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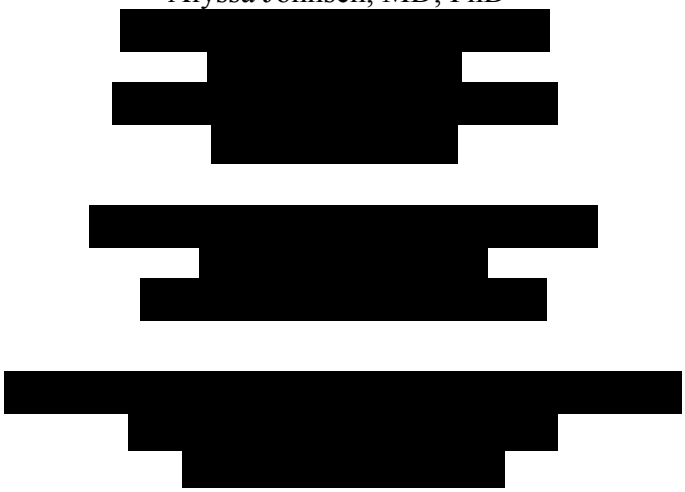
Clinical Protocol IM101567

A Randomized, Head-to-Head, Single-Blinded Study to Assess Changes in the Immune Profile in Response to Treatment with Subcutaneous Abatacept in Combination with Methotrexate versus Subcutaneous Adalimumab in Combination with Methotrexate in Adults with Early Rheumatoid Arthritis who are Naive to Biologic Disease-Modifying Antirheumatic Drugs

Medical Monitor/Study Director

Alyssa Johnsen, MD, PhD



DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	27-Jul-2015	Not applicable

SYNOPSIS

Clinical Protocol IM101567

Protocol Title: A Randomized, Head-to-Head, Single-Blinded Study to Assess Changes in the Immune Profile in Response to Treatment with Subcutaneous Abatacept in Combination with Methotrexate versus Subcutaneous Adalimumab in Combination with Methotrexate in Adults with Early Rheumatoid Arthritis who are Naive to Biologic Disease-Modifying Antirheumatic Drugs

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

Subjects will receive investigational products for a period of 24 weeks. In this protocol, investigational products are:

- abatacept subcutaneous (SC) injection, 125mg/pre-filled syringe (125 mg/mL)
- adalimumab (Humira®) SC injection, 40 mg/prefilled syringe (40 mg/0.8 mL)

Study Phase: IV

[redacted]

Objectives:

Primary Objective:

Not Applicable

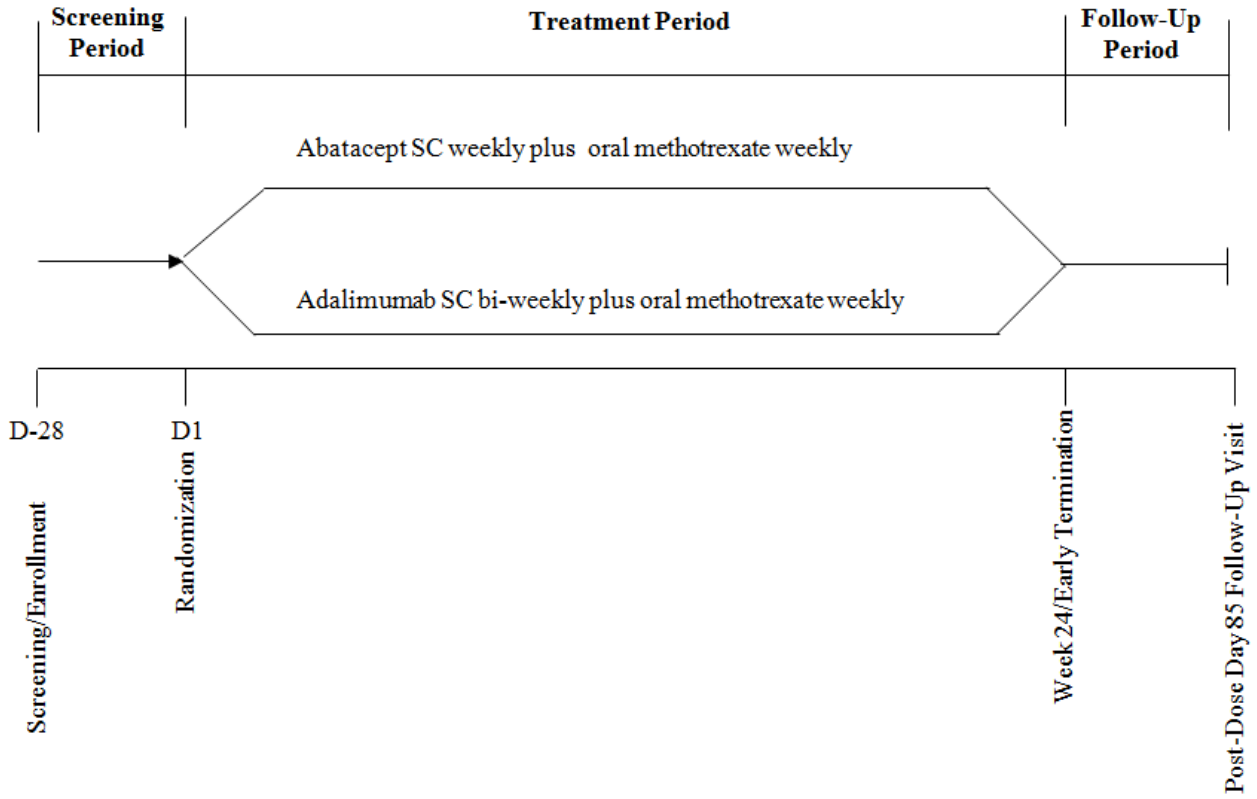
Secondary Objective:

Not Applicable

[redacted]

[redacted]

Study Design: See schematic below for study design.



Screening Period:

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity and safety assessments. Randomization must occur within 28 days of signing the informed consent. Subjects that experience an acute infection or initiate treatment for latent TB may extend the screening period to 42 days

Treatment Period (Day 1 - Week 24):

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

1. Abatacept SC (125 mg) weekly
2. Adalimumab SC (40 mg) once every two weeks

The Treatment Period duration is 24 weeks.

Abatacept and adalimumab administration:

On Day 1, subjects and/or personal caregivers will be trained in self administration of SC injections using pre-filled syringes.

