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.

5.3.6 TB Screening

A chest x-ray and physical examination are considered part of the process to assess a subject's eligibility. In addition to a chest x-ray that does not show any cardiac or pulmonary disease and no suspicion of latent TB, a tuberculin skin test will be performed and interpreted according to local country Health Authorities and/or Medical Society guidelines. Some guidelines have specific recommendations for subjects who are to receive biologics or immunosuppressant therapies (eg, RA experience with biologic agents),[43,44,45] or who are immunocompromised and who have had prior BCG vaccination(s).[46,47] Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG. An interferon gamma release assay (e.g., QuantiFERON® Gold or Tspot/ELISpot) is an acceptable alternative when skin testing for tuberculosis (i.e., PPD) is not appropriate.

5.3.7 Laboratory Assessments

All laboratory assessments will be analyzed centrally with exception of the pregnancy testing.

Blood and/or urine samples will be obtained at all visits noted in Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, and Table 5.1-7 from each subject entered in this study. Any laboratory test result that the investigator considers clinically relevant should be recorded on the appropriate Adverse Event page of the CRF (see Appendix 5)

5.3.7.1 Hematology

- Hemoglobin
- Hematocrit
- Total WBC count, including differential
- Platelet count

5.3.7.2 Blood Chemistry

- Sodium
- Potassium
- Chloride
- Total Protein
- Albumin
- Calcium
- Phosphorus
- Glucose

Creatinine
Blood urea nitrogen (BUN)
Total bilirubin
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyltransferase (GGT)
Alkaline phosphatase

5.3.7.3 Fasting Lipid Panel

Total cholesterol

LDL cholesterol

HDL cholesterol

VLDL cholterol

Triglyceride

NOTE: A subject should be fasting at least 8 hours.

5.3.7.4 Urinalysis (screening visit only)

- pH
- Protein
- Glucose
- Blood

Microscopic examination of the urine sediment is required if blood, protein or glucose is positive on the dipstick.

5.3.7.5 Hepatitis Screen (performed at Screening Visit Only)

The Laboratory result must be available prior to dosing.

- Hepatitis B surface antigen, hepatitis B core antibody -- If positive reflex HBV DNA testing must be performed.
- Hepatitis C antibody. If positive, reflex HCV RNA testing must be performed

5.3.7.6 Pregnancy Tests

Urine/serum pregnancy tests (minimum sensitivity 25 IU/L of β-HCG) must be performed for all WOCBP within 24 hours prior to dosing for visits specified in Tables Table 5.1-1, Table 5.1-2 and Table 5.1-3. If any female subject becomes pregnant, she will be discharged from the study. A pregnancy surveillance form will be completed and submitted to Bristol-Myers Squibb. Serum pregnancy tests will be processed locally.

5.3.7.7 HIV Testing

HIV testing will be performed in countries where the testing is required in screening.

5.4 Efficacy Assessments

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the subject's medical record and should not be provided to BMS, unless specifically requested from BMS.

5.4.1 Primary Efficacy Assessment

The primary efficacy assessment will be the proportion of subjects meeting the ACR criteria for improvement (ACR20) at Day 169.

5.4.2 Secondary Efficacy Assessments

Key Secondary efficacy assessments comprise:

- HAQ responders at Day 169

- ACR20 responders at Day 169 in the TNFi-naïve sub population
- ACR20 responders at Day 169 in the TNF-exposed sub population
- Radiographic non-progressor rates from baseline (Day 1), as described by the total PsA-modified SHS, at Day 169

Other Secondary efficacy assessments comprise:

- PASI50 at Day 169
- ACR50 and ACR70 at Day 169
- Change in SF-36 from baseline to Day 169

5.4.4 Clinical Assessments

Every effort must be made to ensure the same assessor will complete the assessment for each subject at all visits at approximately the same time throughout the study. Visits should be scheduled with the availability of the evaluator(s) taken into account. If the assessor is unable to complete the evaluation, then another qualified individual can take the place of the initial evaluator, but the substitute evaluator should have examined and reviewed the subject with the initial evaluator in order to assure overlapping experience (consistency between subject evaluations). Documentation of who performed the evaluation is to be recorded in source notes.

To be an eligible Joint Assessor, individuals must receive the standardized joint count training provided by BMS or be trained by an individual who did receive the standardized training (documentation filed in the Investigator File and the BMS Study File). Such individuals should have appropriate medical credentials and/or should be individuals with appropriate scientific/medical background who are experienced in performing joint assessments for the BMS Phase 3 RA studies. If the individual does not have medical credentials, documentation of their experience (preferably on a curriculum vitae) must be provided to the BMS site manager, and their eligibility as joint assessor must be confirmed by the BMS medical monitor before the individual's participation in the study as joint assessor.

The Joint Assessor may also perform the enthesitis and dactylitis, as well as assess the Target Lesion and conduct the PASI scoring. Training in these assessments will be provided by BMS and required in order to perform this function.

Additionally a clinical assessor will complete the Physician Global Assessment of Disease Activity (VAS) (Appendix 13), the Physician Global Assessment of Nail Disease Activity (Nail VAS) (Appendix 14) and the Physician Global Assessment of Psoriasis and Arthritis Disease Activity (Appendix 19). These assessments will be source documents in this study. **Assessors should only consider arthritis activity when completing the Physician Global Assessment of Disease Activity VAS.**

Subjects should be instructed not to apply emollients to their skin on the day their study visit until after their visit is complete.

Subjects will complete the HAQ-DI, Subject Global Assessment of Disease Activity (VAS), Subject Global Assessment of Pain (VAS), Subject Global Assessment of Psoriasis and Arthritis Disease Activity, [redacted], SF-36, [redacted] (Appendices 6-12 and 19). These questionnaires will be considered source documents in this study. All subject reported outcomes must be performed prior to all other assessments, including phlebotomy, physical exam, joint and skin assessments. **Subjects must be instructed that the Subject Global Assessment of Disease Activity refers to arthritis activity only.**

Details on the quality of life assessments will be described in Section 5.7.

