Protocol Number: IM006016
IND Number: 122,786
EUDRACT Number 2015-002887-17
Date: 14-Sep-2015
Revised Date: 29-Oct-2017

Clinical Protocol IM006016

Phase 2, Randomized, Multi-Center, Double-Blind, Dose-Ranging, Placebo Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety/Pharmacokinetics of BMS-986142 in Subjects with Moderate to Severe Rheumatoid Arthritis with an Inadequate Response to Methotrexate with or without TNF Inhibitors

Revised Protocol: 03

Study Director and Medical Monitor

Miroslawa Nowak, MD

[redacted]

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	29-Oct-2017	This protocol was updated mainly to incorporate preliminary results of drug-drug interactions studies IM006-031 and IM006-032 as described in Dear Investigator Letter dated 17-Oct-2016. Revisions were also made to provide further clarifications on study timelines, leflunomide washout, inclusion and exclusion criteria, PI expectations on x-ray and MRI results, Physicians Global Assessment of Disease Activity (PGA) and Joint Count Assessments, as well as to include administrative changes.
Revised Protocol 02	04-Aug-2016	Incorporates Amendment 07
Amendment 07	04-Aug-2016	[redacted]
Administrative Letter 03	21-Jun-2016	Editorial revision to Table 5.1-1 Flow Chart for Protocol IM006016 - Screening Period, to align with Section 3.3.1 Inclusion Criteria 2e
Revised Protocol 01	03-May-2016	Incorporates Amendment 05
Amendment 05	03-May-2016	Incorporate changes in response to health authorities' comments and update information collected during course of study.
Administrative Letter 02	16-Dec-2016	Correct the typographical error in the packaging/appearance of the study drugs (BMS-986142, 50 mg and placebo) in Section 4 of the protocol.
Administrative Letter 01	13-Nov-2015	Clarify information on Additional Research Amendment that describes in details Optional Sampling.
Original Protocol	14-Sep-2015	Not Applicable

SYNOPSIS

Clinical Protocol IM006016

Protocol Title: Phase 2, Randomized, Multi-Center, Double-Blind, Dose-Ranging, Placebo Controlled, Adaptive Design Study to Evaluate the Efficacy and Safety/Pharmacokinetics of BMS-986142 in Subjects with Moderate to Severe Rheumatoid Arthritis with an Inadequate Response to Methotrexate with or without TNF Inhibitors

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

BMS-986142 is a reversible Bruton's tyrosine kinase (BTK) inhibitor that will be orally administered in a double-blind fashion to rheumatoid arthritis (RA) subjects currently on a background of methotrexate (MTX) treatment. Four treatments will be administered: placebo, 100, 200, and 350 mg of BMS-986142 daily for 12 weeks. Additionally, new dose levels of BMS-986142 may be added based on the results of Week 4 interim analysis.

Study Phase: 2

Research Hypothesis: At least one of the dose levels of BMS-986142 administered daily is more effective than placebo on a background of methotrexate (MTX) in achieving ACR20 and ACR70 response after 12 weeks of treatment in subjects with moderately-to severely active RA with an inadequate response to MTX with or without TNF inhibitors.

Primary Objective:

To compare the efficacy of BMS-986142 versus placebo (PBO) on a background of MTX as assessed by ACR20 and ACR70 response rates at Week 12.

Secondary Objectives:

1) Assess additional efficacy outcomes of BMS-986142 at Week 12 and over 12 weeks of treatment as measured by ACR20, ACR50 and ACR70 response rates, DAS28-CRP change from baseline, DAS28-ESR change from baseline, Clinical Disease Activity Index (CDAI), Simplified Disease Index (SDAI), and Boolean remission.
2) Assess the safety and tolerability of BMS-986142.
3) Evaluate pre-dose concentration (Ctrough) of BMS-986142.
4) Assess the efficacy of BMS-986142+MTX to -MTX in reducing synovitis, osteitis, bone erosions, and cartilage loss in hands/wrists by MRI at Weeks 4, and 12 from baseline.

[redacted]

Study Design:

This is a 12 week randomized, double-blind (DB), placebo-controlled, dose-ranging study with adaptive design features based on an interim analysis. The study will initially have a Screening Period (with 2 screening visits for subjects that require DMARD washout) that will be followed by up to 12 weeks of DB treatment and then a follow-up period of 30 days. At the end of the DB study period, alternate treatments for RA should be discussed with subjects.

Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC).

Screening Period:

The standard duration of the Screening Period is up to 28 days, with two Screening Visits allowed for subjects who require washout. Should more time be needed, the duration of the Screening Period may be extended up to another week (total of five weeks) depending on current DMARDs washout, drug stabilization, MRI technical issues, and subject scheduling.

The start of the trial is defined as first visit for first subject screened. End of trial is defined as the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

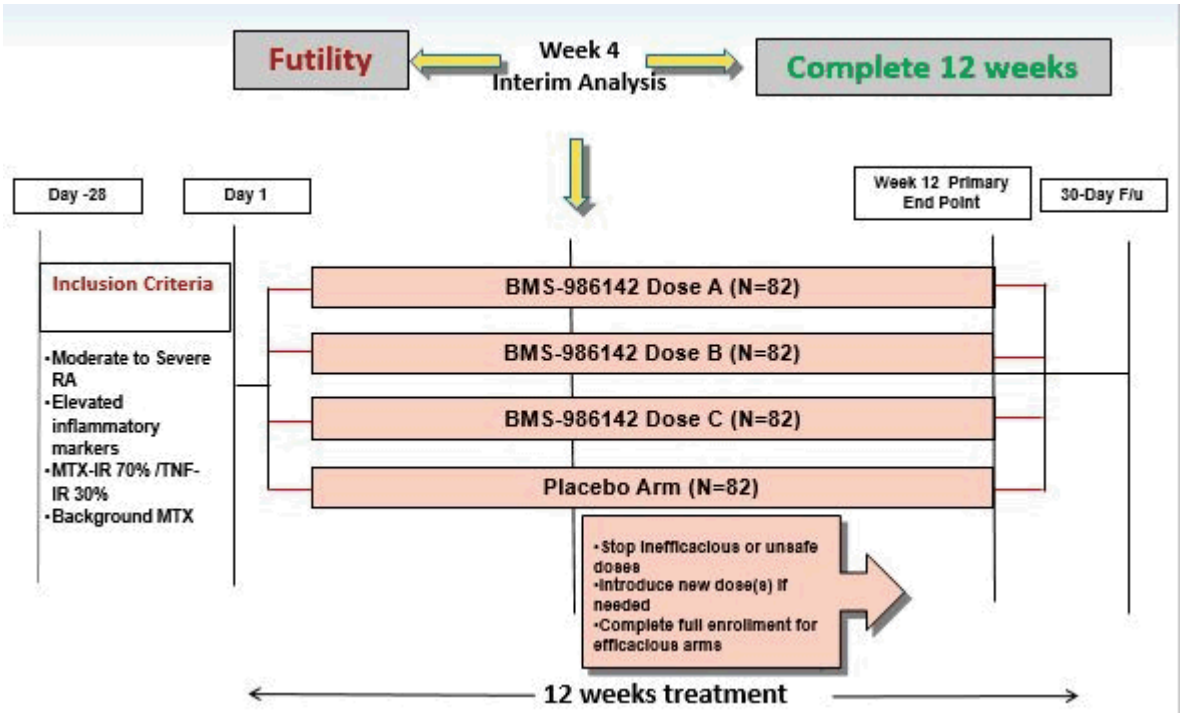
Study Summary: Subjects with moderate to severely active RA who have had an inadequate response to MTX with or without prior inadequate response to up to 2 TNF inhibitors will receive BMS-986142 or placebo daily for up to 12 weeks.

Upon meeting the Inclusion/Exclusion criteria, approximately 328 subjects will be randomized to 1 of the 4 treatment arms as shown in Figure 1 below.

Interim analyses (IA) of clinical and PK data up to 12 weeks will be performed after approximately 20 subjects per treatment arm reach Week 4 (complete 4 weeks of treatment or discontinue) and complete the specified assessments for efficacy (ie, DAS28-CRP), safety, and PK. The purpose of this interim analysis is to adapt study design including dose, and sample size.

Subjects who were enrolled before the IA is completed will continue the originally assigned dose level if they have received at least 1 treatment and the dose is considered safe.

Figure 1: **Study Design Schematic**



Duration of Study:

Approximately 4 weeks for screening, 12 weeks of treatment, and 4 weeks of safety follow-up. Total duration for the study is approximately 20 weeks for the study and safety follow-up.

Number of Subjects:

About 328 subjects will need to be randomized for the 4 arms of this study. The study will utilize an equal randomization scheme that will result in approximately 82 subjects in each arm. Should the IA analysis for futility and dose adaptation suggest that an additional one or 2 dose levels be added, then up to 82 additional subjects per arm may be randomized for up to 408 total potential subjects and randomization ratio will be adjusted accordingly.

At this time, BMS (the Sponsor) has elected to stop recruitment to the study on November 30th 2017. The company regularly reviews its ongoing studies within development programs to determine acceptability of continuation due to changing business needs, benefit-risk and/or the desire to accelerate decisions to advance a program. The Sponsor want(s) to emphasize that the stopping of enrollment in this study, prior to recruiting the planned number of subjects is not related to any adverse events (AEs) associated with the use of BMS-986142.

Study Population:

Men or women (not nursing or pregnant) ≥ 18 years of age with a diagnosis of RA by standard criteria at least 16 weeks prior to screening and who are inadequate responders to MTX with or without inadequate response to up to 2 TNF inhibitors.

Key Inclusion Criteria:
Note: Please see main protocol for complete listing of Inclusion/Exclusion criteria

1. Documented diagnosis of adult-onset RA as defined by standard criteria (ACR/EULAR [2010]) at least 16 weeks prior to screening.
2. ACR global functional status class of 1 to 3.
3. Subjects must be MTX inadequate responders based on investigator's judgment. Subjects must have been taking MTX for at least 3 months at a minimal weekly dose of 15 mg, and at a stable dose for 4 weeks prior to

randomization (Day 1). A lower dose of MTX is permitted, if there is verifiable documentation in the medical record that the subject could not receive or reach a weekly dose of 15 mg due to toxicity or intolerance and the dose is at least 10 mg MTX at the time of screening. In Japan, Korea, Taiwan, Canada, and any other country that requires the same rule, a minimum dose of 7.5 mg per week is permitted.

NOTE: Subjects using parenteral MTX for administration of their weekly dose may be included.

To minimize potential of MTX toxicity, all subjects should receive folic acid, folinic acid, or leucovorin according to manufacturer recommendations and local medical standard of care guidelines.