Methotrexate:

Subjects must have been treated with oral methotrexate for at least 12 weeks prior to randomization with a stable dose for at least 28 days prior to randomization. The stable dose of oral methotrexate should be a minimum targeted

dose of at least 20 mg weekly. A dose of methotrexate < 20 mg/week but ≥7.5 mg/week is permitted if intolerance to higher doses has been recorded in the source documents.

The dose of methotrexate must remain stable throughout the study, and may only be lowered due to intolerance or adverse event. Should intolerance occur and the dose of methotrexate requires reduction, subjects must stay on the lower methotrexate dose for the remainder of the study.

Parenteral administration of methotrexate is not permitted at any time during the study. All subjects must receive folic acid, folinic acid, or leucovorin according to the manufacturer's recommendations.

Post-Treatment Follow-up Period:

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

Study Population: Men or women (not nursing or pregnant) ≥ 18 years old who have early RA, defined as diagnosed with RA by ACR/EULAR 2010 classification (Appendix 1) and have had symptoms of RA for no more than 9 months prior to signing the informed consent. Symptoms of RA are defined as pain, stiffness or swelling in joints which are typically inflamed in RA. Subjects who had a single isolated episode of palindromic symptoms that occurred less than 2 years prior to enrollment are still eligible. Subjects must have a second generation anti-cyclic citrullinated peptide (anti-CCP2) test result that is greater than 3-times the upper limit of normal and be rheumatoid factor (RF) positive at screening according to central laboratory testing. Subjects must have a DAS28CRP ≥ 3.2 (Appendix 2) at screening and have at least 3 tender and at least 3 swollen joints (excluding distal interphalangeals) at screening and at randomization.

Eligible subjects must have been treated with oral methotrexate for at least 12 weeks prior to randomization with a stable dose for at least 28 days prior to randomization. The stable dose of oral methotrexate should be a minimum targeted dose of at least 20 mg weekly, unless the dose of methotrexate was limited by intolerance, in which case 7.5 mg is the minimum required dose.

Investigational [Medicinal] Products (IP/IMP) are as listed:

IP/IMP	Potency
Abatacept SC injection	125mg/pre-filled syringe (125 mg/mL)
Adalimumab SC injection	40 mg/prefilled syringe (40 mg/0.8 mL)

Study Assessments: See Section 5 of the protocol for detailed information regarding study assessments.

Statistical Considerations:

Sample Size: In this study 25 subjects will be randomized per treatment arm.

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- [redacted]

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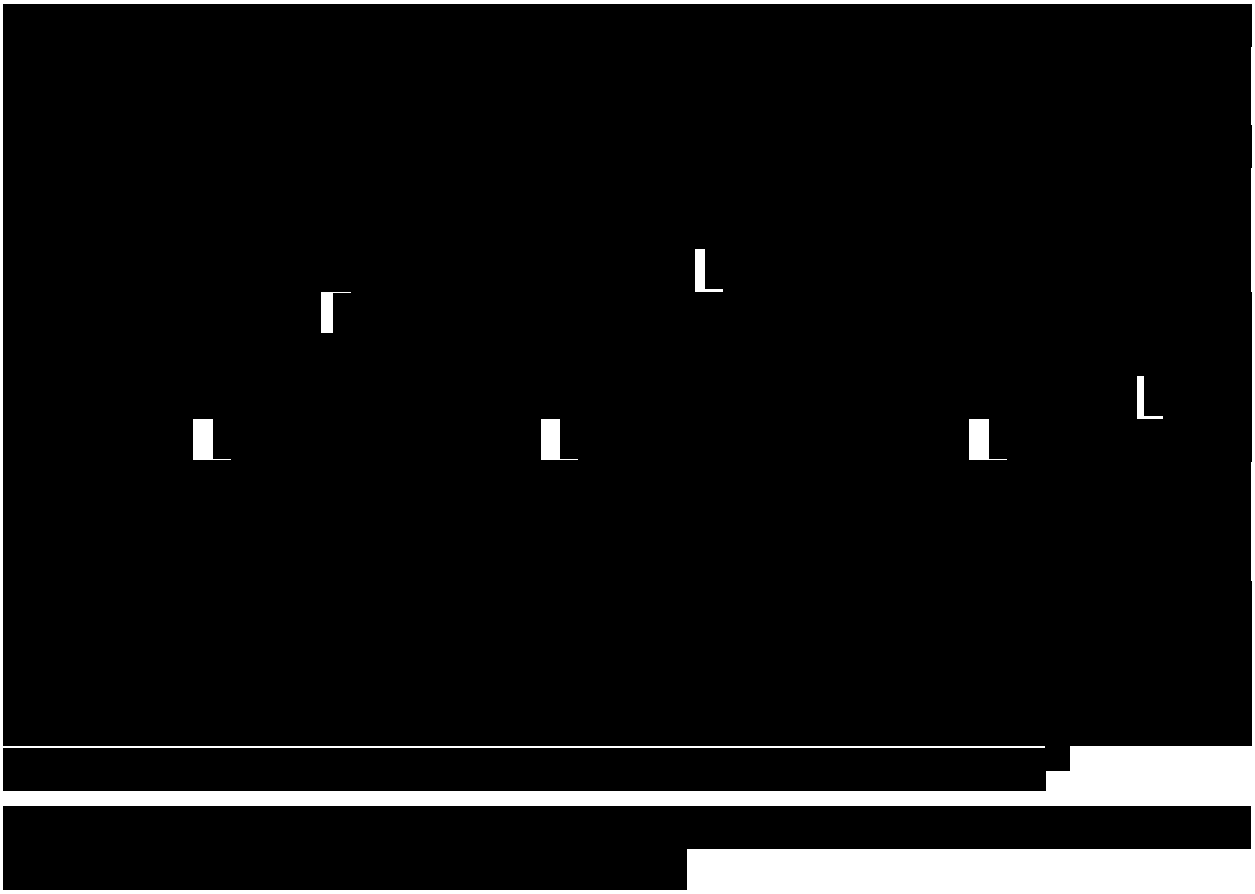


2 ETHICAL CONSIDERATIONS

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 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.

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 (as per country guidelines) 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.