5.4.4.1 Psoriasis Area and Severity Index (PASI)

The Psoriasis Area and Severity Index (PASI) is a system used for the evaluation of the severity of psoriatic lesions and then response to treatment. The PASI produces a numeric score that can range from 0 to 72. The PASI uses a scoring system for the signs of disease (erythema, induration and scaling), as well as a scoring system for estimating the area of involvement for psoriatic lesions (Appendix 17).[48]

The PASI-50 is the proportion of subjects who experience at least 50% improvement of PASI score. The PASI-75 is the proportion of subjects who experience at least 75% improvement of PASI score. The score is based on the current evaluation.

Subjects must have ≥ 3% body surface area (BSA) of psoriatic skin involvement at randomization in order for the PASI assessment to be valid; however, the PASI should be performed at all clinic visits in all subjects in order to capture information of subjects with worsening skin disease. A 1% BSA includes the palm plus thumb/fingers (ie, a handprint).

5.4.4.2 Target Lesion Score (TLS)

This assessment captures changes in psoriasis over time by focusing on one "target" lesion. A lesion of plaque psoriasis of at least 2 cm in diameter that is an evaluable area is selected. The score is based on the rating of the skin erythema, induration, and scaling (rating 0-4 each).

5.4.5 Composite Scores

5.4.5.1 American College of Rheumatology Improvement Criteria (ACR20, ACR50, ACR70)

The ACR20, ACR50 or ACR70 definition of improvement is a 20%, 50% or 70% improvement, respectively, over baseline in tender and swollen joint counts (components #1 and #2) and a 20%, 50% or 70% improvement, respectively, in 3 of the 5 remaining core data set measures (components #3 to #7) (Appendix 15). [52]

5.4.5.2 Disease Activity Score 28 C-Reactive Protein (DAS28-CRP)

A composite measure that incorporates the number of tender and swollen joint (28 joint count), subject's global assessment of disease activity on a visual analog scale, and the C-reactive protein (CRP).[53] (Appendix 16)

DAS 28 = 0.56*sqrt(tender28) + 0.28*sqrt(swollen28) + 0.36*ln(CRP+1) + 0.014*GH + 0.96[54,55,56]

5.4.5.3 Psoriatic Arthritis Disease Activity Score (PASDAS)

A composite measure calculated from the Physician Global Assessment of Psoriasis and Arthritis Disease Activity Visual Analog Scale, the Subject Global Assessment of Psoriasis and Arthritis Disease Activity Visual Analog Scale, the SF36 PCS, the swollen joint count, the tender joint count, the Leeds Enthesitis Index (ESI), the Leeds Dactylitis Index (LDI, Basic), and the hsCRP.[57]

5.4.5.4 Composite Psoriatic Disease Activity Index - Modified (CPDAI)

The Modified CPDAI is a composite index that assesses four (4) domains: peripheral joints, skin, enthesitis, and dactylitis. Each category will be graded as mild, moderate, or severe (0-3), giving an overall attainable score of 0-15. Peripheral joints will be assessed by tender (68) and swollen (66) joint count; skin by the PASI and Dermatology Life Quality Index (DLQI); enthesitis by the number of involved digits on the Leeds Enthesitis Index (LEI) [the Health Assessment Questionnaire (HAQ) is counted if enthesitis is present]; dactylitis by the number of involved digits on the Leeds Dactylitis Index- Basic (LDI - Basic) (the HAQ is counted if dactylitis is present);. [58] [59,60]

5.4.5.5 Minimal Disease Activity

A subject with PsA is classified as achieving MDA [60,61] when meeting 5 of the 7 following criteria:

- tender joint count ≤ 1
- swollen joint count ≤ 1
- PASI ≤ 1 or BSA ≤ 3%
- subject pain VAS ≤ 15

- subject global disease activity VAS ≤ 20
- HAQ ≤ 0.5
- tender entheseal points ≤ 1.

[redacted]

[redacted]

[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

5.7 Outcomes Research Assessments

Subjects will complete the SF-36, Physical Function (HAQ/HAQ-DI), [redacted]. These pages will be source documents in this study. All of these patient reported outcomes must be performed prior to all other assessments, including phlebotomy, physical exam, joint and skin assessments.

5.7.1 Health Assessment Questionnaire Disability Index (HAQ/HAQ-DI)

Scoring conventions are based on the Standard Disability Index of HAQ/HAQ-DI, (Appendix 6) using the 20 response items. The HAQ-DI takes into account the subject's use of aids, devices, or assistance in the scoring algorithm for a disability category. For each of the 8 disability categories there is an "aids/devices" companion variable that is used to record the type of assistance, if any, a subject uses for his/her usual activities. If either "aids/devices" and/or "assistance from another person" are checked for a disability category, the score for this category is set to "2" (much difficulty), if the original score was "0" (no difficulty) or "1" (some difficulty). The HAQ-DI is then calculated by summing the adjusted categories scores and dividing by the number of categories answered. [redacted]

The HAQ is based on a scale of 0-3.

[redacted]

5.7.3 Short Form 36 (SF-36)/Health-Related Quality of Life

The Short Form 36 (SF-36), Version 2.0 (Appendix 10), which covers 8 health dimensions within 2 components, will be used to measure health-related quality of life.[65,66,67] The SF-36 is a subject questionnaire assessing 8 domains of health status: physical functioning, pain, vitality, social functioning, psychological functioning, general health perception, and role limitations due to physical and emotional problems. The instrument can be divided into two summary scores, physical and mental component score.

This tool has been validated for use in RA subjects.[68] It has been recommended by the Food and Drug Administration for measuring broader effects of treatment on health-related quality of life in RA clinical studies.[69]

The physical component summary (PCS) of the SF-36 consists of these 4 subscales:

- physical functioning
- role-physical
- bodily pain
- general health.