4. Subject failed or was intolerant to ≤ 2 TNF inhibitor(s), (failed, defined as the inability to achieve desired efficacy at an approved labeled dose for at least 12 weeks as determined by the investigator). Target population includes at least 70% of patients that had inadequate response to MTX and up to 30% of patients in addition to inadequate response to MTX need to have failure or intolerance to up to 2 TNF inhibitors.
5. Minimum of 6 swollen and 6 tender joints on a 66/68 joint count on Screening Visit #1 for those not requiring washout and on Screening Visit #2 for those requiring DMARD washout.
6. Evidence of swelling in at least 1 joint of hand or wrist by clinical examination on Screening Visit #1 for those not requiring washout and on Screening Visit #2 for those requiring washout.
7. Subjects must have a hsCRP of ≥ 0.8 mg/dL (8mg/L) [by central laboratory values] or an ESR ≥ 28 mm/hr on Screening Visit #1 for those not requiring washout of DMARDs and on Screening Visit #2 for those requiring washout.
8. 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). If re-enrolled, the subject must be re-consented and a new subject number obtained.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for BMS-986142		
Medication	**Potency**	**IP/Non-IP**
BMS-986142-01 Film Coated Tablet	50 mg	IP
Matching Film-Coated placebo for 50 mg BMS-986142-01 tablets	placebo	IP
BMS-986142-01 Film Coated Tablet	150 mg	IP
Matching Film Coated Placebo for 150 mg BMS-986142-01 tablets	placebo	IP
Methotrexate - background therapy subject taking on entry	See protocol Section 3.3.1, Inclusion Criteria 2c for possible doses	Non-IP

Study Assessments:

Efficacy will be assessed using various RA endpoints including ACR 20/50/70 scores, CDAI, SDAI and Boolean remission rates, DAS28-CRP, DAS28-ESR and MRI. Physical function will be assessed via HAQ-DI. Safety (through reporting of adverse events, clinical laboratory results, physical examination, which includes vital signs and ECGs), population pharmacokinetics, and exposure-response relationships will also be assessed.

Statistical Considerations:

Sample Size:
The sample size calculation is driven by the power to compare the proportion of subjects who achieve ACR70 response at Week 12 between each BMS-986142 dose arm and placebo arm. The target population consists of mixed subjects who are MTX-IR (≥ 70%) and TNF-IR (≤ 30%). For co-primary endpoint of ACR70 at Week 12, 82 subjects per arm will provide ~ 90% power to detect a treatment difference of 17% at the type I error rate of $\alpha = 0.05$ (two-sided), assuming the placebo response rate of 2.5%. The assumed treatment difference of 17% is about double of median difference observed from historical data on approved drugs across different mechanism of actions (MOAs).

For the other co-primary endpoint of ACR20 at Week 12, 82 subjects per arm will provide >99% power to detect a difference of 34% over placebo at the type I error rate of $\alpha = 0.05$ (two-sided), assuming placebo response rate of 33%. The assumed treatment difference of 34% and placebo response rate of 33% were based on the observed data from approved drugs across different MOAs.

An interim analysis (IA) will be conducted when about 20 subjects per treatment arm reach week 4 (complete 4 weeks of treatment or discontinue). Based on the totality of efficacy, safety, and PK data at Week 4 IA, the following adaptation(s) may be recommended:

- Stop inefficacious or unsafe dose(s)
- Introduce new dose(s) arms if needed and enroll up to about 82 subjects per new arm
- Complete full enrolment for all efficacious arms (up to about 82 subjects per arm)
- Stop the study enrollment if all dose arms are stopped for safety or futility.

The total sample size (range from 328 to 408 subjects) varies depending on actual enrollment rate, number of dropped dose arm(s) and number of newly added dose arm(s). The details of interim analysis and the criteria to adapt dose arm(s) and stop for futility are specified in the section 8.5.

Endpoints:

Co-Primary

- ACR20 response rate at Week 12
- ACR70 response rate at Week 12

Secondary

- Signs and Symptoms: ACR20/ACR50/70 over time
- Remission and change from baseline: DAS28-CRP, DAS-ESR, SDAI, CDAI, Boolean over time
- PK: Ctrough of BMS-986142
- Change in RAMRIS Scores of synovitis, osteitis, bone erosion and cartilage loss from baseline to Week 4 and Week 12

Statistical Analyses:

Efficacy analysis:

The co-primary endpoint ACR 20 and ACR70 response rate at Week 12 will be summarized for each treatment group using point estimate and 90% confidence intervals (CIs). Treatment difference of ACR 20/ACR70 response rate at Week 12 between each BMS-986142 arm versus placebo will be provided with point estimate and two-sided 95% CIs. The chi-square tests will be used to compare the ACR response rates at Week 12 between each of the active treatment arms and the placebo arm at type I error rate of 0.05. Within each treatment group, the statistical testing will be performed for ACR20 at level of 0.05 first. If it is statistically significant, then the statistical testing will be performed for ACR70. Otherwise, stop testing for this treatment group. All treatment groups will follow the

same testing procedure. All subjects who discontinue prematurely during the treatment period or receive rescue therapy will be counted as non-responder at subsequent visits.

Safety analysis:

All safety presentations will be based on the As-Treated population. Frequency distribution and individual listings of all adverse events, laboratory abnormalities and vital signs will be generated. Changes in clinical laboratory test results from baseline will be provided. No formal statistical tests on the treatment difference will be performed for any safety analyses.

Pharmacokinetic analysis:

Ctrough values will be descriptively summarized by treatment and study days.

Preliminary population PK and dose/exposure-response (ie, DAS28-CRP and selected safety endpoints) analysis will be conducted at the time when Week 4 interim analysis is conducted to assist new dose selection as described in interim analysis section (See section 8.5).

Once the study is completed, the concentration vs. time data from this study combined with PK data from additional studies will be used to further develop a population PK model. This model will be used to evaluate the effects of various covariates on the PK of BMS-986142. [redacted]

Week 4 Interim analysis (IA):

After about 20 subjects per treatment arm have completed at least 4 weeks of the treatment period or discontinued the treatment, an interim analysis will be conducted to assess the efficacy of the BMS-986142 dose arms and the overall safety. The interim analysis will use pre-specified efficacy, safety and PK endpoints. The results of the interim analysis will be reviewed by an unblinded sponsor team who is not involved in the study conduct and who will provide recommendations with regard to the adaptive design decisions to the blinded study team. The details of interim analysis and the criteria to adapt dose arm(s) and stop for futility are specified in the Section 8.5.

TABLE OF CONTENTS

104
105
106
109
110
111
112
113
117
120

[redacted]

1.2 Research Hypothesis

At least one of the dose levels of BMS-986142 administered daily is more effective than placebo on a background of MTX in achieving ACR20 and ACR70 response after 12 weeks of treatment in subjects with moderately-to severely active RA with an inadequate response to MTX with or without TNF inhibitors.

1.3 Objectives

1.3.1 Primary Objectives

To compare the efficacy of BMS-986142 versus placebo (PBO) on a background of MTX as assessed by ACR20 and ACR70 response rates at Week 12.

1.3.2 Secondary Objectives

- Assess additional efficacy outcomes of BMS-986142 at Week 12 and over 12 weeks of treatment as measured by ACR20, ACR50 and ACR70 response rates, DAS28-CRP change from baseline, DAS28-ESR change from baseline, Clinical Disease Activity Index (CDAI), Simplified Disease Index (SDAI), and Boolean remission.
- Assess the safety and tolerability of BMS-986142.
- Evaluate Ctrough of BMS-986142.
- Compare the efficacy of BMS-986142 + MTX to MTX alone in reducing synovitis, osteitis, bone erosion and cartilage loss in hands/wrists by MRI at Weeks 4, and 12, from baseline.

1.5 Overall Risk/Benefit Assessment

As described above, BMS-986142, a highly selective reversible BTK inhibitor, is an immunosuppressive compound currently developed for the treatment of autoimmune inflammatory diseases such as RA. The possible clinical spectrum of use is wide, potentially spanning many autoimmune diseases. The risk/benefit ratio will dictate whether BMS-986142 is a viable new therapy for autoimmune inflammatory disease. BMS-986142 has been administered to healthy normal volunteers for the first time in Study IM006001, and based on an interim analysis of preliminary data from both SAD and MAD parts of the study; it has been well tolerated with a favorable safety profile. The only safety signal that has been identified is a potential for mild, reversible, asymptomatic increases in hepatic transaminases (as described in section 1.4.4). In order to mitigate risks related to immunosuppression BMS will implement:

- Extended exclusion criteria for serious infections. Complete blood count (CBC) differential counts and measurement of serum Ig-levels (IgG, IgA and IgM) and pro inflammatory cytokines will be monitored throughout the study
- Prescreening for latent Tuberculosis as well as viral infections like hepatitis B and C
- Any vaccination with live vaccines will be prohibited during the study as well as within 30 days prior to the first dose of study medication.

In the case of BMS-986142, the preclinical safety studies have highlighted a few idiosyncratic adverse events, which were reversible and manifested at exposures higher than the ones that we have explored in the FIH study. The pancreatic manifestation in rats appeared to be species specific but to assure safety of subjects in the FIH study, monitoring of pancreatic enzymes, such as amylase and lipase, as well as fasting glucose was implemented. There was no safety signal detected with regard to the pancreas, and no dose related pattern in any abnormalities on interim analysis of data in any of these tests. Therefore, amylase and lipase will not be routinely monitored in this study. Fasting glucose level will be monitored as part of standard safety laboratory panel.

[redacted]

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

All potential serious breaches must be reported to 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:

- 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- 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.
- 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.
- Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a 12 week randomized, double-blind, placebo-controlled, dose-ranging study with adaptive design features based on an interim analysis. Subjects with moderate to severely active RA who have had an inadequate response to MTX or up to 2 TNF inhibitors will receive BMS-986142 or placebo daily for up to 12 weeks, followed by a 30-day follow-up period.

Four treatments will be administered: placebo, 100, 200, and 350 mg of BMS-986142 daily for 12 weeks. Based on the interim analysis, the doses may be adaptive.

Screening Period:

Upon obtaining the informed consent, a subject's eligibility will be determined. To be eligible, subjects must be considered an inadequate responder to MTX therapy or have experienced an inadequate response to MTX and inadequate response to at least one, but not more than two, TNF inhibitors by a treating physician or investigator, see inclusion criteria (see section 3.3.1.

Subjects receiving non-biologic DMARDs must discontinue all DMARDs except MTX prior to the beginning of BMS-986142 treatment as follows:

- DMARDs including but not limited to sulfasalazine, chloroquine, hydroxychloroquine azathioprine, minocycline, oral or parenteral gold, quinacrine, d-penicillamine, cyclosporine and sirolimus, and must be washed out for 4 weeks prior to screening visit #2.
- Leflunomide: subjects should not be on leflunomide at the time of screening.