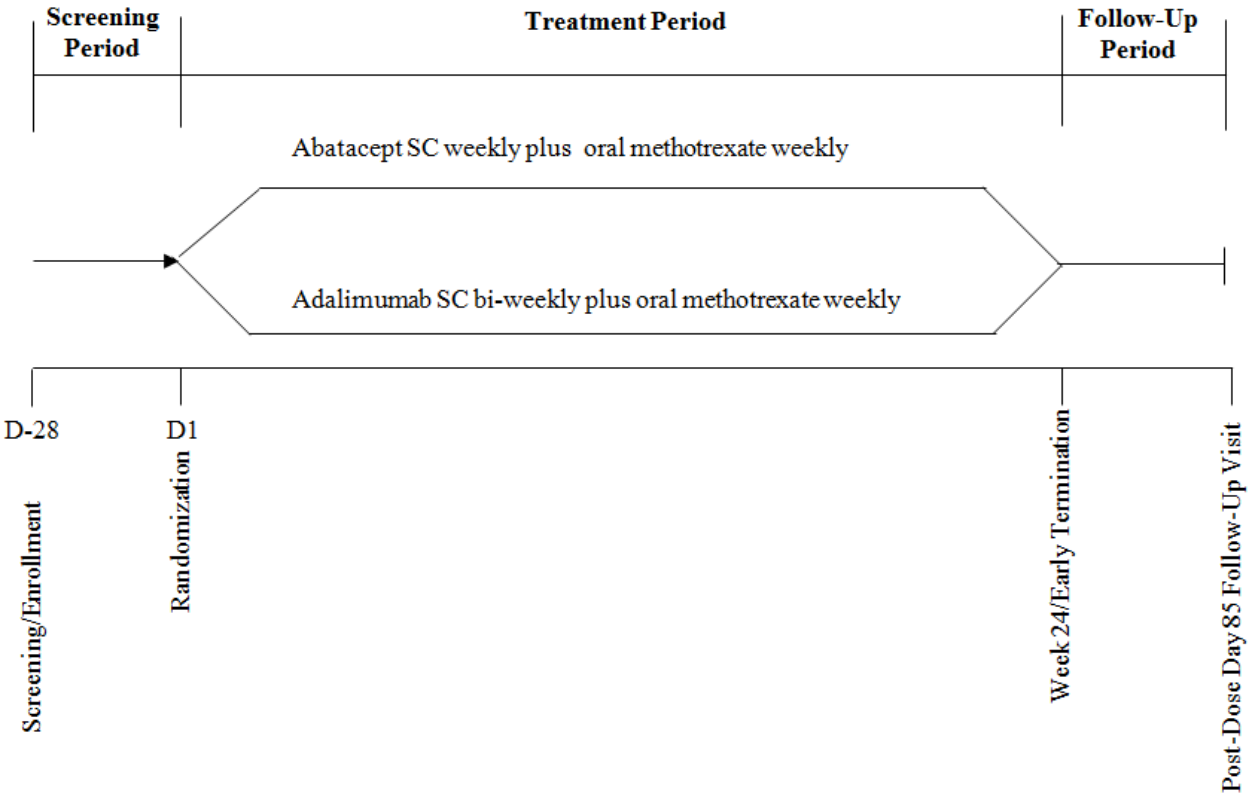
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an exploratory, randomized, single-blinded assessment study in subjects who have recently been diagnosed with rheumatoid arthritis according to ACR/EULAR 2010 classification (Appendix 1), and having symptoms of RA for 9 months or less prior to screening, and have been on MTX for at least 12 weeks with a stable dose of MTX for at least 28 days prior to randomization and are naive to biologic DMARD. It consists of a screening period of up to 28 days, followed by a 24 week Treatment Period, followed by 85 day follow-up period.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



3.1.1 Screening Period

Eligibility will be based on specified inclusion and exclusion criteria, medical history, disease activity and safety assessments. Randomization must occur within 28 days of signing the informed consent. Subjects that experience an acute infection or initiate treatment for latent TB may extend the screening period to 42 days.

Eligible subjects will have been diagnosed with rheumatoid arthritis by ACR/EULAR 2010 classification (Appendix 1) and have had symptoms of RA for no more than 9 months prior to signing the informed consent. Symptoms of RA are defined as pain, stiffness or swelling in joints which are typically inflamed in RA. Subjects who had a single isolated episode of palindromic symptoms that occurred less than 2 years prior to enrollment are still eligible. In order to recruit a cohort of subjects with similar biomarker profiles, subjects must have an anti-CCP2 test result that is greater than 3-times the upper limit of normal[19] and be RF positive at screening according to central laboratory testing. Subjects must have a DAS28CRP $\geq$ 3.2 (Appendix 2) at screening and have at least 3 tender and at least 3 swollen joints (excluding distal interphalangeals [DIPs]) at screening and at randomization.

Subjects must have been treated with oral methotrexate for at least 12 weeks prior to randomization with a stable dose for at least 28 days prior to randomization. The stable dose of oral methotrexate should be a minimum targeted dose of at least 20 mg weekly. A dose of

methotrexate < 20 mg/week but ≥7.5 mg/week is permitted if intolerance to higher doses has been recorded in the source documents.

To minimize potential methotrexate toxicity, all subjects must receive folic acid, folinic acid, or leucovorin according to the manufacturer recommendations, methotrexate label instructions, and the local medical standard of care guidelines.

Subjects receiving oral corticosteroids must be on a stable dose and at the equivalent of ≤ 10 mg prednisone daily for at least 4 weeks prior to randomization. Subjects may not have received an IM, IV or IA administration of a corticosteroid within 4 weeks prior to randomization.

3.1.2 Treatment Period (Day 1 to Week 24)

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

1) Abatacept SC (125 mg) weekly
2) Adalimumab SC (40 mg) once every two weeks

The Treatment Period duration is 24 weeks.

Abatacept and adalimumab administration:

On Day 1, subjects and/or personal caregivers will be trained in self administration of SC injections using pre-filled syringes.

Methotrexate:

Subjects must have been treated with oral methotrexate for at least 12 weeks prior to randomization with a stable dose for at least 28 days prior to randomization. The stable dose of oral methotrexate should be a minimum targeted dose of at least 20 mg weekly. A dose of methotrexate < 20 mg/week but ≥7.5 mg/week is permitted if intolerance to higher doses has been documented in the source documents.

The dose of methotrexate must remain stable throughout the study, and may only be lowered due to intolerance or adverse event. Should intolerance occur and the dose of methotrexate requires reduction, subjects should stay on the lower methotrexate dose for the remainder of the study.

Parenteral administration of methotrexate is not permitted at any time during the study. All subjects must receive folic acid, folinic acid, or leucovorin according to the manufacturer's recommendations.

3.1.3 Post-Treatment Follow-up Period

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

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied 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.

Treatment codes will not be provided to the investigators after completion of the study as the study drug is provided in an open-labeled fashion to sites during the 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 has signed the informed consent.