The mental component summary (MCS) of the SF-36 consists of these 4 subscales:

- vitality
- social functioning
- role-emotional
- mental health

The 8 subscales will be scored using norm-based methods that have standardized the scores to a mean of 50 and a standard deviation of 10 in the general population. The scores range from 0 to 100, with a higher score indicating better quality of life. The two summary scores (PCS and MCS) will be calculated by taking a weighted linear combination of the 8 individual subscales.

[redacted]

[redacted]

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory

finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 6 months of discontinuation of dosing. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

[redacted]

[redacted]

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted

immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

[redacted]

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1) Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.2.2 Nonserious Adverse Events Related to Study Condition

All SAEs of psoriatic arthritis or plaque psoriasis exacerbation must be reported according to SAE guidelines in Section 6.1.

Do not report non-serious adverse events of psoriatic arthritis or plaque psoriasis exacerbation as a non-serious adverse event.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted

- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important.

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not Applicable

8 STATISTICAL CONSIDERATIONS

[redacted]

8.2 Populations for Analyses

The following analysis populations are defined:

- Intent-to-treat (ITT) analysis population: all randomized subjects who receive at least one dose of study medication. Subjects will be grouped according to the treatment group to which they are randomized.
- Per-protocol (PP) analysis population: all randomized subjects who receive at least one dose of study medication. Subjects will be grouped according to the treatment group to which they are randomized. Subjects with relevant protocol deviations (to be defined in the statistical analysis plan) will be excluded.
- As-treated analysis population: all randomized subjects who receive at least one dose of study medication. Subjects will be grouped on an as-randomized basis unless the subject received the incorrect medication for the entire period of treatment. In that case, the subject will be analyzed in the treatment group associated with the incorrect medication they received.
- Immunogenicity analysis population: all subjects who receive at least one dose of study medication and who had at least 1 immunogenicity result reported after start of study medication.

8.3 Endpoints

8.3.1 Primary endpoint

- Proportion of ACR20 responders at Day 169

8.3.2 Secondary endpoints

8.3.2.1 Key secondary endpoints

- Proportion of HAQ responders (a reduction of at least 0.35 from baseline) at Day 169
- Proportion of ACR20 responders at Day 169 in the TNFi naive subpopulation
- Proportion of ACR20 responders at Day 169 in the TNFi exposed subpopulation
- Proportion of non-progressors in total PsA-modified SHS (defined as a change from baseline in total PsA-modified SHS ≤ 0) at Day 169

8.3.2.2 Other secondary endpoints

- Proportion of subjects achieving a PASI50 (achieving at least 50% improvement from baseline in PASI) at Day 169 in subjects with baseline BSA $\geq 3\%$
- Proportion of ACR50 responders at Day 169
- Proportion of ACR70 responders at Day 169
- Mean change from baseline in physical (PCS) and mental functions (MCS) of SF-36 at Day 169
- Proportion of subjects with at least one positive immunogenicity response up to Day 169
- Safety (proportion of subjects with adverse events, deaths, SAEs, and AEs leading to discontinuation and proportion of laboratory marked abnormalities) up to Day 169

[redacted]

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Summary statistics of all demographic variables and baseline characteristics will be generated by treatment group using the intent-to-treat (ITT) analysis population. Baseline assessments are the last evaluations made prior to the start of study drug.

8.4.2 Efficacy Analyses

All efficacy analyses will be for the intent-to-treat (ITT) analysis population, except if stated otherwise. In general, no formal statistical testing will take place except for the primary, the key secondary efficacy endpoints (including the ACR20 responders in the two TNFi subgroups) and the proportion of subjects achieving PASI50 at Day 169.

8.4.2.1 ACR20

Primary analysis at Day 169

The primary efficacy analysis regarding the comparison between abatacept and placebo in the proportion of ACR20 responders at Day 169 will be performed with a 2-sided Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by prior TNFi use (Yes, No), MTX use (Yes, No) and BSA (< 3%, ≥ 3%) at a 5% significance level. The Chi square p-value and the relative risk along with its 95% confidence interval will be provided at Day 169. In addition, the absolute treatment difference will be provided along with its 95% two-sided confidence interval based on the stratum-specific sample size weighting method [73] at all timepoints up to Day 169.

All subjects who prematurely discontinue the study after receiving study medication will have missing data imputed as ACR20 non-responder at all scheduled protocol visits subsequent to the point of discontinuation. Rescue medication and early escape after Day 113 as described in sections 3.1.2 and 3.1.3 will be allowed. After receiving this rescue medication, the as-observed ACR20 response will be used in the ACR20 analysis up to Day 169; however, for subjects switching to open label abatacept in the early escape period, the subjects will be imputed as non-responders for the ACR20 responder analyses up to Day 169. The primary analysis will be done for the intent-to-treat (ITT) analysis population.

Sensitivity Analysis at Day 169

The following sensitivity analyses for the primary analysis of ACR20 response at Day 169 will be performed:

- analysis applying the per-protocol analysis population.
- To investigate if imbalances in demography characteristics and/or baseline characteristics do not have an impact on the primary result, a logistic regression including treatment, prior TNFi use, MTX use, BSA, demographic variables (age, gender, and weight) and baseline variables (duration of disease, tender joints, swollen joint, HAQ DI, pain, subject global assessment of disease activity, physician global assessment of disease activity, CRP and current oral corticosteroid use) will be performed.

Subgroup Analysis by TNFi use

The efficacy analysis regarding the comparison between abatacept and placebo in the proportion of ACR20 responders at Day 169 in the prior TNFi users subgroup and in the TNFi naive subgroup separately will be with a 2-sided Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by MTX use and BSA at a 5% significance level. The Chi-square p-value and the

relative risk along with its 95% confidence interval will be provided for both subgroups at 24 weeks. In addition, the absolute treatment difference will be provided along with its 95% two-sided confidence interval based on the stratum-specific sample size weighting method[73] for both subgroups at 24 weeks. The handling of missing data, rescue medication, and early escape will be performed in same way as done for ACR20 responders for the full population.