For subjects who were recently treated with leflunomide prior to screening: Subjects will be allowed to enroll only if they are willing to undergo the following drug elimination procedure (recommended to achieve non-detectable plasma levels [less than 0.02 mg/L or 0.02 mcg/mL]

- Administer cholestyramine 8 grams 3 times daily for 11 days. (The 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly); then

- Verify plasma levels less than 0.02 mg/L (0.02 mcg/mL) by two separate tests at least 14 days apart. If plasma levels are higher than 0.02 mg/L, additional cholestyramine treatment should be considered.

For subjects who are no longer treated with leflunomide prior to screening for at least 10 weeks: Leflunomide plasma levels will be obtained at Screening; if the levels are non-detectable [less than 0.02 mg/L or 0.02 mcg/mL], the subject is eligible to enroll immediately if they have not been treated with leflunomide within 10 weeks prior to Screening. If there are still detectable leflunomide plasma levels, the subject may enroll only if they follow the above drug elimination procedure.

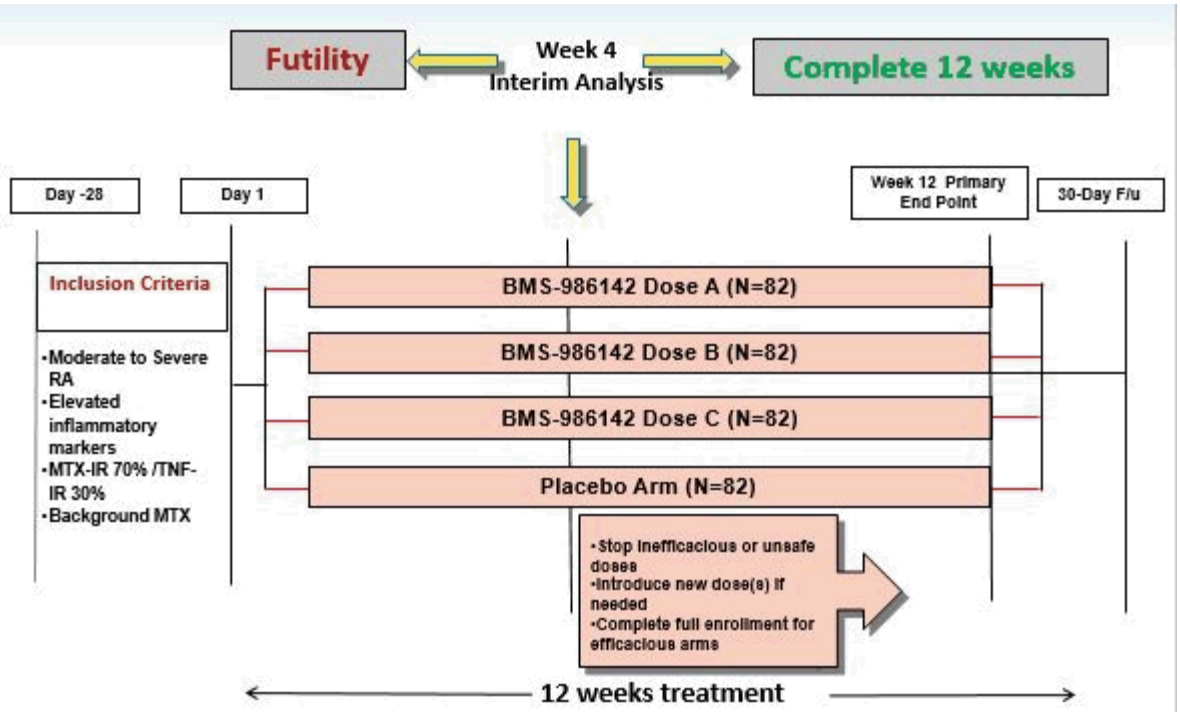
The standard duration of the Screening Period is up to 28 days, with two Screening Visits allowed for subjects who require washout.

Should more time be needed, the duration of the Screening Period may be extended up to another week (total of five weeks) depending on current DMARDs washout, drug stabilization, MRI technical issues, and subject scheduling.

Double-Blind Period:

Upon meeting the Inclusion/Exclusion criteria and completing the screening period, approximately 328 subjects will be randomized to 1 of the 4 treatment arms in an equal ratio as shown in the study schematic Figure 3.1-1 below.

Figure 3.1-1: Study Design Schematic



During this period, the dose of methotrexate, NSAIDs, and oral prednisone (or its equivalent) should remain stable. Intra-articular corticosteroid injections and intramuscular injections are not permitted. Analgesics are permitted with certain restrictions (see Section 3.3).

At the end of the DB period, alternate therapies for RA should be discussed with subjects.

The start of the trial is defined as first visit for first subject screened. End of trial is defined as the last visit or scheduled procedure shown in the Time & Events schedule for the last subject. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

Interim Analyses:

Interim Analyses (IA) of clinical and PK data will be performed after approximately 20 subjects per treatment arm reach Week 4 (complete 4 weeks of treatment or discontinue) and complete the specified assessments for efficacy (ie, DAS28-CRP), safety, and PK. Details of interim analyses are described in Section 8.5 (Interim analysis).

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.

3.3 Study Population

Men or women (not nursing or pregnant) ≥ 18 years of age with a diagnosis of RA by standard criteria at least 16 weeks prior to screening and who are inadequate responders to MTX or up to 2 TNF inhibitors.

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 form.

2. Target Population

a) Documented diagnosis of adult-onset RA as defined by standard criteria (ACR/EULAR [2010]) at least 16 weeks prior to screening. See Appendix 2.

b) ACR global functional status class of 1 to 3.

c) Subjects must be MTX inadequate responders based on investigator's judgment. Subjects must have been taking MTX for at least 3 months at a minimal weekly dose of 15 mg, and at a stable dose for 4 weeks prior to randomization (Day 1). A lower dose of MTX is permitted, if there is verifiable documentation in the medical record that the subject could not receive or reach a weekly dose of 15 mg due to toxicity or intolerance and the dose is at least 10 mg MTX at the time of screening. In Japan, Korea, Taiwan, Canada, and any other country that requires the same rule, a minimum dose of 7.5 mg per week is permitted.

NOTE: Subjects using parenteral MTX for administration of their weekly dose may be included.

To minimize potential of MTX toxicity, all subjects should receive folic acid, folinic acid, or leucovorin according to manufacturer recommendations and local medical standard of care guidelines.

d) Subject failed or was intolerant to ≤ 2 TNF inhibitor(s), (failed, defined as the inability to achieve desired efficacy at an approved labeled dose for at least 12 weeks as determined by the investigator). Target population includes least 70% of patients that had inadequate response to MTX and up to 30% of patients in addition to inadequate response to MTX need to have failure or intolerance to up to 2 TNF inhibitors.

Note: If subject is an MTX-IR only, then subject only needs to fulfill inclusion 2c. If subject is both MTX-IR and has failed up to 2 TNF inhibitors, then both inclusion 2c and 2d need to be fulfilled.

e) Minimum of 6 swollen and 6 tender joints on a 66/68 joint count on Screening Visit #1 for those not requiring washout and on Screening Visit #2 for those requiring DMARD washout.

f) Evidence of swelling in at least 1 joint of hand or wrist by clinical examination on Screening Visit #1 for those not requiring washout and on Screening Visit #2 for those requiring washout.

g) Subjects must have an hsCRP of ≥ 0.8 mg/dL (8mg/L) [by central laboratory values or by local laboratory values in special circumstances as approved by MM] or an ESR

≥ 28 mm/hr on Screening Visit #1 for those not requiring washout of DMARDs and on Screening Visit #2 for those requiring washout.

h) 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). If re-enrolled, the subject must be re-consented and a new subject number obtained.

3. Age and Reproductive Status

a) Males and Females, ages ≥ 18 years old, inclusive.

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

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986142 plus 90 days post-treatment completion or longer if required based on country specific guidelines for MTX use (please refer to MTX product label for details on your country specific guidelines).

e) Male subjects must be willing to refrain from sperm donation during the entire study and for 5 half-lives of study drug plus 90 days (duration of sperm turnover) for a total of 93 days after dosing has been completed or longer if required based on country specific guidelines for MTX use (please refer to MTX product label for details on your country specific guidelines). Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with BMS-986142 plus 5 half-lives of BMS-986142 (~3 days) plus 90 days (duration of sperm turnover) for a total of 93 days post-treatment completion or longer if required based on country specific guidelines for MTX use (please refer to MTX product label for details on your country specific guidelines).

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

g) Women/men who are not using hormonal contraceptives (oral, parenteral or implantable).

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.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects are expected to use one of the highly effective methods of contraception listed below. Per country guidelines, a less effective method of contraception may be required to be added to the one highly effective method based on background use of MTX that is a known teratogen. Male subjects must inform their female

partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

- Nonhormonal IUDs
- Bilateral tubal occlusion
- Vasectomised partner with documented azoospermia 90 days after procedure
  - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Complete abstinence
  - Complete abstinence is defined as the complete avoidance of heterosexual intercourse.
  - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of study and for the duration of time as specified above under Duration of Mandatory Contraception.
  - It is not necessary to use any other method of contraception when complete abstinence is elected.
  - Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.3.
  - Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
  - The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Male or female condom with or without spermicide*

HORMONE BASED METHODS OF CONTRACEPTION

- 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.

* A male and a female condom must not be used together.

BIRTH CONTROL METHODS WHICH ARE CONSIDERED UNACCEPTABLE IN CLINICAL TRIALS

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicide only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception.

CONTRACEPTIVE RECOMMENDATIONS FOR MALE SUBJECTS AND THEIR WOCBP PARTNERS

Male subjects should always inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with:
   i) documented juvenile rheumatoid arthritis
   ii) Felty's syndrome

b) Biologic treatments other than TNF inhibitors.

c) Subjects who are currently receiving immunomodulators other than methotrexate.

d) Subjects who have been treated with Intramuscular (IM) or Intra-articular glucocorticosteroids within 4 weeks of randomization (Day 1).

   Oral steroid use is permitted, but only if ≤ 10 mg/day of prednisone (or prednisone equivalents)

2. Medical History and Concurrent Diseases

a) Subjects at risk for tuberculosis (TB). Specifically, subjects with:
   i) Current clinical, radiographic or laboratory evidence of active TB.
   ii) A history of active TB within the last 3 years even if it was treated.
   iii) A history of active TB greater than 3 years ago unless there is documentation that the prior anti-TB treatment was appropriate in duration and type.
   iv) Therapy for Latent TB which has not been completed as per local country guidelines.
   v) This exclusion criteria was a duplicate of Exclusion 2b and was removed in Amendment 5, bullet is being left to maintain numbering.