2. Target Population

a) Subjects have early RA, defined as symptoms of RA that started ≤ 9 months prior to screening and a diagnosis made by the ACR/EULAR 2010 criteria for the classification of RA (Appendix 1)

b) Subjects must be naive to biologic DMARDs

c) Subjects must be naive to conventional synthetic DMARDs other than methotrexate

d) Subjects must be naive to targeted synthetic DMARDs[25] such as tofacitinib, baricitinib, and investigational therapies for RA.

e) Subjects must have been treated with oral methotrexate for at least 12 weeks prior to randomization with a minimum targeted dose of 20 mg/week methotrexate and at least the last 28 days being a stable dose. Subjects can be randomized if the minimum stable targeted dose of methotrexate is < 20 mg/week but ≥ 7.5 mg/week if intolerance to higher doses has been documented in the source documents.

f) Subjects have an anti-CCP2 test that is > 3x ULN and are positive for RF according to central lab testing during screening.

g) Subjects must have at least a DAS28 C-reactive protein (CRP) ≥ 3.2 (Appendix 2) at screening.

h) Subjects must have currently at least 3 tender and at least 3 swollen joints (excluding DIPs) at screening and at randomization

i) Subjects receiving oral corticosteroids must be on a stable dose and at the equivalent of ≤ 10 mg prednisone daily for at least 4 weeks. Subjects may not receive an IM, IV or IA administration of a corticosteroid within 4 weeks prior to randomization.

j) 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 / has not been treated), still meets all inclusion/exclusion criteria, and no more than

9 months have elapsed since the onset of symptoms of RA prior to re-enrollment. If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Men and women, ages ≥ 18 years (or age of majority)

b) Women of childbearing potential (WOCBP) 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 study drug.

c) Women must not be breastfeeding and must agree not to breastfeed during the study and for 100 days thereafter

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug (70 days) plus 30 days (duration of ovulatory cycle) for a total of 100 days post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug, plus 5 half-lives of the study drug (70 days) plus 90 days (duration of sperm turnover) for a total of 160 days post-treatment completion.

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of **two methods** of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation

- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*

* A male and female condom must not be used together

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with autoimmune disease other than RA [eg, psoriasis, systemic lupus erythematosus (SLE), vasculitis, seronegative spondyloarthritis, Inflammatory Bowel Disease, Sjogren's syndrome] or currently active fibromyalgia.

b) Prior history of or current inflammatory joint disease other than RA (such as psoriatic arthritis, gout, reactive arthritis, Lyme disease).

2. Medical History and Concurrent Diseases

a) Subjects at risk for tuberculosis (TB) defined as follows:

i) Current clinical, radiographic or laboratory evidence of active TB. Chest x-rays (posterioranterior and lateral) obtained within the 3 months prior to randomization will be permitted but the images must be available and reviewed by the investigator. TB testing (IFN-γ release assay or PPD) performed in the past month prior to Screening will be accepted; however, a copy of the report must be placed in the subject binder.

ii) A history of active TB

iii) Subjects with a positive TB screening test indicative of latent TB will not be eligible for the study unless they:

(1) Have no evidence of current TB based on chest x-ray performed during the screening period and by history and physical exam, and

(2) They are actively being treated for TB or the site has documentation of successful prior treatment of latent TB. Treatment regimens should be dictated by local guidelines as long as the treatment dose and duration meet or exceed local health authority guidelines. If permitted by local guidelines regarding treatment with biologic medications, subjects may be randomized prior to completion of treatment as long as they have completed at least 4 weeks of treatment and they have no evidence of current TB on chest x-ray at screening.

b) Subjects with recent acute infection defined as:

i) Any acute infection within 60 days prior to randomization that required hospitalization or treatment with parenteral antibiotics.

ii) Any acute infection within 30 days prior to randomization that required oral antimicrobial or antiviral therapy.

c) Subjects with history of chronic or recurrent bacterial infection (such as chronic pyelonephritis, osteomyelitis, and bronchiectasis etc.).

d) Subjects with any history of infection of a joint prosthesis or artificial joint.

e) Subjects who have a history of systemic fungal infections (such as histoplasmosis, blastomycosis, or coccidiomycosis).

f) Subjects with history of recurrent herpes zoster (more than 1 episode) or disseminated (more than 1 dermatome) herpes zoster or disseminated herpes simplex, or ophthalmic zoster will be excluded. Symptoms of herpes zoster or herpes simplex must have resolved more than 60 days prior to screening.

g) Subjects with history of Human Immunodeficiency Virus (HIV) infection or who test positive for HIV at screening.

h) Subjects with history of primary immunodeficiency

i) Subjects who have present or previous malignancies, except documented history of cured non-metastatic squamous or basal skin cell carcinoma, or cervical carcinoma *in situ*, with no recurrence in the 5 years prior to screening. Subjects who had 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.

j) Current clinical findings or a history of a demyelinating disorder

k) New York Heart Association (NYHA) Class III or IV heart failure

l) Any previous or current medical conditions that are warnings against the use of TNF inhibitor agents.

m) Current clinical findings of severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, psychiatric, cardiac, endocrine, 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.

n) Subjects who have received any live vaccines within 3 months of the study drug administration or are scheduled to receive live vaccines during the study. Study subjects should not be administered a live virus vaccine for a minimum of 3 months following the last dose of study medication. Subjects who are in close contact with others who have received a live vaccine may be enrolled at the investigator's discretion.

o) Subjects who have undergone a major surgical procedure within the 60 days prior to randomization.

p) Subjects for whom 5 or more joints cannot be assessed for tenderness or swelling (ie due to surgery, fusion, amputation, etc).

q) 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

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

3. Physical and Laboratory Test Findings

a) Hepatitis B surface antigen (HBsAg)-positive, or Hepatitis B core antibody (HBcAb)-positive subjects with detectable hepatitis B viral DNA

b) Hepatitis C antibody (HcAb)-positive subjects 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) Serum creatinine > 2 times upper limit of normal.

g) Serum ALT or AST > 2 times upper limit of normal.

h) Evidence of active cardiac or pulmonary disease on chest X-rays

i) Any 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 products and/or its excipients.

5. Prohibited Treatments and/or Therapies

a) Subjects who have had previous exposure to abatacept or adalimumab

b) Subjects who have had previous exposure to any DMARD other than methotrexate

c) Subjects who have been exposed to any treatment with an approved or investigational biologic DMARD including but not limited to infliximab, etanercept, anakinra,

rituximab, tocilizumab, golimumab, and certolizumab, or an investigational or approved targeted non-biologic DMARD, such as tofacitinib or baricitinib

d) Subjects who have received an IM, IV or IA administration of a corticosteroid within 4 weeks prior to randomization (Day 1)

e) Subjects currently taking NSAIDs must have been on a stable dose, as assessed by the Investigator, for at least 14 days prior to randomization.