[redacted]

8.4.2.2 HAQ

Primary analysis of HAQ responders at Day 169

The efficacy analysis regarding the comparison between abatacept and placebo in the proportion of HAQ responders at Day 169 will be performed with a 2-sided Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by prior TNFi use, MTX use and BSA at a 5% significance level. The Chi-square p-value and the relative risk along with its 95% confidence interval will be provided at Day 169. In addition, the absolute treatment difference will be provided along with its 95% two-sided confidence interval based on the stratum-specific sample weighting method [73] at all timepoints up to 24 weeks. The handling of missing data, rescue medication and early escape will be performed in same way as done for ACR20 responders.

[redacted]

[redacted]

8.4.2.3 PsA-Modified Total Sharp/van der Heijde Score (SHS)

Primary analysis of non-progressors using total PsA-modified total Sharp/van der Heijde score (SHS)

The efficacy analysis regarding the comparison between abatacept and placebo in the proportion of non-progressors using total PsA-modified total Sharp/van der Heijde score (SHS) at Day 169 will be performed with a 2-sided Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by prior anti-TNF use, MTX use and BSA at a 5% significance level. The Chi square p-value and the relative risk along with its 95% confidence interval will be provided at Day 169. In addition, the absolute treatment difference will be provided along with its 95% two-sided confidence interval based on the stratum-specific sample weighting method at Day 169.

All subjects who prematurely discontinue the study after receiving study medication and prior to Day 169 window (± 8 weeks from the scheduled Day 169 visit) will have missing data imputed as progressors at Day 169. Rescue medication and early escape on Day 113 as described in sections 3.1.2 and 3.1.3 will be allowed. After receiving this rescue medication the as-observed x-ray data will be used in the x-ray analyses at Day 169, however, for subjects switching to open label abatacept in the early escape period, the subjects will be imputed as progressor at Day 169.

Sensitivity analyses at Day 169

The following sensitivity analyses are planned:

- The non-progressor analysis at Day 169 will be repeated, but the observed data at Day 169 after switching to open label abatacept in the early escape period will be used instead of treating these subjects as progressors.
- The non-progressor analysis at Day 169 will be repeated, but a non-progressor will be defined as a change from baseline in total PsA-modified SHS ≤ SDC (smallest detectable change).
- The non-progressor analysis at Day 169 will be repeated, but a non-progressor will be defined as a change from baseline in total PsA modified SHS ≤ 0.5.

[redacted]

[redacted]

8.4.2.4 PASI50

Primary analysis at Day 169

The efficacy analysis regarding the comparison between abatacept and placebo in the proportion of subjects achieving a PASI50 (achieving at least 50% improvement from baseline in PASI) at Day 169 in subjects with baseline BSA ≥ 3% will be performed with a 2-sided Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by prior TNFi use, and MTX use at a 5% significance level. The Chi square p-value and the relative risk along with its 95% confidence interval will be provided at Day 169. In addition, the absolute treatment difference will be provided along with its 95% two-sided confidence interval based on the stratum-specific sample weighting method[73] at Day 169. The handling of missing data, rescue medication and escape will be performed in same way as done for ACR20 responders.

[redacted]

8.4.2.5 ACR50 and ACR70

The proportion of subjects with an ACR50, and ACR70 response at the different timepoints up to Day 169 will be summarized per treatment group using point estimates and 95% confidence intervals. Differences in ACR50, and in ACR70 response rates at the different timepoints will be summarized using point estimates and 95% confidence intervals based on the stratum-specific sample weighting method.[73] A stratification by prior TNFi use, MTX use and BSA will be applied.

[redacted]

The handling of missing data, rescue medication, and escape will be performed in same way as done for ACR20 responders. All these analyses will be done for the intent-to-treat (ITT) analysis population (all subjects randomized and treated in the study will be included in the analyses).

In general, no p-values will be provided for ACR50 and ACR70 at any of the timepoints.

[redacted]

8.4.2.7 Statistical Testing Procedure

If the 2-sided test for the primary endpoint (proportion of ACR20 responders at Day 169) is statistically significant at alpha = 5%, then a hierarchical approach for statistical testing will be used for the secondary endpoints. This procedure allows for preserving of the overall Type I error rate of 0.05 for the study. Hierarchical ordering of the secondary endpoints is as follows:

- Proportion of HAQ responders at Day 169
- Proportion of ACR20 responders at Day 169 in the TNFi naive subpopulation
- Proportion of ACR20 responders at Day 169 in the TNFi exposed subpopulation
- Proportion of non-progressors in total PsA-modified SHS (defined as a change from baseline in total PsA-modified SHS ≤ 0) at Day 169

P-values will be presented for each of these endpoints. However, no claim will be based on endpoints that have a rank lower than that endpoint whose null hypothesis was the first that could not be rejected. That is, no claim will be based on endpoints that have a rank lower than that endpoint whose test was the first to be non-statistically significant. A clear distinction will be made between p-values whereby claims can and cannot be made.

8.4.3 Safety Analyses

The evaluation of drug safety is primarily based on clinical adverse events and laboratory abnormalities reported during the study.

Frequency distributions and listings of all adverse events, deaths, serious adverse events, adverse events leading to discontinuation and adverse events of special interests will be generated. Adverse Events of Special Interest are infections, malignancies, autoimmune disorders, and injection site reactions.

Laboratory marked abnormalities, using pre-defined abnormality criteria, will also be descriptively summarized. There will be no statistical testing of treatment group differences with respect to the frequency of adverse events or laboratory marked abnormalities.

The following safety analysis time points will be defined:

- Safety from start of study up to Day 169. This analysis will be on the as-treated analysis population. The summaries will be presented by treatment group.