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

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

d) Subjects with herpes zoster symptoms that resolved less than 60 days prior to screening visit (enrollment).

e) Subjects with evidence (as assessed by the investigator) of active or latent bacterial or viral infection at the time of potential enrollment, including subjects with history or evidence of Hepatitis B or Hepatitis C, history or evidence of Human Immunodeficiency Virus (HIV) infection.

f) Subjects with autoimmune disease other than RA (eg, Systemic lupus erythematosus [SLE], multiple sclerosis [MS], vasculitis).

g) Significant concurrent medical condition at the time of screening or baseline visit, including, but not limited to, the following:

- Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary or local active infection/infectious illness) that, in the Investigator's judgment will substantially increase the risk to the subject if he or she participates in the study.
- Cancer or history of cancer or lymphoproliferative disease within the previous 5 years (other than resected cutaneous basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence).
- Class III or IV congestive heart failure as defined by the New York Heart Association
- Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and/or any history of significant cerebrovascular disease within 24 weeks before screening
- Any other concomitant medical conditions that, in the opinion of the investigator, might place the subject at unacceptable risk for participation in this study.

h) Subjects with surgery on more than 5 joints.

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

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

k) Subjects who have received treatment with an investigational drug within 28 days or less than 5 terminal half-lives of elimination (whichever is longer) of randomization (Day 1).

l) Subjects who have been administered live vaccines within 30 days prior to dosing.

m) Subjects with the inability to have a MRI performed; reasons include the following: magnetizable metallic parts/devices (including cardiac pacemaker) on and in the body, severe claustrophobia, body size incompatible with the scanner, severe renal insufficiency (ie, GFR $\leq$ 30 mL/min/1.73m^2). See Section 3.3.4 for MRI contraindications.

3. Physical and Laboratory Test Findings

a) Subjects with positive tests for current or previous Hepatitis B infection as indicated by screening using Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (anti-HBs) and Hepatitis B core antibody (anti-HBc). Subjects with positive HBsAg or anti-HBc antibody are excluded from the study (See Appendix 1). Subjects with negative Hepatitis B surface antigen but with high risks for latent HBV infections including subjects with known family history of HBV infection, HBV carrier, personal medical history of hepatitis or blood transfusion history must also be tested for quantitative HBV DNA. Subjects with positive findings are excluded from the study.

b) Hepatitis C antibody-positive subjects who are also HCV positive by confirmatory testing such as PCR.

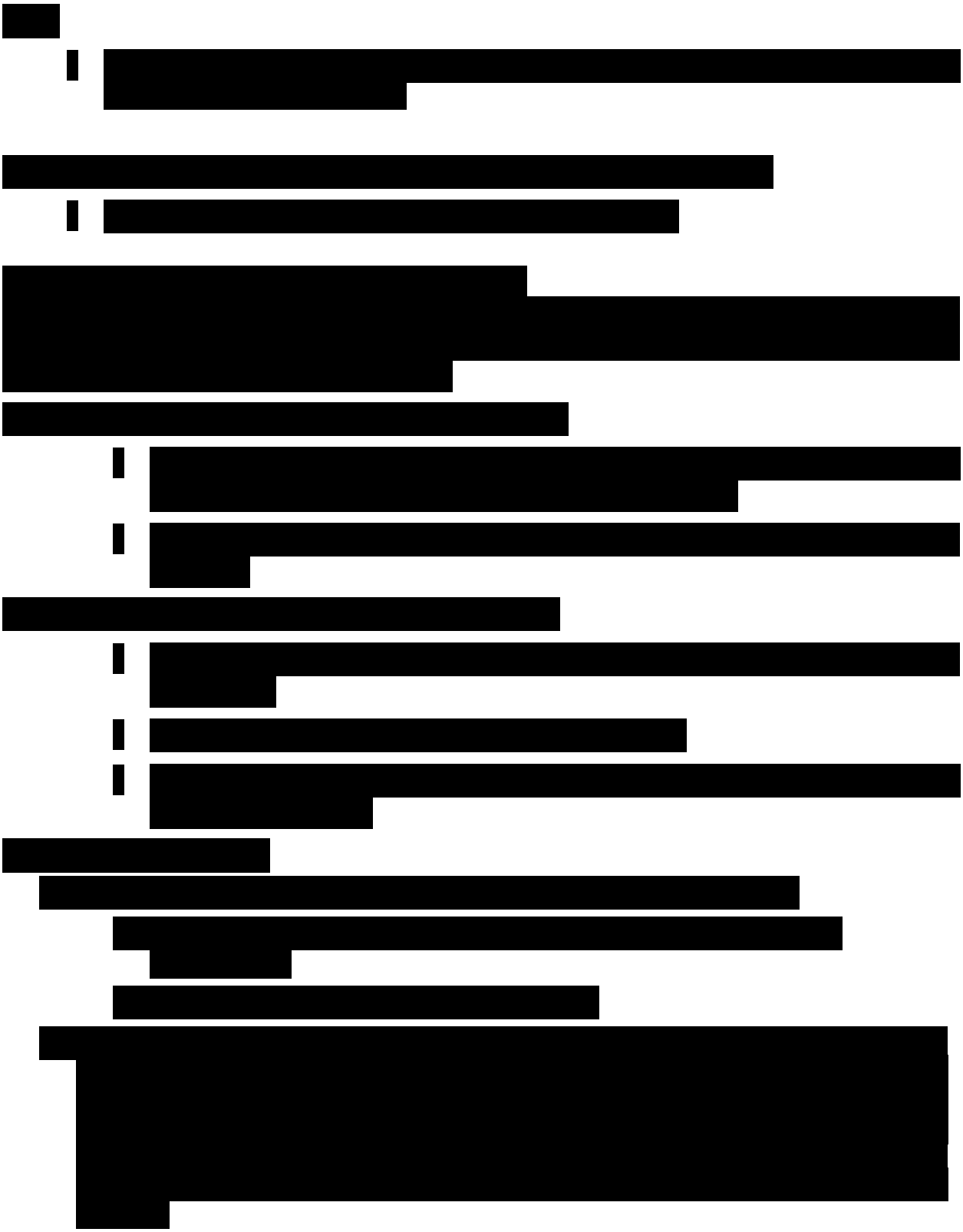
c) Have any clinically significant laboratory abnormalities including but not limited to:
   i) Hepatic
      (1) ALT ≥ 1.5 x ULN (upper limit of normal)
      (2) AST ≥ 1.5 x ULN
      (3) Total bilirubin ≥ 1.5 x ULN
   ii) Hematology
      (1) Hemoglobin < 9 g/dL
      (2) Absolute neutrophil count < 1,000/mm3 (1.0 x 10^9/L)
      (3) Platelets < 100,000/mm3 (100 x 10^9/L)

d) Any other significant laboratory abnormalities or ECG findings that, in the opinion of the Investigator, might place the subject at unacceptable risk for participation in this study (please discuss with Medical Monitor if there are any questions in regards to inclusions/exclusion criteria)

4. Allergies and Adverse Drug Reaction

a) Subjects who have a known allergy to gadolinium or contrast agents.

[redacted]



[redacted]

7. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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

c) Subjects who are illiterate. This study requires the use of an ePRO device which requires the subject to complete responses to the questions. Due to potential bias the questions cannot be read to the subjects.

3.3.3 Women of Childbearing Potential

A 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.

- 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. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal

3.3.4 MRI Contraindications

The radiologist at the site's MRI facility is responsible for determining if a subject is contraindicated from having this procedure. If the subject is contraindicated, the subject must be dropped from the study. The following is a list of some common conditions that may preclude the subject from having MRI of the hands or wrists. However, this should not be used as a substitute for local clinical standards of care. The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator, and the standard set by the local Ethics Committee:

1. Subjects who have a history of claustrophobia.
2. Subjects who have a physical limitation related to fitting in the bore of the magnet (ie, body weight in excess of 250 pounds or 113.4 kilograms).
3. Subjects with tattooed eye-liner or tattoos directly on the hand or wrist (area to be imaged).
4. Subjects who have a history of allergic reaction to contrast agents.
5. Subjects who had exposure to a radiological contrast agent within the 72 hours prior to the MRI examination.
6. Subjects who have a fused joint in the wrist or joint replacements in the hand or wrist that are being evaluated by the MRI examination.
7. Subjects with a pacemaker, epicardial pacemaker wires, MRI-incompatible cardiac valve prostheses, MRI-incompatible vascular clips less than two-months old, or MRI-incompatible aneurysm clips of any age.
8. Subjects with MRI-incompatible cochlear implants.
9. Subjects with spinal nerve stimulators.
10. Subjects with an infusion pump.
11. Subjects with metallic fragments in the eyes/orbits or in the vicinity of the brain or major neurovascular structures of the body, subjects with an employment history which involves exposure to welding, or subjects who have shrapnel any place in their body.
12. Subjects with severe renal insufficiency (ie, glomerular filtration rate or GFR < 30mL/min/1.73m2), are excluded from the study as they are at increased risk of Nephrogenic Systemic Fibrosis following administration of gadolinium-based MRI contrast agents. Subjects with GFR 30 - 60mL/min/1.73m2 should be followed carefully following the administration of gadolinium-based MRI contrast agents.

3.4.2 Other Restrictions and Precautions

The prescribing label of all concomitant medications used as subject's background therapy should be evaluated by the investigator for continued administration during the subject's participation in this study (eg, known toxicities, drug-drug interactions).
Lists of concomitant medication requiring precautions and restrictions due to the potential drug-drug interactions are presented in Section 3.3.

3.4.2.1 Immunizations

Live vaccines should not be administered to subjects during the study (including the screening period). Inactivated vaccines (eg, influenza) are allowed however the efficacy may be attenuated. No data are available on the therapeutic effect of vaccinations in subjects receiving a BTK inhibitor. A subject who discontinues from the study should not receive a live vaccine injection until 30 days after discontinuing study medication.

3.4.2.2 Infectious Complications

Subjects who develop significant infectious complications during the study should be treated appropriately and have study medication withheld, and restarted only when clinically resolved and the investigator considers it appropriate.