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

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, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

Females 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 judgement 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]

[redacted]

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Use of prohibited medication
- Pregnancy
- Missed Doses:
  - Missed greater than 6 doses of abatacept OR greater than 3 doses of adalimumab for any reason during the study
  - Missed greater than 4 consecutive doses of abatacept OR greater than 2 consecutive doses of adalimumab for any reason during the study
- Any clinical adverse event (AE), laboratory abnormality 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.
- Subject's request to stop study treatment or withdrawal of informed consent
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness

All subjects who discontinue study drug 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 including post-treatment study follow-up 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 drug 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 Study Drug Study Follow up

Subjects who discontinue study drug may continue to be followed. Subjects who withdraw consent (according to Section 3.6.1) or are lost to follow-up (according to Section 3.6.2) will not

be followed in this study; all other subjects will continue to be followed for collection of follow up data as required and in line with Section 5, Study Procedures and Assessments.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug 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 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP).

4.1 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 products are:

Table 4.1-1: Investigation Product for IM101-567

Product Description / Class and Dosage Form	Potency	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Abatacept SC injection	125 mg/prefilled syringe (125 mg/mL)	Open label	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
Adalimumab SC injection	40 mg/prefilled syringe (40mg/0.8 mL)	Open Label	Clear; colorless solution; essentially free of visible particulate	Store refrigerated, 2-8° C (36-46 ° F). Do not freeze. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light

BMS will supply the investigational products described above.

4.2 Non-investigational Product

In this protocol, non-investigational product(s) include include methotrexate, corticosteroids, NSAIDs, (including aspirin), folic acid, and/or folinic acid (leucovorin). BMS will not provide non-investigational products.

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 non-investigational products.

4.3 Storage 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.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) 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).

4.4 Method of Assigning Subject Identification

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

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

4.5 Selection and Timing of Dose for Each Subject

On “Office Visit” days, study medication should be administered AFTER all assessments have been completed, including blood draws for assessment of immunogenicity and possible drug concentrations.

4.5.1 Abatacept Treatment Arm

On Day 1, subjects will self-administer abatacept 125 mg SC from a pre-filled syringe. On Day 8, subjects will self-administer abatacept 125 mg SC. Thereafter, subjects will self-administer abatacept 125 mg SC once every 7 days, up to and including Week 23 (Day 162).

Treatment duration is 167 days for all randomized subjects (who have not discontinued study therapy).

4.5.1.1 Self-Administration of Subcutaneous Injection

Each pre-filled syringe contains one weekly dose of abatacept, 125 mg/mL. Subjects will be trained to self-administer their weekly SC injection. Training should be performed by investigational personnel who are considered qualified trainers by the principal investigator. A procedure guide will be provided by BMS. The subject should be able to self-administer the SC injection between office visits, or have an office-trained caregiver do so.

On office visit days, SC injections should be given AFTER all assessments are completed, including blood draws. If a caregiver is responsible for giving the injections, he or she should accompany the subject to office visits.

4.5.1.2 Administration Window

SC injections of study medication may be administered ± 3 days around the target day. The last dose before each office visit should be administered at least 4 days before the scheduled visit date. If a SC injection is not given within the administration window, the next SC injection should be given on the next scheduled target administration day.

4.5.1.3 Dose Modifications

Dose Modifications in the Absence of Adverse Events

Subjects should complete their scheduled SC injections as described above. Subjects who miss the dose window should skip the SC injection and wait until the next targeted administration day.

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. **Under no circumstances should the dose of study drug be altered due to an adverse event.**

4.5.2 Adalimumab Treatment Arm

Subjects randomized to adalimumab will self-administer an initial dose of adalimumab 40 mg SC from a pre-filled syringe on Day 1. On Day 15, subjects will self-administer adalimumab 40 mg SC. Thereafter, subjects will self-administer adalimumab 40 mg SC once every 14 days, up to and including Week 22 (Day 152).

Treatment duration is 167 days for all randomized subjects (who have not discontinued study therapy).

4.5.2.1 Self-Administration of Subcutaneous Injection

Each pre-filled syringe contains one bi-weekly dose of adalimumab, 40 mg/mL. Subjects will be trained to self-administer their bi-weekly SC injection. Training should be performed by investigational personnel who are considered qualified trainers by the principal investigator. A procedure guide will be provided by BMS. The subject should be able to self-administer the SC injection between office visits, or have an office-trained caregiver do so.

On office visit days, SC injections should be given AFTER all assessments are completed, including blood draws. If a caregiver is responsible for giving the injections, he or she should accompany the subject to office visits.

4.5.2.2 Administration Window

SC injections of study medication may be administered ± 7 days around the target day. The last dose before each office visit should be administered at least 7 days before the scheduled visit date. If a SC injection is not given within the administration window, the next SC injection should be given on the next scheduled target administration day.

4.5.2.3 Dose Modifications

Dose Modifications in the Absence of Adverse Events

Subjects should complete their scheduled SC injections as described above. In exceptional cases, the administration window may be extended to ± 7 days. Beyond that, the subject should skip the SC injection and wait until the next targeted administration day.

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. **Under no circumstances should the dose of study drug be altered due to an adverse event.**

4.5.3 Guidelines for Methotrexate

Subjects must enroll on a stable minimum targeted dose of 20 mg/week. Subjects may enroll with MTX doses < 20 mg/week but ≥ 7.5 mg/week if intolerance to higher doses has been recorded in the source documents. All subjects must be maintained on the enrollment MTX dose, unless toxicity or intolerability occurs during the course of the study. In that event, the dose may be reduced or held as medically necessary for adverse events. However, MTX should be returned to the baseline dose as soon as possible, or to the maximally tolerated dose below the baseline dose, but not less than 7.5 mg/week for the duration of the study. MTX should be given orally.

4.6 Blinding/Unblinding

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

Clinical Assessors will be blinded to treatment allocation so as to preserve the objectivity of study-related assessments (tender and swollen joint count, Physician's Global Assessment of Disease Activity, AE causality assessment) and routine clinical care (laboratory result review, medication adjustment). To preserve blinding, they must be shielded from treatment allocation. This will be the responsibility of the Study/Research Coordinators who need not be blinded to treatment allocation. At the beginning of each study visit throughout the study duration, the subject should be reminded that the Clinical Assessor is blinded to treatment allocation and that care must be taken to prevent revealing treatment allocation. They should be instructed to:

- not discuss study drug by name
- not discuss the color or use of the pre-filled syringe
- not discuss how often injections are performed
- only discuss injection site reactions of significant concern.