[redacted]

[redacted]

8.4.6 Outcomes Research Analyses

The changes from baseline in SF-36 PCS and MCS scores will be analyzed using a longitudinal repeated measures analysis on the OC dataset. The model will include the fixed categorical effects of treatment, week, prior TNFi use, MTX use, BSA, week-by treatment interaction, prior TNFi-use-by-week interaction, MTX use-by-week interaction, BSA-by-week interaction as well as the continuous fixed covariate of baseline SF36 score and baseline SF36-by-week interaction. An unstructured covariance matrix will be used to represent the correlation of the repeated measures within each subject. Treatment estimates and associated standard errors will be presented as well as treatment differences with 95% confidence intervals (treatment differences only for timepoints up to Day 169). No p-value will be provided.

For the analysis at Day 169 all timepoints up to Day 169 will be included, [redacted]

[redacted]

8.5 Interim Analyses

No interim analyses are planned.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion

- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as the source documents:

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Early Escape	At Week 16 (Day 113) any subject who has not achieved at least a 20% improvement in the tender joint count and the swollen joint count (both must improve) compared to baseline will be designated an "Early Escape" and will receive open-label abatacept 125 mg SC. All Day 113 as well as early escape assessments will be performed at this time.
Rescue Therapy	Per the investigator's discretion, certain therapies are allowed to treat a flare of arthritis or psoriasis according the specified protocol once during the double-blind period and once during the open-label period.
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Inadequate Response to Non-Biologic Therapy	Prior treatment with MTX, leflunomide, or sulfsalazine at a therapeutic dose for at least 3 months (For MTX, therapeutic dose is define as at least 15 mg weekly.), that was discontinued for lack of efficacy or was associated with ongoing active disease.
Intolerance to Non-Biologic Therapy	Discontinuation or dose limitation of MTX, sulfasalazine, or leflunomide due to an adverse event.
Inadequate Response to TNFi Therapy	Prior treatment with a TNFi at an approved dose for at least 3 months, which was discontinued for lack of efficacy or was associated with ongoing active disease.
Intolerance to TNFi Therapy	Discontinuation or dose limitation of a TNFi due to an adverse event.