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

- Male subjects must discontinue treatment if their female partners become pregnant during the trial. After discontinuation, male subjects are required to continue using a method of contraception that prevents the exposure of the fetus to the male's semen (ie, male condom, female condom, complete abstinence, etc.) for the entire length of the pregnancy or 93 days, whichever is less
- Subject's request to stop study treatment or withdrawal of informed consent
- Investigator judgement
- 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
- 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
- Unblinding a subject for any reason (emergency or non-emergency)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

In this study, ACR20 and ACR70 and other efficacy measures are key endpoints of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

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

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

Table 4-1: Study Drugs for BMS-986142 Blinded Treatment

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-986142-01 Film Coated Tablet	50 mg	IP	Blinded Label	Plain, yellow, round, film coated tablet HDPE Bottle	Store 2 to 8°C ; Store in a tightly closed container
Placebo for BMS-986142-01 Film Coated Tablet, 50 mg	Placebo	IP	Blinded Label	Plain, yellow, round, film coated tablet HDPE Bottle	Store 2 to 8°C ; Store in a tightly closed container
BMS-986142-01 Film Coated Tablet	150 mg	IP	Blinded Label	Plain, yellow, oval film coated tablet HDPE Bottle	Store 2 to 8°C ; Store in a tightly closed container
Placebo for BMS-986142-01 Film Coated Tablet, 150mg	Placebo	IP	Blinded Label	Plain, yellow, oval film coated tablet HDPE Bottle	Store 2 to 8°C ; Store in a tightly closed container

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 Product(s) (also described in Table 4-1) are:

- BMS-986142, 50 mg (round), 35 tablets/bottle
- BMS-986142, 150 mg (oval), 35 tablets/bottle
- Matching Placebo (round) for 50 mg BMS-986142, 35 tablets/bottle
- Matching Placebo (oval) for 150 mg BMS-986142, 35 tablets/bottle

4.2 Non-investigational Product

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

In this protocol, non-investigational product(s) include, but are not limited to:

- Methotrexate (subject must be on this DMARD before study screening to be eligible for study)
- Prednisone or other Glucocorticoids
- NSAIDs and analgesics.

The Sponsor will not be providing these medications since they are part of subject's standard of care.

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).

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing information for BMS-986142.

4.3.1 Administration Window

If abnormal laboratory test results or clinical adverse events indicate toxicity that, in the judgment of the investigator, could place the subjects at risk, study medication administration should be skipped and the investigator should notify the BMS Study Medical Monitor. Subjects may receive further study medication only if resolution of the adverse event or abnormal laboratory finding is documented or, at a minimum, the subject's status returns to what it was at baseline.

4.4 Method of Assigning Subject Identification

At the time of the screening visit, immediately after written informed consent is obtained and before performing any study-related procedures, the investigator or coordinator will call into the Interactive Voice Response System (IVRS or IWRS) designated by BMS for assignment of a 5-digit subject number that will be unique across all sites. Enrolled subjects, including those not dosed, will be assigned unique sequential subject numbers by the IVRS system starting with 00001, 00002, 00003, etc. for identification throughout the study. This subject number must not be reused for any other participant in the study.

After completion of all screening evaluations, on Day 1, all eligible subjects will be randomly assigned to 1 of 4 treatment arms (BMS-986142, 100 mg; BMS-986142, 200 mg; BMS-986142, 350 mg; and Placebo) in an equal ratio. To randomize a subject, a phone call will be placed into the randomization option of the IVRS in order to obtain a subject's randomized treatment assignment. Randomization will be assigned in the order in which subjects qualify for treatment, not in the order of study enrollment. The IVRS will be available 24-hours a day, 7 days a week, via a toll-free number. Randomization will be stratified by prior treatment status (MTX-IR vs TNF-IR) and geographic region.

If a subject meets re-screening criteria highlighted in see Section 3.3.1, they must be re-consented, the investigator or coordinator will call into the Interactive Voice Response System (IVRS or IWRS) designated by BMS for assignment of a 5-digit subject number that will be unique across all sites.

Specific instructions (including an enrollment/randomization worksheet) for the central enrollment and randomization procedure using an IVRS will be provided to the site.

Randomized schedules will be generated and kept by the Randomization Group within Drug Supply Management of Bristol-Myers Squibb. The randomization ratio may be adjusted if any dose arm will be discontinued and/or new dose arm will be added based on Week 4 interim analysis.

At all study visits when study drug is dispensed, each subject will be assigned specific container numbers by the IVRS. Container numbers will be assigned non-sequentially and will correspond to the numbers printed on the containers and bottles containing study drug, and will be recorded on the appropriate eCRF.

4.5 Selection and Timing of Dose for Each Subject

Selection and timing of doses are described for each period below.

4.5.1 Double Blind Period

All drug dosing should occur after all study-related assessments, including blood draws, are completed.

After randomization, study drug will be dispensed according to the assignment by the IVRS system. Doses of BMS-986142 at 100 mg, 200 mg, 350 mg or matching placebo are to be administered orally q24h (one time/day) with water and may be taken with or without food. Four tablets, one from each bottle, will be taken, all at the same time, once/day every day. **On Day 1, and at Week 2, 4, 8, and 12 study drug will be administered in the morning at the study site and after blood samples have been collected.** However, at other visits, drug should be taken at approximately the same time each day.

Study drug is blinded and is supplied in bottles. Each subject will be dispensed a set of four (4) bottles at each study visit. Each bottle contains 35 tablets of blinded study drug. The 5 additional tablets in each bottle allow for the ± 5 day window between each visit in the double-blind phase of the study. Study drug bottles that were dispensed to the subject must be brought back to the study site by the subject at Weeks 2, 4, 8, and 12 during the double-blind period.

4.6 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

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

For this study, the method of unblinding for emergency purposes is IVRS.

For information on how to unblind in case of an emergency, consult the IVRS manual

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

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

The Bioanalytical Sciences department or its designate will be unblinded to the randomized treatment assignments in order to minimize unnecessary analysis of samples from control group subjects.

To implement the adaptive design that is planned in advance, an interim analysis will be conducted prior to the formal locking of the study database. In order to allow for a high quality and/or validated data analysis and a timely analysis of data, the unblinded team may consist of up to two people from each relevant function role within BMS.

- Global Biometric Sciences - Up to 2 statisticians and 2 programmers
- Clinical Pharmacology and Pharmacometrics - Up to 2 pharmacometric and pharmacokinetic scientists and 2 pharmacometric programmers
- [redacted]
- Bioinformatics -Up to 2 bioinformaticians

This configuration ensures that the unblinded team has the resources to independently conduct its own analyses. The study team does not have access to any unblinded data and is not involved in the review or discussion of unblinded data.

4.7 Treatment Compliance

Treatment compliance in this study will be determined by counts of returned tablets of study drug and information provided by questioning the subject.

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.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Flow Chart for Protocol IM006016 - Screening Period[a]

Procedure	Screening Visit #1	Screening Visit #2[b]	Notes
Eligibility Assessments			
Informed Consent	X		
Inclusion/Exclusion Criteria	X	X	
Medical History	X		
Enroll subjects (contact Central Randomization System)	X		Contact IVRS for subject number after signing consent. If subject does not meet eligibility criteria, contact IVRS to screen fail subject.
Safety Assessments			
Physical Examination	X	X	
ECG	X		
Chest X-ray (CXR)	X		Required only if not performed within 6 months of signing informed consent or if documentation of previous CXR is not on file.
Height and Weight	X		

Table 5.1-1: Flow Chart for Protocol IM006016 - Screening Period[a]			
Procedure	**Screening Visit #1**	**Screening Visit #2[b]**	**Notes**
Vital Signs	X	X	
TB screening test(s)	X		See Section 5.3.2 for important details
Adverse Events Assessment	X	X	
HBsAg, HBcAb, HbsAb	X		May also include HBV DNA testing where required locally
Hepatitis C antibody	X		If positive, reflex to HCV confirmation such as PCR
HIV testing	X		Performed locally; at discretion of investigator
Laboratory Assessments			
Hematology (CBC with differential)	X	X	
Chemistry panel	X	X	Must include liver function testing; see Section 5.3.5 for details. For screening, PI discretion if fasting glucose is needed. Must include leflunomide level if appropriate.
Estimated Glomerular Filtration Rate (eGFR)	X	X	As performed by Modification of Diet in Renal Disease (MDRD) Study equation
Urinalysis	X		
Urine pregnancy test	X	X	WOCBP only; See Section 3.3.3
ESR (performed locally)	X	X	Unblinded result that may be communicated to study staff to determine eligibility
hsCRP	X	X	
Assessments			
Tender (68)/swollen (66) Joint Count	X	X	6 Swollen/Tender joints required at this visit for eligibility
ACR Functional Status assessment	X		
Efficacy Assessment			
MRI of clinically dominant hand/wrist	X		Perform approximately 14 days prior to randomization to allow review by central imaging lab and perform repeat if required See Section 5.4.4.1

a Screening is within 28 days if possible, to a maximum of 5 weeks if necessary which includes both SV1 and SV2; see Section 3.1 for information

b Screening Visit #2 is for subjects that are required to undergo washout for hydroxychloroquine/chloroquine and/or sulfasalazine

Table 5.1-2: Flow Chart for Protocol IM006016 - Double-Blinded Treatment Period[a]							
Subjects who discontinue at any time during the Treatment Period must complete the Early Termination (ET) Visit assessments							
Procedure	**Day 1**	**Wk 2** (approx. D 15)	**Wk 4** (approx. D 28)	**Wk 8** (approx. D 56)	**Wk 12 or ET** (approx. D 84)	**30 day FU Visit** (approx. Day 114 **)**	**Notes**
Safety Assessments							
Physical Exam	X				X	X	
Height and Weight	X				X	X	
ECG	X		X		X	X	Not required if early termination (ET) visit
Vital Signs	X	X	X	X	X	X	See Section 5.3.1 for details
Adverse Events Assessment	X	X	X	X	X	X	
Laboratory Assessments							
Hematology (CBC with differential)	X	X	X	X	X	X	
Chemistry panel	X	X	X	X	X	X	**Must include liver function testing**; see Section 5.3.5 for details. For double-blinded period, fasting glucose is required.
Estimated Glomerular Filtration Rate (eGFR) - AUDIT	X	X	X	X	X	X	As performed by Modification of Diet in Renal Disease (MDRD) Study equation
Fasting lipid panel	X			X	X	X	At least 10 hour fasting prior to collection of sample
IgM, IgA, and IgG	X		X		X	X	
Urinalysis	X				X	X	
Rheumatoid Factor	X				X	X	
Anti-CCP2	X		X		X	X	

Table 5.1-2: Flow Chart for Protocol IM006016 - Double-Blinded Treatment Period[a]

Subjects who discontinue at any time during the Treatment Period must complete the Early Termination (ET) Visit assessments