To comply with requirements for Case Report Form Completion (CRF), a qualified physician who is an investigator or subinvestigator who is unblinded to study drug assignment will be needed to promptly review, sign, and date the CRF.

The site should maintain two distinct sets of source documents, one set accessible to the unblinded site staff and one set for the blinded Clinical Assessor.

Care should be taken by the Study/Research Coordinator to retrieve any study drug and sharps container returned by the subject at the beginning of each visit to shield the assessor from inadvertent exposure to subject allocation. Similarly, study drug dispensing should be done after blinded assessments. Both retrieval and dispensing of study drug should be done in an area shielded from the blinded assessor(s).

The joint count assessment should be performed after completion of the patient report outcomes (PRO), vital sign assessment, and AE assessment. The Clinical Assessor will similarly be reminded at the beginning of each study visit throughout the study duration that they are performing a blinded-assessment for the study and to not ask question or elicit comments that may reveal treatment allocation as outlined above. Every effort must be made to ensure the same

evaluator(s) will complete the assessment for each subject. If the usual evaluator is not available, another trained evaluator blinded to study drug allocation for the subject may perform the clinical assessment. In the event that no blinded evaluator is available during the study visit, blinded clinical assessment measures (tender and swollen joint counts and physician global assessment of disease activity) should not be reported.

The Sponsor will be unblinded to the treatment assignments of the subject in the trial as it is not possible to restrict access to the dosing CRF pages. However, the Sponsor's medical monitor, protocol manager, biomarker representative, and statistician will make every effort to review data in an unbiased fashion. However, the impact on the study is believed to be minimal based on the primary objective.

The BMS Bioanalytical Science Department or its designee will be unblinded to the randomized treatment assignments in order to accurately perform sample analysis for the PK and immunogenicity samples.

Unblinding of study drug allocation for safety purposes is not necessary because all study drug provided to the site is open-labeled.

4.7 Treatment Compliance

All subjects are expected to receive study therapy as outlined in the protocol. Subjects will use diary cards to document self-injection of study drug between clinic visits. Permitted dose modifications are described in Section 4.5. Conditions under which therapy must be discontinued due to non-compliance are outlined in Section 3.5.

4.8 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 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 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.

4.9 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 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: Flow Chart for Protocol IM101-567 - Screening Period

Procedure	Screening Visit[a]	Extended Screening Visit[b]	Notes
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Medical History	X	X	
Enroll Subject	X		Contact IVRS for subject number. If subject does not meet eligibility criteria, contact IVRS to screen fail subject.
Safety Assessments			
Physical Examination	X	X	
Height and Weight	X		
Vital Signs	X	X	Body temperature, seated blood pressure, and heart rate.
Adverse Events Assessment	X	X	
Prior and Concomitant Medication	X	X	
TB Screening Test	X		TB testing (IFN-γ release assay or PPD) performed locally within the month prior to Screening will be accepted. A copy of the report must be filed in the subject binder. See Section 5.3.5 for important details.
Chest X-ray (CXR)	X		Required only if the results of a CXR performed within the 3 months prior to enrollment are not available.
Laboratory Tests			
Hematology (CBC)	X	X	
Chemistry	X	X	
Urinalysis	X		

Table 5.1-1: Flow Chart for Protocol IM101-567 - Screening Period

Procedure	Screening Visit[a]	Extended Screening Visit[b]	Notes
HBsAg	X		If positive, obtain HBV DNA (see Section 5.3.6.4)
Hepatitis C Antibody	X		If positive, reflex to HCV confirmation such as PCR
HIV	X		
Quantitative Immunoglobulins (IgG, IgA, IgM)	X		
Urine Pregnancy Test	X	X	WOCBP only; see Section 5.3.6.5. Performed locally.
ESR	X	X	Performed locally, kits provided centrally.
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]		
[redacted]	[redacted]		
Disease Assessments			
Tender (68)/swollen (66) Joint Count	X	X	
Subject Global Assessment of Disease Activity	X	X	See Appendix 5

a The duration of the screening period should not exceed 28 days.

b Subjects that experience an acute infection or initiate treatment for latent TB may extend the screening period to 42 days. Under these circumstances, all screening procedures except subject consenting, IVRS enrollment, height/weight, immunoglobulins, urinalysis, anti-CCP2, RF, chest x-ray, TB testing, HepB/C and HIV should be repeated prior to randomization.

Table 5.1-2: Flow Chart for Protocol IM101567 - Treatment Period[a]

Procedure	Day 1 (Rand)	Week 4	Week 8	Week 12 (Phone Visit)	Week 16	Week 20 (Phone Visit)	Week24/ Early Termination	Notes
Randomize Subject Using IVRS	X							
Eligibility Assessments								
Inclusion/Exclusion Criteria	X							Review of I/E criteria that are relative to the Randomization day
Safety Assessments								
Physical Examination	X							
Vital Signs	X	X	X		X		X	Body temperature, seated blood pressure, and heart rate.
Weight	X						X	
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	X	Causality determined by a blinded Clinical Assessor
Laboratory Assessments								
Hematology (CBC)	X	X	X		X		X	
Chemistry Panel	X	X	X		X		X	
Urine Pregnancy Test	X	X	X	X	X	X	X	WOCBP only; see Section 5.3.6.5. Performed locally. Pregnancy testing also performed prior to dosing at Weeks 12 and 20.
MTX polyglutamate	X	X	X		X		X	
ANA and reflex ENA panels	X	X	X		X		X	
Anti-dsDNA	X	X	X		X		X	
Anti-cardiolipin antibodies	X	X	X		X		X	

Table 5.1-2: Flow Chart for Protocol IM101567 - Treatment Period[a]

Procedure	Day 1 (Rand)	Week 4	Week 8	Week 12 (Phone Visit)	Week 16	Week 20 (Phone Visit)	Week24/ Early Termination	Notes
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]
[redacted]	[redacted]				[redacted]		[redacted]	[redacted]
[redacted]	[redacted]				[redacted]		[redacted]	[redacted]
[redacted]	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	

Table 5.1-2: Flow Chart for Protocol IM101567 - Treatment Period[a]

Procedure	Day 1 (Rand)	Week 4	Week 8	Week 12 (Phone Visit)	Week 16	Week 20 (Phone Visit)	Week24/ Early Termination	Notes
Efficacy Assessment								
Tender (68)/swollen (66) Joint Count	X	X	X		X		X	Performed by a blinded Clinical Assessor
Subject Assessment of Pain	X	X	X		X		X	See Appendix 4
Subject Global Assessment of Disease Activity	X	X	X		X		X	See Appendix 5
Physician Global Assessment of Disease Activity	X	X	X		X		X	Performed by a blinded Clinical Assessor; See Appendix 6
Physical Function (HAQ-DI)	X	X	X		X		X	See Appendix 7
Study Drug Administration								
Contact IVRS	X	X	X		X		X	Contact is required to randomize the subject on Day 1 and to dispense medication at each office visit.
Train subjects and/or caregiver on how to self-inject and how to fill out the diary cards	X							
Dispense diary cards	X	X	X		X			
Collect and review diary cards		X	X		X		X	
Dispense urine pregnancy kits for WOCBP for home use every 4 weeks			X		X			Not applicable if serum pregnancy testing is required per local regulations.

Table 5.1-2: Flow Chart for Protocol IM101567 - Treatment Period[a]

Procedure	Day 1 (Rand)	Week 4	Week 8	Week 12 (Phone Visit)	Week 16	Week 20 (Phone Visit)	Week24/ Early Termination	Notes
Dispense urine pregnancy kits for possible use during Follow-up Period							X	See Table 5.1-3
Dosing of weekly abatacept/biweekly adalimumab	X	X	X	X	X	X		Must be administered weekly (abatacept) or biweekly (adalimumab) between visits. See Section 4.5
Dispense monthly abatacept or adalimumab monthly kits	X	X	X		X			Two monthly kits are dispensed at Week 8 and Week 16.
Reconciliation of abatacept or adalimumab monthly kits		X	X		X		X	

[a] All visits and procedures during the Treatment Period must occur within ± 3 days of the expected visit.

[b] These samples will only be evaluated to determine serum abatacept or adalimumab concentration in the event there is a corresponding positive immunogenicity result.

Table 5.1-3: Flow Chart for Protocol IM101567 - Follow-Up Period

Procedure	Day 85 after last dose[a]	Notes
Safety Assessments		
Vital Signs	X	Body temperature, seated blood pressure, and heart rate.
Adverse Events Assessment	X	
Concomitant Medication Review	X	
Laboratory Assessments		
Urine Pregnancy Test	X	WOCBP only; see Section 5.3.6.5. Performed locally.

[a] Visit must occur within ± 10 days of the expected day of the visit. The follow-up visit should ideally be an in-person visit. If this is not possible, a telephone follow-up visit will be performed to confirm the results of the urine pregnancy test as well as adverse event and concomitant medication review. Vital signs will not be collected as part of a telephone follow-up phone visit.

5.1.1 Retesting During Screening, Extended Screening, or Rescreening

All screening procedures are to be performed within 4 weeks of the randomization visit except as described below.

Retesting:

A single retest of the anti-CCP2, RF and hsCRP within the Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Period, may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

Extended Screening:

Subjects that experience an acute infection or initiate treatment for latent TB may extend the screening period to 42 days, as long as the infection did not require hospitalization or administration of parenteral antibiotics agents. Under these circumstances, all screening procedures except IVRS enrollment, height/weight, immunoglobulins, urinalysis, anti-CCP2, RF, chest x-ray, TB testing, HepB/C and HIV should be repeated prior to randomization.

Rescreening:

This study permits the rescreening of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated), still meets all inclusion/exclusion criteria, and no more than 9 months have elapsed prior to enrollment since the onset of symptoms of RA. If rescreened, the subject must be re-consented. A subject may be rescreened only once. Medical Monitor approval is required and rescreens are not permitted less than 28 days after signing the first informed consent. The subject will need to sign a new informed consent and be reenrolled with a new subject number via the IVRS. Some tests such as chest x-ray, may not need to be repeated if they were performed within the protocol defined window.

5.1.2 Order of Study Assessments

Study assessments should be performed in the following order:

1) Patient reported outcomes (PROs) questionnaires
2) AE collection
3) Vital signs
4) Joint assessments
5) Investigator assessments

6) Blood draws
7) Study drug administration

5.2 Study Materials

The following materials will be provided for use during the trial:

- Diary cards to record SC dosing administration and the monthly pregnancy test results for WOCBPs (mandatory)
- Written instructions on how to use the SC syringes
- eCRF instructions
- Pregnancy Surveillance Forms
- Subject and Investigator-rated questionnaires/scales (paper)
- Drug Inventory binder (optional)
- 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
- Tote bags to transport cooler bags, sharp containers and study drug
- For WOCBP urine pregnancy kits/instructions will be provided to be used between office visits.

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 treatment early 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 Physical Examination

Physical examinations may be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician Assistant (PA), or Nurse Practitioner (NP).

The physical examination should include examination of the heart, lungs, abdomen, the lymph nodes, liver, spleen and skin. A physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any other body systems as clinically indicated.

5.3.2 Chest X-ray

A posterior-anterior and lateral chest x-ray, performed during screening, is required for all subjects unless performed within 3 months prior to obtaining written informed consent and documentation of the earlier x-ray is on file. Investigators must ensure that the results of the chest x-ray satisfy criteria for eligibility. The chest x-ray result will be recorded on the appropriate page of the eCRF.

5.3.3 Physical Measurements

Weight and height is to be recorded at screening. Weight will also be recorded at Day 1 and Week 24/Early Termination.

5.3.4 Vital Signs

Vital signs (seated blood pressure, heart rate, and temperature) will be recorded during every office visit and prior to dose administration, when applicable. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.

5.3.5 TB Screening

Chest x-ray, history, 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 evidence or 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),[27,28,29] or who are immunocompromised and who have had prior BCG vaccination(s).[30,31] Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG. An interferon gamma release assay (eg, QuantiFERON® Gold or Tspot/ELISpot) is an acceptable alternative when skin testing for tuberculosis (ie, PPD) is not appropriate.

5.3.6 Laboratory Assessments

All laboratory assessments will be analyzed centrally except if noted otherwise.

Blood samples will be obtained at all visits noted in Time and Events Schedule. Any laboratory test result that the investigator considers clinically relevant should be recorded on the appropriate Adverse Event page of the CRF (see Appendix 8).

5.3.6.1 Hematology

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

5.3.6.2 Blood Chemistry

Sodium	Creatinine
Potassium	Blood urea nitrogen (BUN)
Chloride	Total bilirubin
Total Protein	Alanine aminotransferase (ALT)
Albumin	Aspartate aminotransferase (AST)
Calcium	Gamma-glutamyltransferase (GGT)
Phosphorus	Alkaline phosphatase
Glucose	hsCRP
Rheumatoid Factor	ANA and reflex ENA panels
MTX polyglutamate	ESR*
Quantitative Immunoglubulins (IgG, IgA, IgM)	

*Performed locally, kits provided centrally.

5.3.6.3 Urinalysis

- pH
- Protein
- Glucose
- Blood

5.3.6.4 Hepatitis Screen

The Laboratory results must be available on Day 1 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

5.3.6.5 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 Section 5.1. A serum test must be performed for confirmation of any positive urine test result. Urine tests can be processed locally and can be self-administered by the subject between office visits, if permitted by local regulations. If any female subject becomes pregnant, she will stop receiving study treatment immediately and enter the Post Treatment Follow-up Period. A pregnancy surveillance form will be completed and submitted to Bristol-Myers Squibb. Serum pregnancy tests will be processed centrally.

5.3.6.6 HIV Testing

HIV testing will be performed for all subjects.

5.4 Efficacy Assessments

Questionnaires and investigator/subject assessments will be completed prior to study drug administration.

Physicians Global Assessment

The Physicians Global Assessment of Disease Activity (PGA) can be performed by the investigator or sub-investigator. The sub-investigator may be a Doctor of Medicine (MD) or Doctor of Osteopathy (DO).

Joint Count Assessments

The Joint Count Assessor may perform the PGA for the same subject. For both assessments every effort should be made to ensure the same assessor is used for a given subject throughout the study.

Training and instruction on joint count assessments will be discussed at the Investigator's Meeting or at other trainings and workshops. Any assessors at a site who were not trained by a centralized BMS trainer should receive instruction by their site primary assessor who has undergone the centralized BMS training. The secondary assessor may conduct joint counts for the trial only after having performed satisfactorily at least 3 patient assessments under the supervision of the primary assessor. Additional information related to joint assessor training will be provided by BMS or a delegate.

Joint Count Assessors 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.

Visits should be scheduled with the availability of the assessor taken into account. If the assessor is unable to complete the evaluation, then another qualified individual can take the place of the initial evaluator, as long as the restrictions, described above, are still met. The substitute evaluator will have also examined and reviewed the subject with the initial assessor to ensure consistency between subject evaluations.

Patient Reported Outcomes

Subjects will complete the Global Assessment of Disease Activity (VAS), HAQ-DI, and Assessment of Pain (VAS).

5.4.1 Imaging Assessment for the Study

Not Applicable.

[redacted]

[redacted]

[redacted]

5.7 Outcomes Research Assessments

The following assessments will be performed:

a) Subject Assessment of Pain: Pain reported by patients, measured on 10 cm VAS. See Appendix 4.

b) Subject Assessment of Physical Functioning: The Health Assessment Questionnaire (HAQ), published in 1980, is one of the most widely used, comprehensive, validated, patient-oriented outcome assessment instruments available. HAQ disability index takes into account the subject's use of aids, devices, or assistance in the scoring algorithm for a disability category. See Appendix 8.

c) Subject Assessment of Disease Activity: Global disease assessment of disease activity by patients measured on 10 cm VAS. See Appendix 5.

[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 study drug 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 study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal 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).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.5.1 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited 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 85 days of discontinuation of the Treatment Period. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must 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 must 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 must 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 of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must 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.

6.3 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 study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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 of awareness of the event 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 administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (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

8.1 Sample Size Determination

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

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

The population will be enriched to allow for assessment of important changes in the immune phenotype by including only subjects who are anti-CPP2 positive.

8.2 Populations for Analyses

The as-treated analysis population will contain all subjects who received at least 1 dose of study medication. The treatment that is received will be used in the analysis. This population will be used for all analyses, including demography, biomarker, efficacy and safety analyses.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

No primary endpoints are defined for this protocol.

8.3.2 Secondary Endpoint(s)

No secondary endpoints are defined for this protocol.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Summary statistics of all demographics and baseline characteristics will be provided by treatment group using the as-treated analysis population.

[redacted]

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, events leading to discontinuation and adverse events of special interest 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.

8.4.4 Pharmacokinetic Analyses

Not Applicable.

[redacted]

8.4.6 Outcomes Research Analyses

Not applicable

8.4.7 Other Analyses

Not applicable

8.5 Interim Analyses

Not applicable

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 done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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.

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.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

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 study drug (inventoried and dispensed) is maintained at the study site to include investigational product. 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.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ABA	abatacept
ACPA	anti-citrullinated protein antibody
ACR	American College of Rheumatology
ADA	adalimumab
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANC	absolute neutrophil count
anti-CCP	anti-cyclic citrullinated peptide
anti-CCP2	commercially available test for ACPA
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the time-concentration curve
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
cm	centimeter
CRF	Case Report Form, paper or electronic
CRP	C-reactive protein
DIP	distal interphalangeal
dL	deciliter
DMARD	disease-modifying anti-rheumatic drug
dsDNA	double-stranded DNA
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th Edition)
ECG	electrocardiogram

Term	Definition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ENA	extractable nuclear antigen
ESR	Erythrocyte Sedimentation Rate
ET	early termination
EU	European Union
EULAR	European League Against Rheumatism
F	Fahrenheit
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HBcAb	Hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
Hgb	hemoglobin
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
hsCRP	high-sensitivity C-reactive protein
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IM	intramuscular
IMP	investigational medicinal products

Term	Definition
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mg	milligram
MHC	major histocompatibility complex
min	minute
mL	milliliter
mmHg	millimeters of mercury
MRHD	maximum recommended human dose
MTD	maximum tolerated dose
MTX	methotrexate
μg	microgram
N	number of subjects or observations
N/A	not applicable
NIMP	non-investigational medicinal products
NP	nurse practitioner
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PA	physician assistant
PBMC	Peripheral blood mononuclear cell
PGA	Physicians Global Assessment of Disease Activity
PO	per os (by mouth route of administration)
PT	prothrombin time
QC	quality control
QD, qd	quaque die, once daily

Term	Definition
RA	rheumatoid arthritis
RBC	red blood cell
RF	Rheumatoid factor
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SLE	systemic lupus erythematosus
SOP	Standard Operating Procedures
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TB	tuberculosis
TNF	tumor necrosis factor
WBC	white blood cell
US	United States
WHO	World Health Organization
WOCBP	women of childbearing potential