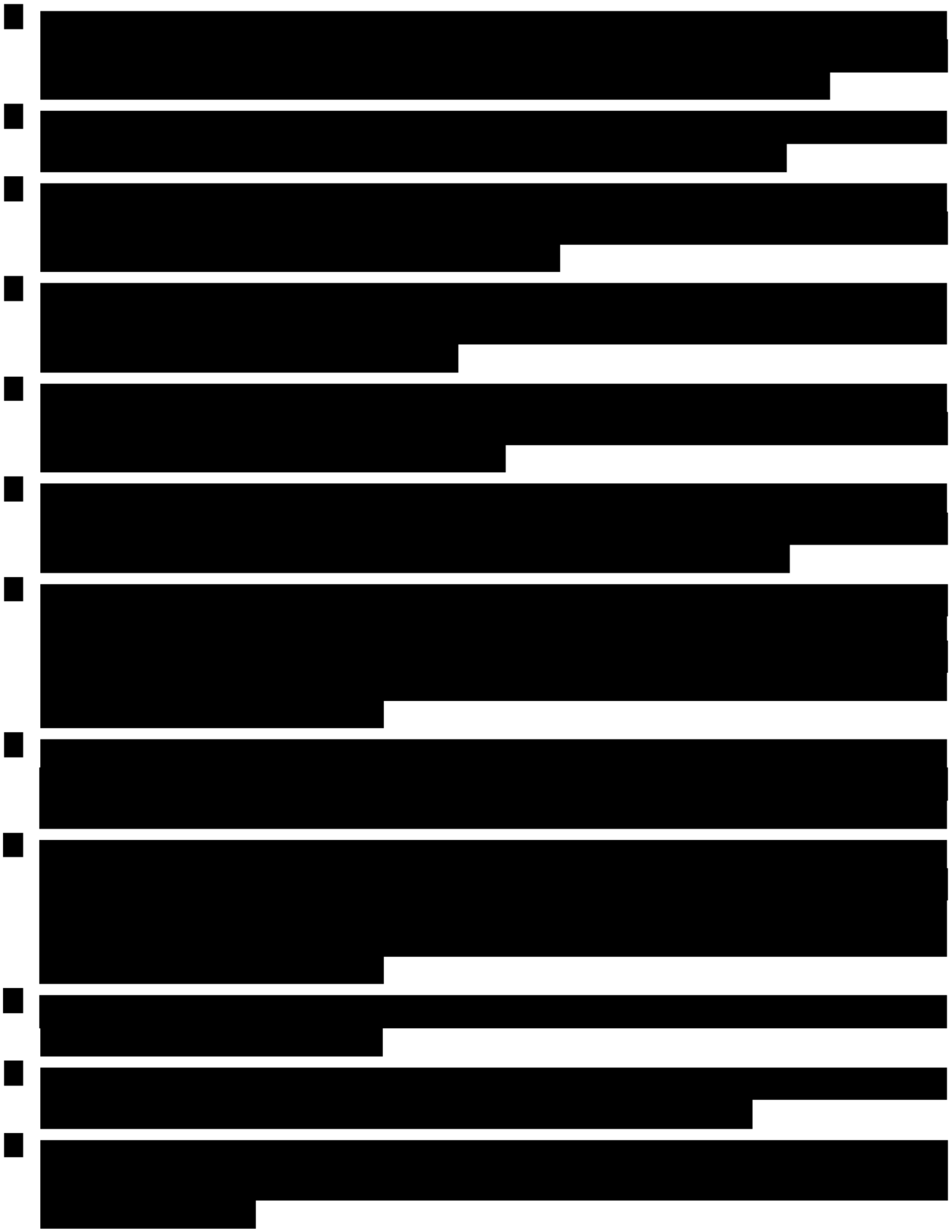
11 LIST OF ABBREVIATIONS

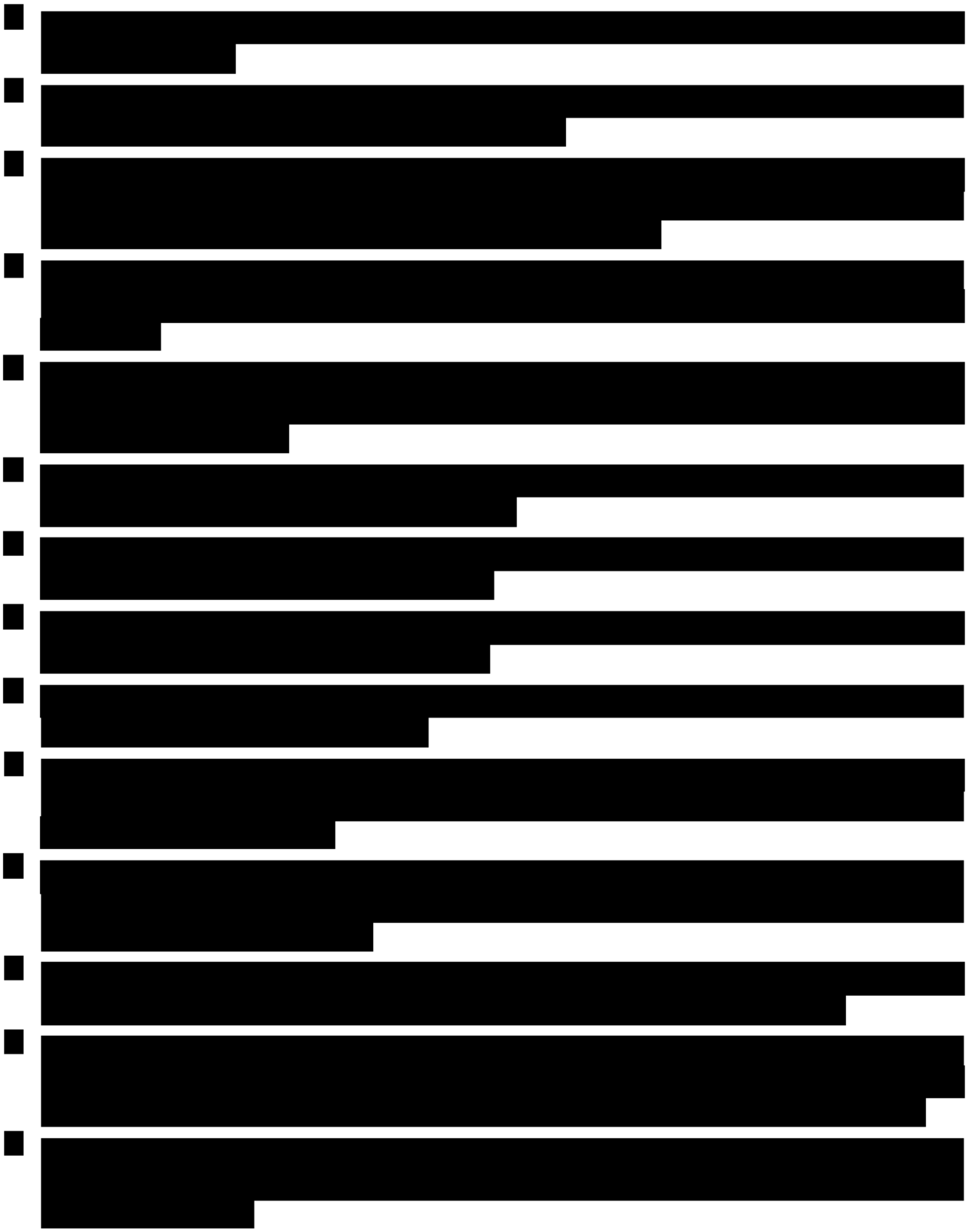
ABA	Abatacept
ACIP	Advisory Committee on Immunization Practices
ACR	American College of Rheumatology
ACR20	20% ACR response
ACR50	50% ACR response
ACR70	70% ACR response
AE	Adverse event
ALT	Alanine transferase
ANOVA	Analysis of variance
APC	Antigen presenting cells
AS	Ankylosing Spondylitis
AST	Aspartate aminotransferase
[redacted]	[redacted]
BMS	Bristol Myers Squibb
BSA	Body Surface Area
BUN	Blood urea nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CDC ACIP	Center for Disease Control Advisory Committee on Immunization Practices
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CPDAI	Composite Psoriatic Disease Activity Index
CRF	Case Report Form
CRP	C reactive protein
CTA	Clinical trial agreement
CV	Coefficient of Variation
DI	Disability Index
DILI	Drug Induced Liver Injury
DMARDs	Disease modifying anti-rheumatic drugs
DNA	Deoxyribonucleic Acid
DO	Doctor of Osteopathy
ECG	Electrocardiogram
ECL	Electrochemiluminescence
eCRF	Electronic Case Report Form
ESR	Erythrocyte sedimentation rate
EU	European Union
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	Folicle Stimulating Hormone

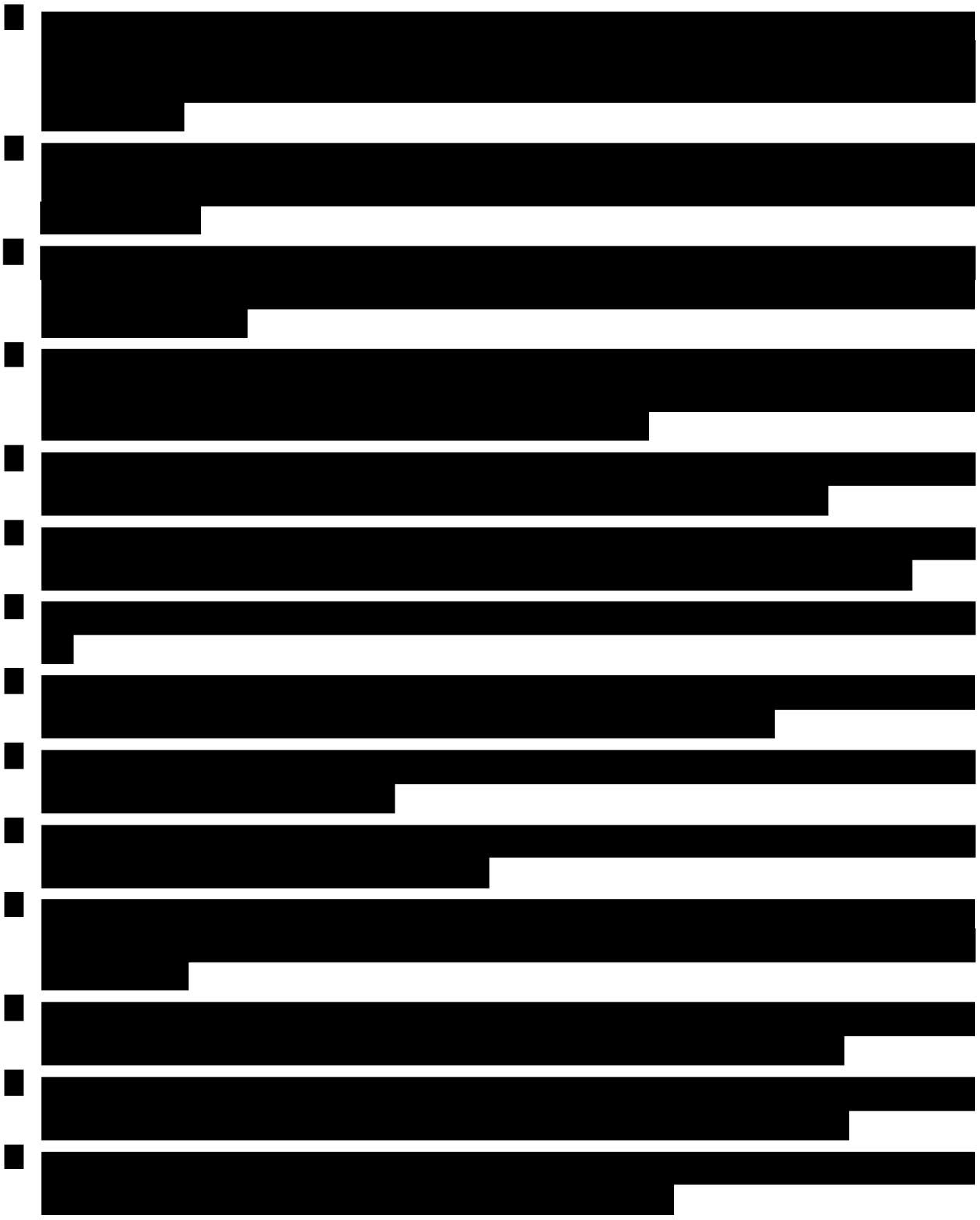
FUV	Follow-up Visit
GCP	Good Clinical Pratice
GGT	Gamma glutanyl transferase
HAQ	Health Assessment Questionnaire
HBV	Hepatitis B virus
HCG	Human chorionic gonadtropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
HGB	Hemoglobin
HRT	Hormone Replacement Therapy
IA	Intra-articular
ICH	International Conference on Harmonisation
INH	Isoniazid
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IM	Intramuscular
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive Voice Response System
[redacted]	[redacted]
LDL	Low density lipoproteins
MCS	Mental Component Score
MD	Medical Doctor
MDA	Minimal Disease Activity
MMF	Mycophenolae Mofetil
MMP	Matrix metalloproteinases
MS	Multiple Sclerosis
MTX	Methotrexate
[redacted]	[redacted]
NP	Nurse Practitioner
NSAID	Non-Steroidal Anti-Inflammatory Drug
PA	Physician's Assistant
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Score
PD	Pharmacodynamic
PK	Pharmacokinetics
PP	Per protocol
PPK	Population pharmacokinetics
PPD	Purified protein derivative skin test

PsA	Psoriatic arthritis
PUVA	Psoralen Plus Ultraviolet A
RA	Rheumatoid Arthritis
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SC	Subcutaneous
SDD	Smallest detectable difference
SF-36	Short Form 36
SHS	Sharp/van der Heidje Score
SLE	System Lupus Erythmatous
SNP	Single Nucleotide Polymorphisms
SJC	Swollen Joint Count
SOP	Standard operating procedure
TB	Tuberculosis
TL	Target Lesion
TLS	Target Lesion Score
TJC	Tender Joint Count
TNFi	Tumor necrosis factor-α inhibitors
UVB	Ultraviolet B
VAS	Visual Analog Scale
VLDL	Very low density lipoproteins
WBC	White Blood Count
WHO	Wood Health Organization
WOCBP	Women of Child Bearing Potential

[redacted]







APPENDIX 1 CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS (CASPAR) CRITERIA

CASPAR CRITERIA (Specificity 0.987, Sensitivity 0.914)	
Inflammatory articular disease (joint, spine or entheseal)	
With 3 or more point from the following	
1. Current psoriasis (scores 2 points)	*Psoriatic skin or scalp disease present today as judged by a rheumatologist*
2. Personal history of psoriasis (if current psoriasis not present)	*A history of psoriasis that may be obtained from patient, family doctor, dermatologist or rheumatologist*
3. Family history of psoriasis (if personal history of psoriasis or current psoriasis not present)	*A history of psoriasis in a first or second degree relative according to patient report*
4. Psoriatic nail dystrophy	*Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination*
5. A negative test for rheumatoid factor	*By any method except latex but preferably by ELISA or nephlemetry, according to the local laboratory reference range*
6. Current dactylitis	*Swelling of an entire digit*
7. History of dactylitis (if current dactylitis is not present)	*A history of dactylitis recorded by a rheumatologist*
8. Radiological evidence of juxta-articular new bone formation	*Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain xrays of hand or foot*

APPENDIX 2 GUIDANCE ON CONTRACEPTION

The investigator shall describe the length of time that strict precautions against pregnancy must be observed and provide guidance on the use of appropriate methods for sexually active subjects and their partners. Women and men who are not capable of reproduction or choose to be abstinent shall be exempt from following the pregnancy prevention requirements specified below.

DURATION OF MANDATORY CONTRACEPTION:

For Abatacept:

Females: WOCBP must use a highly effective method of contraception throughout the study and for 100 days after the last dose of study drug.

Males: Because the concentration of abatacept in the semen is expected to be low, no contraception is required for males subjects taking the study drug.

For Teratogenic Concomitant Medications:

Males and females taking a teratogenic medication should follow contraception guidelines and duration described in the label for the concomitant medications in addition to those required for abatacept.

CONTRACEPTIVE METHODS:

A. Highly Effective Methods of Contraception

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP are expected to use one of the highly effective methods of contraception listed below:

1. Male condoms with spermicide
2. Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. IUDs, such as ParaGard®
4. Tubal ligation
5. Vasectomy

For abatacept, WOCBP must use a highly effective method of contraception.

For teratogenic concomitant medications: Males and females taking a teratogenic medication should follow contraception guidelines and duration described in the label for the concomitant medications in addition to those required for abatacept.

B. Abstinence

- Abstinence is an acceptable form of contraception for all study drugs.
- Subjects who choose abstinence must continue to have pregnancy tests, as specified in Section 5.3.7.6 of the body of the protocol.

- Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego abstinence.

APPENDIX 3 AMERICAN COLLEGE OF RHEUMATOLOGY 1991 REVISED CRITERIA FOR THE CLASSIFICATION OF FUNCTIONAL STATUS IN RHEUMATOID ARTHRITIS

American College of Rheumatology 1991 Revised Criteria for the Classification of Functional Status in Rheumatoid Arthritis	
Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities
*Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are subject-desired and age- and sex-specific.	

APPENDIX 5 LABORATORY GUIDELINES: PATIENT STUDIES (REVISED AUGUST 13, 1999)

Laboratory test results, which meet these criteria, and the Investigator feels is clinically relevant should be described on the Adverse Event Form. Those which are judged to be SERIOUS events require the completion of a Serious Adverse Event Form (see Sections 6.1.1 and 6.3).

[NOTE: LLN = lower limit of normal; ULN = upper limit of normal.]

albumin - <0.9xLLN or if pretreatment value is <LLN, <0.75x pretreatment

alkaline phosphatase - >2 x ULN; or if pretreatment >ULN, 3x pretreatment value

basophils (%) - >3% if 0-1% pretreatment, >3x pretreatment value if pretreatment >1%

bilirubin

a. direct - >1.5x ULN, or if pretreatment above ULN, >2x pretreatment

b. total - >2x upper limit of normal, or if pretreatment above ULN, >4 x pretreatment value

blasts - >0

blood urea nitrogen (BUN) - >2x pretreatment

calcium - <0.8x LLN or >1.2x ULN; <0.75x pretreatment if pretreatment below LLN, or >1.25x pretreatment if pretreatment above ULN; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

chloride - <0.9x LLN or >1.1x ULN; or <0.9x pretreatment if pretreatment below LLN, or >1.1x pretreatment if pretreatment above ULN; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

creatinine - >1.5x pretreatment value

eosinophils (%) - >3x pretreatment and > 8% if pretreatment normal; if pretreatment >ULN, >3 x pretreatment

erythrocytes - <0.75x pretreatment value

glucose - <0.8x LLN or >1.5x ULN; if pretreatment <LLN then <0.8x pretreatment; if pretreatment >ULN then >2x pretreatment; <LLN if >ULN pretreatment, or >ULN if <LLN pretreatment

hematocrit - <0.75x pretreatment

hemoglobin - >3 g/dL decrease from pretreatment value

lactic dehydrogenase (LDH) - >1.5x ULN; if pretreatment value is above ULN, >3x pretreatment value

leukocyte (WBC) count - <0.75 x LLN or >1.25x ULN; <0.8x pretreatment if pretreatment <LLN or >1.2x pretreatment if pretreatment >ULN; >ULN if pretreatment <LLN or <LLN if >ULN pretreatment

lymphocytes (%) - <0.5x LLN or >2.0 x ULN, or <0.5x pretreatment if below LLN pretreatment; >2.0x pretreatment if above ULN pretreatment. >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

monocytes (%) - >2x ULN; >2x pretreatment if pretreatment above ULN

neutrophil count (neutrophils+bands) - <0.67x pretreatment if pretreatment <1000/mm^3; otherwise, <1000/mm^3.

phosphate - <0.75 x LLN or >1.25x ULN; <0.67x pretreatment value if below LLN pretreatment, or >1.33x pretreatment if above ULN pretreatment; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

platelet count - <0.67x LLN or >1.5 x ULN; if below normal pretreatment, <0.5x pretreatment value and <100,000/mm^3

potassium - <0.9x LLN or >1.1x ULN; <0.9x pretreatment if pretreatment below LLN, or >1.1x pretreatment if pretreatment above ULN; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

protein, total - <0.9x LLN or >1.1x ULN; <0.9 x pretreatment if below LLN pretreatment, or >1.1x ULN if above ULN pretreatment; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

SGOT and SGPT (ASAT and ALAT) - >3 x upper limit of normal; if pretreatment above ULN, >4x pretreatment value

sodium - <0.95x LLN or >1.05x ULN; <0.95x pretreatment if below LLN pretreatment, >1.05x pretreatment if above ULN pretreatment; >ULN if <LLN pretreatment, or <LLN if >ULN pretreatment

uric acid - >1.5x ULN; if pretreatment above ULN, >2x pretreatment value

urinalysis

a) urinary protein - >1 gram/24 hours and 2x pretreatment value

b) urinary RBC - >5/HPF or, >4x pretreatment if pretreatment value 5/HPF

c) urinary WBC - >5/HPF or, >4x pretreatment if 5/HPF pretreatment

d) creatinine clearance (glomerular filtration rate) - <0.67x pretreatment value

e) urine dipstick measurements: Protein, blood, sugar, and acetone- 2+, or if 1+pretreatment, 2x pretreatment. Do not evaluate protein if quantitative protein determination done

stool hemoccult - positive if negative pretreatment