Procedure	**Day 1**	**Wk 2** (approx. D 15)	**Wk 4** (approx. D 28)	**Wk 8** (approx. D 56)	**Wk 12 or ET** (approx. D 84)	**30 day FU Visit** (approx. Day 114 **)**	**Notes**
ANA	X				X	X	
Anti- Ro (SS-A) and Anti-La (SS-B)	X				X	X	
Urine pregnancy test	X		X	X	X	X	WOCBP only; results confirmed prior to administration of study drug. See Section 3.3.3
ESR (performed locally)	X	X	X	X	X	X	Performed locally. Every effort should be made to ensure the person analyzing the ESR results is not involved in the efficacy assessments (see Section 5.4)
hsCRP	X	X	X	X	X	X	
Pharmacokinetics	X	X	X	X	X		See Section 5.5.1 for details
Efficacy Assessments							
Tender (68)/ Swollen (66) Joint Count	X	X	X	X	X	X	Must have at least 6 swollen/tender joints prior to randomization
Subject Assessment of Pain	X	X	X	X	X	X	QoL assessments; see Section 5.8
Subject's Global Assessment of Disease Activity	X	X	X	X	X	X	
Physician's Global Assessment of Disease Activity	X	X	X	X	X	X	
Physical Function (HAQ-DI)	X	X	X	X	X	X	
Fatigue (VAS)	X				X	X	
SF-36	X				X	X	

Table 5.1-2: Flow Chart for Protocol IM006016 - Double-Blinded Treatment Period[a]							
Subjects who discontinue at any time during the Treatment Period must complete the Early Termination (ET) Visit assessments							
Procedure	**Day 1**	**Wk 2** (approx. D 15)	**Wk 4** (approx. D 28)	**Wk 8** (approx. D 56)	**Wk 12 or ET** (approx. D 84)	**30 day FU Visit** (approx. Day 114 **)**	**Notes**
Stiffness	X				X	X	
Bristol Rheumatoid Arthritis Multidimensional Questionnaire (BRAF-MDQ)	X				X	X	
MRI (same hand/wrist imaged at screening)			X		X		**Subjects who terminate the study early require an MRI at the early termination (ET) visit only if ET < 4 weeks or > 8 weeks from date of randomization and should have their early termination (ET) MRI NO MORE than 7 days from their Early Termination (ET) Visit** See Section 5.4.4.1
Study Drug Administration							
Randomize through IVRS system	X						
Dosing of Study Medication	Daily						On Day 1, subjects will be observed for 2 hours after dosing administration
Dispense Study Medication	X		X	X			
Reconciliation of Study Medication		X	X	X	X	X	

[a] For the Double-Blind part of the study, visits have windows of ±5 days around the calculated visit date

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in 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 Procedural Outline 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.

5.2 Study Materials

All investigator sites within this study will use an Electronic Data Capture (EDC) tool to submit study data to BMS. Electronic Case Reports Forms and drug logs will be provided by BMS. An electronic device (ePRO) will be provided to complete questionnaires and investigator/subject assessments. Urine pregnancy test kits, laboratory specimen collection kits and instructions for collection will be provided by the central laboratory vendor. IVRS worksheets and instruction manuals will be provided by the IVRS vendor. Sites will be provided with the Common Terminology Criteria for Adverse Event grading (CTCAE). Link is below:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Subjects will also be provided with cooler bags and gel packs for transporting study drug as it needs to be kept refrigerated.

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked basic cardiac life support (BCLS)] cart will be immediately available on the premises. The site will have urine collection containers, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C or below), as well as containers and dry ice for shipment and storage of blood and urine samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will source marketed product from a single commercial lot.

BMS will provide a BMS-approved protocol and any amendments or administrative letters (if required), and investigator brochure. Case report forms (electronic or hard copy) will be provided by BMS. [redacted]

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 discontinue will complete the Week 12/Early Termination (ET) Visit assessments for the corresponding period. Subjects who complete the study will complete the 30-day follow-up visit assessments. The Early Termination Visit should be as soon as possible after the last dose of study medication (investigational product) and prior to the subject receiving a prohibited concomitant medication.

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

Every effort must be made to ensure the same evaluator will complete the assessments for each subject at all visits.

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 your institutional or medical practice 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 the sponsor. Safety assessments include the following:

- Adverse Events
- Safety laboratory values
- Physical examination
- Vital signs
- ECG

5.3.1 Adverse Event and Vital Sign Assessments

At Day 1 of the double-blind (DB) period, vital signs collection (blood pressure, heart rate, respiration rate, temperature) will occur prior to first dose of study medication is given from the assigned kit. At subsequent visits, vital sign collection will be completed prior to the administration of the dose of assigned study drug.

Subjects will be observed at the site for a minimum of 2 hours after receiving their first dose of study medication (tablets) on Day 1 of the DB Period The observation period should be extended if clinically indicated.

Any adverse events that occur will be reported on the appropriate eCRF (see Section 6.1.1.)

All subjects who receive a dose of investigational product will be evaluated for safety testing. Safety outcomes include adverse events (AEs), clinically significant changes in vital signs, laboratory test abnormalities, and clinical tolerability of the investigational product. The Investigator will determine the severity of each adverse event as mild, moderate, severe, or very

severe. Laboratory findings which the investigator feels are clinically relevant should be recorded as adverse events. In addition, the investigator will determine the relationship of the AE to the administration of the investigational product.

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

5.3.2 Tuberculosis Screening

Detailed medical and social history should be obtained to assess subject's risk for tuberculosis. Chest x-ray, physical examination, and medical history should be used to assess for active tuberculosis (TB).

Acceptable methods of testing for active or latent tuberculosis include tuberculin skin testing or Interferon release assays such as ELISpot or QuantiFERON® testing for tuberculosis. A tuberculin skin test will be performed and interpreted according to local country health authorities and/or medical society guidelines (ie, that provide recommendations for tuberculin skin testing for subjects who are to receive biologics, who are immunosuppressed, who have a prior history of BCG vaccination, or have a prior positive test).[17,18,19,20,21] Tuberculin skin testing and interferon release assays are not contraindicated for persons who have been vaccinated with BCG.

After tuberculin skin testing is performed at screening, the 48 to 72 hour reading must be completed prior to administration of study drug. Negative test results for Interferon release assays should also be confirmed prior to administration of study drug.

If Interferon release assay results are indeterminate, one of two options for tuberculosis testing should be performed as follows: 1) The Interferon release assay test should be repeated. The second Interferon release assay result will replace the first test result. 2) Tuberculin skin testing should be performed as an alternative method of screening. If the second Interferon release assay test result is also indeterminate, tuberculin skin testing should be performed and the subject should not be enrolled into the study until a negative tuberculin skin test is documented.

5.3.3 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be recorded at the times noted in the Time and Events Table 5.1-1 and Table 5.1-2)

5.3.4 Physical Examination

A complete medical history will be obtained at the screening visit.

Complete and/or interim physical examinations may be performed by a Doctor of Medicine (MD), Doctor of Osteopathy (DO), Physician's Assistant (PA), or Nurse Practitioner (NP). While the interim physical examination may not be as comprehensive as the initial full examination, key aspects of the interim examination should evaluate important body systems as

clinically indicated. These body systems include at a minimum, the heart, lungs, abdomen, and skin. Evaluation of lymph nodes, liver, spleen, breast and other body systems is at the discretion of the examiner. An interim physical examination may note any changes in the subject's condition (body systems) since the last assessment and does not preclude examination of any of the body systems as clinically indicated.

Every effort should be made to ensure the same evaluator will complete the physical examination for each subject at specified visits throughout the study. Documentation of who performed the examination is to be recorded in source notes.

5.3.5 Laboratory Test Assessments

A central/local laboratory will perform the analyses and will provide reference ranges for these tests.

Detailed instructions on the collection, processing, and shipping of all blood and urine samples will be provided to the investigator in a separate manual at or before the time of study initiation.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

Serum Chemistry

Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Lactate dehydrogenase (LDH)
Creatinine
Blood Urea Nitrogen (BUN)
Uric acid
Fasting glucose (for screening, PI discretion if fasting is needed. For double-blinded period, fasting is required)
Total Protein
Albumin
Sodium
Potassium
Chloride
Calcium
Phosphorus
Magnesium
Creatine kinase
Liver function testing

Lipid Panel (includes fasting lipids)

ESR (local lab)

hsCRP

Urinalysis

Protein
Glucose

Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick

Serology

Serum for hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody
Auto-immune serology: ANA, Anti-Ro, Anti-La, Anti CCP2, Rheumatoid Factor
Immunoglobulin levels: IgM, IgA and IgG.
HIV testing (investigator discretion; local lab)

Other Analyses

Pregnancy test (WOCBP only: screening, predose, discharge).
Follicle stimulating hormone (FSH) (screening only for women only)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (see Section 6.1.1).

5.4 Efficacy Assessments

Efficacy assessments are described in the following sections. See Appendix 3 for detailed definitions.

5.4.1 Primary Efficacy Assessment

- ACR20 response rate at Week 12
- ACR70 response rate at Week 12

5.4.2 Secondary Efficacy Assessments

- Signs and Symptoms: ACR20/ACR50/70 over time
- Remission and change from baseline: DAS28-CRP, DAS-ESR, SDAI, CDAI, Boolean over time
- PK: predose concentration (Ctrough) of BMS-986142 at time-points specified in Table 5.5.1-1
- MRI assessment of change from baseline in synovitis, osteitis (bone marrow edema), bone erosion and cartilage loss (joint space narrowing) in hands/wrists at timepoints specified in Table 5.1-2

5.4.4 Imaging Assessments

Any incidental findings of potential clinical relevance on chest x-ray or any additional imaging performed that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment. Images will be submitted to imaging core lab for central analysis. Assessment of hand and wrist MRI by Investigator is not expected.

5.4.4.1 MRI Assessment

MRI scanners used in the study must be deemed qualified by BMS/assigned Imaging Core Lab prior to subject scans. The hand/wrist that is clinically most swollen at Screening Visit will be imaged using a whole body MRI system. Of note, the Screening Visit MRI is considered the baseline MRI assessment for this study. The SAME hand/wrist that was imaged at Screening will be imaged at Week 4, and Week 12 on the SAME MRI scanner as was used at screening. The Screening Visit MRI is to be performed approximately 14 days prior to randomization. Week 4 and Week 12 MRIs are to be performed ± 7 days of the scheduled Week 4 visit and Week 12 visit, respectively. **Subjects who terminate the study early require an MRI at the early termination (ET) visit only if ET < 4 weeks or > 8 weeks from date of randomization and should have their early termination (ET) MRI NO MORE than 7 days from their Early Termination (ET) Visit.**

Sites should schedule two MRI appointments with radiology department 7 days apart in the event that a MRI exam needs to be repeated due to technical difficulties. Technical issues with MRI identified at the investigator site or Imaging Core Lab should be re-imaged within 7 days of notification.

Subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) or GFR < 30 mL/min/1.73m2), will be excluded from the study, as they are at increased risk of

Nephrogenic Systemic Fibrosis, a rare, but serious, condition associated with the use of gadolinium-based MRI contrast agents.

Synovitis, osteitis (bone marrow edema), bone erosion and cartilage loss (joint-space narrowing) will be scored according to the OMERACT RAMRIS[22]. Change at follow-up from baseline in each RAMRIS score will be calculated. Scoring will be performed centrally by 2 independent, experienced readers who will be blinded to clinical details, radiographic findings, treatment arm and MRI sequence (Screening, Week 4, Week 12, and/or ET, if applicable).

Additional information is provided in a separate MRI imaging manual.

5.4.5 Clinical Assessor Requirements

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), Physicians Assistant (PA) or Nurse Practitioner (NP).

If possible, the Joint Count Assessor should not perform the PGA for the same subject and will be blinded to all other assessments for that subject (eg, safety evaluation, laboratory test assessments etc). If possible, the PGA assessor should not perform the Joint Count Assessments for the same subject. For both assessments: 1) Every effort should be made to ensure the same assessor is used for a given subject throughout the study and 2) The clinical assessor cannot be unblinded to study medication assignment for the subject. - AUDIT

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 and all efforts are made to assure consistency between subject evaluations.

Training and instruction on joint count assessments will be discussed at the Investigator's Meeting or at workshops.

5.5 Pharmacokinetic Assessments

Pharmacokinetics of BMS-986142 will be derived from plasma concentration versus time data. The pharmacokinetic parameters to be assessed include:

- Ctrough Predose (Trough): observed plasma concentration at time-points specified in Table 5.5.1-1

Individual subject pharmacokinetic parameter values will be derived.

5.5.1 Pharmacokinetics: Collection and Processing

Table 5.5.1-1 lists the sampling schedule to be followed for the assessment of pharmacokinetics. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 5.5.1-1: Pharmacokinetic Sampling Schedule for BMS-986142[a]

Study Week (Day)	Event	Time[b] (Relative To BMS-986142 Dose Hour: Min	BMS-986142 Blood Sample for Plasma
Week 1 (Day 1)		02:00	X
		04:00	X
		06:00	X
Week 2 (Day 15)	predose	00:00	X
		01:00	X
		03:00	X
		06:00	X
Week 4	predose	00:00	X
Week 8	predose	00:00	X
Week 12	predose	00:00	X
AE[a]	AE		X

[a] For subjects who discontinue due to an adverse event, the listed sample can be taken at the discretion of the Investigator.

[b] Targeted time listed, actual time needs to be recorded in CRF

5.5.2 Pharmacokinetic Sample Analyses

The plasma samples will be analyzed for BMS-986142 by a validated LC-MS/MS assay. Pharmacokinetic samples collected from a subject who received placebo will not be analyzed.

In addition, plasma samples will be archived for potential metabolite analysis, if the need arises and to the extent possible.

5.5.3 Labeling and Shipping of Biological Samples

Detailed instructions for the pharmacokinetic blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

[redacted]

[redacted]

[redacted]

5.8 Outcomes Research Assessments

Questionnaires and investigator/subject assessments will be completed, prior to study drug administration, on an electronic tablet (ePRO) and information gathered on this device will serve as the source document where possible.

The following assessments will be performed:

a) ACR Physician's Global Assessment of Disease Activity VAS: See Appendix 4
b) ACR Subject Assessment of Physical Function Scale (HAQ): 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 5.
c) ACR Subject Assessment of Disease Activity VAS: Global disease assessment of disease activity by patients measured on 10 cm VAS. See Appendix 6
d) ACR Subject Assessment of Pain VAS: Pain reported by subjects, measured on 10 cm VAS. See Appendix 7.
e) Joint Count Assessment Components for DAS28-CRP (Right and Left side). Disease Activity Score. See Appendix 8.
f) Fatigue VAS is a brief, valid measure for monitoring fatigue an important symptom in RA and its effects on patients with RA. See Appendix 9
g) Stiffness related questions are a valid measure for monitoring stiffness, an important symptom in RA, and its effects on patients with RA. Questions about stiffness will be asked of each subject and recorded in the CRF.
h) SF-36: Short Form-36. Questionnaire on health assessment. See Appendix 10.
i) Bristol Rheumatoid Arthritis Multidimensional Questionnaire (BRAF-MDQ): Fatigue assessment. See Appendix 11.

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.)

Sponsor or designate will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

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 6.4 for reporting pregnancies).

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

NOTE:

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

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure

- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 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 30 days of discontinuation of dosing.

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 sponsor or designate 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 sponsor or designate using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

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.

All significant drug-related laboratory abnormalities must be followed to resolution or stabilization.

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

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)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details).

Potential drug induced liver injury is defined as:

AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

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

A Data Monitoring Committee (DMC) will monitor overall efficacy and safety data regularly to ensure that the benefits and risks of study participation remain acceptable. Based on the regular reviews of emerging data, the DMC may recommend to the Sponsor alteration and/or termination of the trial or a treatment group, or cessation of further enrollment into a treatment group.

Data summaries and listings will be provided to the DMC to facilitate their safety assessment at the regularly scheduled times as well as on an ad hoc basis if needed. The DMC will review safety data including serious adverse events and events of special interest, focusing on early signal detection. Further details on the frequency, content and methods of data reports to the DMC will be outlined in the Charter of that Committee along with the processes and procedures the committee will follow.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size calculation is driven by the power to compare the proportion of subjects who achieve ACR70 response at Week 12 between each BMS-986142 dose arm and placebo arm. The target population consists of mixed subjects who are MTX-IR (≥ 70%) and TNF-IR (≤ 30%). For co-primary endpoint of ACR70 at Week 12, 82 subjects per arm will provide ~ 90% power to detect a treatment difference of 17% at the type I error rate of $\alpha = 0.05$ (two-sided), assuming the placebo response rate of 2.5%. The assumed treatment difference of 17% is about double of median difference observed from historical data on approved drugs across different mechanism of actions (MOAs).

If the placebo response rate in ACR70 at Week 12 is higher than planned 2.5% (eg, 5%), 82 subjects per arm can still provide 84% power to detect a difference of 17%.

For the population of MTX-IR (≥ 70%), 57 subjects per arm will provide 78% power to detect a treatment difference of 18% in ACR70 at the Type 1 error rate of $\alpha = 0.05$ (two-sided), assuming the placebo response rate is 2.5%.

For the other co-primary endpoint of ACR20 at Week 12, 82 subjects per arm will provide >99% power to detect a difference of 34% over placebo at the type I error rate of $\alpha = 0.05$ (two-sided), assuming placebo response rate of 33%. The assumed treatment difference of 34% and

placebo response rate of 33% were based on the observed data from approved drugs across different MOAs.

For the population of MTX-IR (≥ 70%), 57 subjects per arm will provide 95% power to detect a treatment difference of 35% in ACR20 at the Type 1 error rate of $\alpha = 0.05$ (two-sided), assuming the placebo response rate is 40%.

An interim analysis (IA) will be conducted when about 20 subjects reach week 4 (complete 4 weeks of treatment or discontinue). Based on the totality of efficacy, safety, and PK at Week 4 IA, the following adaptation(s) may be recommended:

- Stop inefficacious or unsafe dose(s)
- Introduce new dose(s) arms if needed and enroll (up to about 82 subjects per arm)
- Complete full enrolment for all efficacious arms (up to about 82 subjects per arm)
- Stop the study enrollment if all dose arms are stopped for safety or futility;

The total sample size varies depending on the interim analysis results (range from 328 to 408 subjects). The details of interim analysis and the criteria to adapt dose arm(s) and stop for futility are specified in the Section 8.5.

8.2 Populations for Analyses

- All Enrolled Subjects, defined as all subjects who sign an informed consent;
- All Randomized Subjects, defined as all subjects who are randomized to a treatment;
- All Randomized and Treated Subjects, defined as modified intent-to-treat (mITT) subjects who are randomized and receive at least one dose of study medication;
- All Treated Subjects, defined as all subjects who receive at least one dose of study treatment;
- [redacted]
- Pharmacokinetic Population, defined as all subjects who receive any study medication and have any available concentration-time data.

All subjects who receive at least one dose of study treatment (all treated subjects) will be included in the safety analysis population and mITT subjects will be included in the efficacy analysis population. More details will be provided in the statistical analysis plan.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

Co-Primary endpoints:

- Proportion of subjects who achieve ACR70 response rate at Week 12

- Proportion of subjects who achieve ACR20 response rate at Week 12

8.3.2 Secondary Endpoint(s)

8.3.2.1 Efficacy Endpoints

- Proportion of subjects who achieve ACR20 over time from baseline to Week 12
- Proportion of subjects who achieve ACR50 over time from baseline to Week 12
- Proportion of subjects who achieve ACR70 over time from baseline to Week 12
- Proportion of subjects who achieve DAS28-CRP < 2.6 over time from baseline to Week 12
- Proportion of subjects who achieve DAS28-ESR < 2.6 over time from baseline to Week 12
- Proportion of subjects who achieve CDAI ≤ 2.8 over time from baseline to Week 12
- Proportion of subjects who achieve SDAI ≤ 3.3 over time from baseline to Week 12
- Proportion of subjects who achieve Boolean Remission over time from baseline to Week 12
- Change from baseline in DAS28-CRP score over time up to Week 12
- Change from baseline in DAS28-ESR score over time up to Week 12
- Change from baseline in CDAI score over time up to Week 12
- Change from baseline in SDAI score over time up to Week 12
- Change from baseline in RAMRIS scores of synovitis, osteitis (bone marrow edema), bone erosion and cartilage loss (joint-space narrowing) (MRI) to Week 4, and Week 12

8.3.2.2 Safety Endpoints

- Incidence and severity of all Adverse Events (AEs), Serious AEs, and pre-established Events of Special Interest
- Incidence and severity of clinically significant changes in vital signs
- Incidence and severity of clinically significant electrocardiogram (ECG) abnormalities
- Incidence and severity of clinically significant abnormalities in general laboratory tests

8.3.2.3 Pharmacokinetic Endpoints

Ctrough: Predose (Trough) level plasma concentration of BMS-986142 at time points specified in Section 5.5.1.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by means and standard deviation for continuous variables, and frequency distribution for categorical variables. Summary will be performed on mITT analysis population.

8.4.2 Efficacy Analyses

Primary efficacy analysis:

The Chi-square tests will be used to compare the ACR70 response rates at Week 12 between each of the active treatment arms and the placebo arm. The p-value will be provided for each comparison between the active treatment and the placebo arm. In addition, the difference of the response rates between each active treatment and the placebo will be estimated and their corresponding 95% confidence interval will be calculated.

All subjects discontinuing prematurely during the double-blind period, regardless of reason, will be counted as non-responders at subsequent visits. Summaries will be performed using mITT analysis population. The same analysis will be performed for ACR20 response at Week 12.

Secondary efficacy analysis:

- Proportion of subjects who achieve ACR20 over time from baseline to Week 12
- Proportion of subjects who achieve ACR50 over time from baseline to Week 12
- Proportion of subjects who achieve ACR70 over time from baseline to Week 12
- Proportion of subjects who achieve DAS28-CRP < 2.6 over time from baseline to Week 12
- Proportion of subjects who achieve DAS28-ESR < 2.6 over time from baseline to Week 12
- Proportion of subjects who achieve CDAI ≤ 2.8 over time from baseline to Week 12
- Proportion of subjects who achieve SDAI ≤ 3.3 over time from baseline to Week 12
- Proportion of subjects who achieve Boolean Remission over time from baseline to Week 12

For each of the above endpoints, the estimate and its corresponding 95% confidence interval will be calculated for the difference of the proportions between each active treatment arm and the placebo arm at the specified visit, similar to the primary analysis.

For each of the following endpoints, the mixed effect model will be fit with treatment and visit as the fixed effects and measurements within each subject as the repeated measurements. The baseline value will be added into the model as a covariate if necessary. Based on the mixed effect model, the estimate and 95% confidence interval will be calculated for the difference between each active treatment and the placebo at each specified visit:

- Change from baseline in DAS28-CRP score over time up to Week 12
- Change from baseline in DAS28-ESR score over time up to Week 12
- Change from baseline in CDAI score over time up to Week 12
- Change from baseline in SDAI score over time up to Week 12
- Change from baseline in RAMRIS Scores of synovitis, osteitis, bone erosion and cartilage loss to Week 4 and Week 12

The details of the analyses, endpoints and grouping schemes (treatment groups) will be provided in the statistical analysis plan (SAP).

8.4.3 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed. The pre-established Events of Special Interest will be listed and summarized. The safety summaries will be performed using all treated subjects.

8.4.4 Pharmacokinetic Analyses

Ctrough values will be descriptively summarized by treatment and study days.

Preliminary population PK and dose/exposure-response (ie, DAS28-CRP and selected safety endpoints) analysis will be conducted at the time when Week 4 interim analysis is conducted.

Once study is completed, the concentration vs. time data combined with PK data from additional studies will be used to further develop a population PK model. This model will be used to evaluate the effects of various covariates on the PK of BMS-986142. [redacted]

[redacted]

[redacted]

8.4.6 Outcomes Research Analyses

The descriptive summary of baseline and change from baseline over time will be performed for BRAF-MDQ, Fatigue VAS and Stiffness VAS scores will be performed by treatment and visit.

8.4.7 Other Analyses

Not applicable

8.5 Interim Analyses

After about 20 subjects per treatment arm have completed at least 4 weeks of the treatment period or discontinued the treatment, an interim analysis will be conducted to assess the efficacy of the BMS-986142 dose arms and the overall safety. The interim analysis will use pre-specified efficacy, safety and PK endpoints. The results of the interim analysis will be reviewed by an unblinded sponsor team who is not involved in the study conduct and who will provide recommendations with regard to the adaptive design decisions to the blinded study team.

Efficacy analysis (DAS28) using Bayesian modeling and dose/exposure response analysis:

The interim analysis will be performed on all available data of DAS28 change from baseline up to Week 12 using a Bayesian predictive approach.[23] This analysis assumes that the DAS28 at Week 4 and at Week 12 in the subjects who have not yet been observed will be similar to what was observed for the subjects included at Week 4 and Week 12, respectively. As such the unobserved data will be simulated from the predictive distribution conditional on the interim data and the prior distribution of the treatment difference (using a non-informative prior). Under the Bayesian framework, the posterior distribution of the treatment difference (BMS-986142 active

dose – Placebo) will be constructed to determine the predictive probability of ΔΔDAS28 improvement greater than a cutoff value at the planned end of the trial for each dose arm.

Note: ΔΔDAS28 improvement: The difference of change from baseline in DAS28-CRP between active dose arm and placebo arm. The lower is DAS28 score, the better is the disease status.

The Bayesian predicative analysis and the dose/exposure response analysis will be used to facilitate decision-making if new BMS-986142 dose(s) will be needed to fully characterize dose-efficacy relationship. Pre-specified efficacy endpoint (DAS28) will be assessed with exposure endpoints to guide the selection of new dose levels in different scenarios as described below. Considering the safety margin estimated from non-clinical studies, new dose levels based on the interim analysis will not be greater than 350 mg/day.

If the predictive probability of ΔΔDAS28 improvement being greater than 1.0 is high (eg, > 80%) in all active arm(s), the BMS team may recommend to maintain the study design and treatment arms. In this scenario, all enrolled subjects will continue the treatments without modifications and also be included in the final analysis for the existing dose arm. The BMS team may also recommend adding an additional dose arm at lower dose level than current active doses to explore the suboptimal dose. In this case, approximately 40 subjects will be randomized into the suboptimal dose arm along with existing efficacious dose arms. The new suboptimal dose level may be selected based on dose/exposure response analysis.

If the predictive probability of ΔΔDAS28 improvement being greater than 1.0 is high (eg, >80%) in 2 BMS-986142 arms (mid and high dose arms), then the BMS team may recommend to maintain the study design and these 2 treatment arms. The enrolled subjects will be carried over in the existing dose arm and also be included in the final analysis for the existing dose arm. The subjects enrolled in the low dose arm will continue the treatment if they have received at least 1 treatment and treatment is considered safe before the interim analysis is completed. The decision to continue enrolling subjects into this treatment arm will depend on the collective assessment of the efficacy endpoints (beyond DAS28) and safety data. Even if the relationship between dose/exposure and response is adequately characterized from the interim analysis, a lower, sub-optimal dose (approximately 40 subjects) may be added if further subgroup analysis and collective data suggest a distinct trend in each subgroup.

If the predictive probability of ΔΔDAS28 improvement being greater than 1.0 is high (eg, > 80%) in 1 BMS-986142 arm (high dose arm), then the BMS team may recommend to maintain the study design and this treatment arm. The enrolled subjects will be carried over in the existing dose arm and also be included in the final analysis for the existing dose arm. The subjects enrolled in the low and mid dose arms will continue the treatment if they have received at least 1 treatment and treatment is safe before the interim analysis is completed. The decision to continue enrolling subjects into these two treatment arms will depend on the collective assessment of the efficacy endpoints (beyond DAS28) and safety data. Even if the relationship between dose/exposure and response is adequately characterized from the interim analysis, a lower, sub-optimal dose (approximately 40 subjects) may be added if further subgroup analysis and collective data suggest a distinct trend in each subgroup.

If the predictive probability of ΔΔDAS28 improvement being greater than 0.6 is low (eg, < 20%), that dose arm is deemed futile in terms of DAS28CRP change from baseline. However, the final futility will also incorporate the results from other efficacy endpoints as defined below.

The proposed stopping rules at the interim analysis, based on the futility assessment and the overall safety assessment, are as follows:

- Rule 1: If safety issues are identified in all dose arms or all dose arms are futile, stop the study
- Rule 2: Drop the dose arm(s) with safety issues identified
- Rule 3: Drop the futile dose arm(s) and the dose arm cannot be dropped until the lower dose arm has been dropped.

If the predictive probability of ΔΔDAS28 improvement being greater than 0.6 is lower than 20% in all active treatment arms, BMS team may recommend stopping enrollment and continuing the study up to 12 weeks.

Descriptive efficacy analysis (other efficacy endpoints):

In addition to Bayesian predictive analysis above, the following clinical data will be summarized at the time of Week 4 interim analysis to facilitate decision-making.

- ACR20/50/70 response over time
- DAS28-CRP < 2.6, DAS28-ESR < 2.6, CDAI ≤ 2.8, SDAI ≤ 3.3 and Boolean remission over time
- Change from baseline in DAS28-CRP, DAS28-ESR, CDAI, SDAI over time.
- Subgroup analysis of above endpoints by region where applicable (e.g., if any region consists of more than 50% of total subjects and region is classified by North America, Latin America, Europe and Rest of World. One or more regions may be combined for analysis if only limited data in individual region is available).

Descriptive safety analysis:

For the following pre-specified safety endpoints:

- AE/SAE (including but not limited to hypertension, diarrhea, neutropenia)
- Change from baseline in vitals including systolic blood pressure (SBP) and diastolic blood pressure (DBP).

The study will be stopped if intolerable safety events are identified in all treatment arms. If intolerable safety events are identified in 1 or 2 treatment arms, these arms will be dropped and

the study will be continued with caution. New dose levels may be added based on the exposure response analysis (not greater than 350 mg daily).If intolerable safety events show a clear relationship with higher exposure of BMS-986142, a lower dose will be selected where the predicted exposure in ~ 90% of subjects does not exceed the exposure ranges associated with safety findings.

Based on the totality of safety and efficacy considerations, ineffective doses will be stopped at Week 12 and unsafe dose will be stopped immediately.

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. Certain CRF pages and/or electronic files may serve as the source documents: This includes the joint count, the subject's assessment of Pain, the subject's Global Assessment of Disease Activity, the Physician Global Assessment of Disease Activity, the Subject's Assessment of Physical function (HAQ-DI), the Fatigue Scale (VAS), Stiffness information, the SF-36, and the Bristol Rheumatoid Arthritis Multidimensional Questionnaire (BRAF-MDQ). See Appendices 4-11.

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 (those supplied by BMS). 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:

- National Coordinating Investigator
- Subject recruitment (eg, among the top quartile of enrollers)
- 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
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AT	aminotransaminases
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CFR	Code of Federal Regulations
CLcr	creatinine clearance
CLNR	nonrenal clearance
CLR	renal clearance
CLS	cardiac life support
cm	Centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450

Term	Definition
D/C	discontinue
dL	deciliter
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	Bioavailability
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	Gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
kg	kilogram

Term	Definition
λz	terminal disposition rate constant
L	liter
mg	milligram
Mg++	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MRI	magnetic resonance imaging
MS	mass spectrometry
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
QC	quality control
QD, qd	quaque die, once daily
RAMRIS	rheumatoid arthritis magnetic resonance imaging scoring system
RBC	red blood cell

Term	Definition
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_Cmax	Cmax treatment ratio
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity