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Revised Date: 15-Nov-2018

CLINICAL PROTOCOL IM101682

A Randomized, Open-Label, Parallel-Group, Single-dose, Biocomparability Study of the Pharmacokinetics of the Abatacept (BMS-188667) Drug Product Converted from Drug Substance of a New Abatacept Drug Substance Process Relative to the Current Abatacept Drug Process in Healthy Participants

Short Title:

A Study to Evaluate the Pharmacokinetics of Abatacept Converted From Drug Substance by Two Different Processes

Revised Protocol Number: 01

Incorporates Administrative Letters 01 and 02

Study Director

Medical Monitor
Uma Arumugam, MD

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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 01	15-Nov-2018	Exclusion criterion modified, adverse event appendix updated, and incorporation of changes described in protocol administrative letters dated 26-Sep-2018 and 22-Oct-2018.
Administrative Letter 02	22-Oct-2018	• Updated the address and phone number for the Study Director • To align the start of the collection period of nonserious adverse events in Section 2 with Section 9.2.1 • Aligned terminology describing study participants
Administrative Letter 01	26-Sep-2018	• Updated the address and phone number for the Study Director • Aligned the start of the collection period of nonserious adverse events in Section 2 with Section 9.2.1 • Aligned terminology describing study participants
Original Protocol	07-Sep-2018	Not applicable.

[redacted]

SUMMARY OF KEY CHANGES FOR REVISED PROTOCOL 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title page	Address and phone number for Study Director updated.	[redacted]
Section 2, Schedule of Activities	Modified time of the start of the collection of nonserious AEs on Day 1.	[redacted]
Section 6.2, Exclusion Criteria	Exclusion criterion 3a modified.	[redacted]
Section 7.7.2.1, Precautions, Infectious Complications	Subject was replaced with participant.	[redacted]
Appendix 3, Adverse Events and Serious Adverse Events. Definitions and Procedures for Recording, Evaluating, Follow Up and Reporting	Appendix 3 replaced with current version.	[redacted]
All	Minor formatting and typographical corrections	[redacted]

TABLE OF CONTENTS

1 SYNOPSIS

Not applicable.

2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented in Table 2-1 and Table 2-2.

Table 2-1: Screening Procedural Outline (IM101682)

Procedure	Screening Visit	Day -1 Visit	Notes
Eligibility Assessments			
Informed Consent	X		A participant is considered enrolled only when a protocol specific informed consent is signed.
Inclusion/Exclusion Criteria	X	X	
Medical History	X		Include any toxicities or allergy related to previous treatments.
Admission to the Clinical Facility		X	
Safety Assessments			
Physical Examination (PE)	X	X	If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and predose evaluation. In addition to the PE, a skin exam will be conducted on Day -1. See Section 9.4.1.1.
Physical Measurements	X	X	Includes height, weight, and BMI. Body weight only on Day -1.
Vital Signs	X	X	Includes body temperature, respiratory rate, and seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly in the seated position for at least 5 minutes.
Concomitant Medication Use	X	X	
12-Lead Electrocardiogram (ECGs)	X	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests			Includes blood and urine samples. Participants are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests. See Section 9.4.4.
Serology	X		Includes hepatitis C antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antigen antibody (anti-HBc), and HIV-1 and -2 antibodies. Results must be available and reviewed prior to admission on Day -1.

Table 2-1: Screening Procedural Outline (IM101682)

Procedure	Screening Visit	Day -1 Visit	Notes
Urine Drug Test (Including Cotinine)	X	X	Screening results must be available and reviewed prior to admission on Day -1. Day -1 results must be available and reviewed prior to dosing on Day 1.
Alcohol Urine or Breath Test	X	X	Screening results must be available and reviewed prior to admission on Day -1. Day -1 results must be available and reviewed prior to dosing on Day 1.
Pregnancy Test (quantitative results)	X	X	For WOCBP only. Serum only. Screening results must be available and reviewed prior to admission on Day -1. Day -1 results must be available and reviewed prior to dosing on Day 1.
Follicle Stimulating Hormone (FSH)	X		Women only. Refer to Appendix 4. Results must be available and reviewed prior to admission on Day -1.
Tuberculosis (TB) Screening	X		QuantiFERON®TB Gold test. A QuantiFERON-TB Gold test performed within 4 weeks of dosing on Day 1 is acceptable as long as there is documentation of a negative result.
Hematology and Serum Chemistry	X	X	Screening results must be available and reviewed prior to admission on Day -1. Day -1 results must be available and reviewed prior to dosing on Day 1. See Section 9.4.4.
Thyroid Function Test	X		Thyroid-stimulating hormone (TSH) with reflex to free thyroxine (free T4), free triiodothyronine (free T3). Results must be available and reviewed prior to admission on Day -1.
Urinalysis	X	X	Screening results must be available and reviewed prior to admission on Day -1. Day -1 results must be available and reviewed prior to dosing on Day 1. See Section 9.4.4
Chest X-ray	X		A posterior-anterior and lateral chest x-ray will be performed. Results must be available and reviewed prior to admission on Day -1. See Section 9.4.7
Adverse Event Reporting			
Monitor for Serious Adverse Events	X	X	All SAEs must be collected from the date of participant's written consent until 101 days post dose. If a participant prematurely discontinues, all SAEs must be collected 30 days post last visit.

Table 2-2: On Treatment Procedural Outline(IM101682)

Procedure	Day 1	Day 2	Day 4	Day 8	Day 15	Day 22	Day 29 ± 2 Days	Day 43 ± 2 Days	Day 57 ± 2 Days	Day 71 ± 2 Days Study Discharge[a]	Notes
Safety Assessments											
Physical Examination (PE)		X					X			X	
Targeted PE	X										Day 1 predose. Targeted examination of skin. Photographs may be taken of any areas affected by rash that develop after the start of the infusion (including evolving changes). See Section 9.4.1.1. Continued monitoring of rashes will occur as needed. Targeted examination of other systems based on clinical symptoms.
Inspection of IV injection site	X										Predose and 1 hour post end of the infusion. Additional inspections (including photography of any changes) may be conducted as warranted. See Section 9.4.1.1.
Physical Measurements										X	Weight only.
Vital Signs	X[b]	X	X	X	X	X	X	X	X	X	See note in screening procedures.
Electrocardiogram (ECGs)	X[c]									X	See note in screening procedures.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 2-2: On Treatment Procedural Outline(IM101682)

Procedure	Day 1	Day 2	Day 4	Day 8	Day 15	Day 22	Day 29 ± 2 Days	Day 43 ± 2 Days	Day 57 ± 2 Days	Day 71 ± 2 Days Study Discharge[a]	Notes
Laboratory Tests											
Hematology and Serum Chemistry		X			X		X		X	X	See note in screening procedures and Section 9.4.4.
Pregnancy Test					X		X		X	X	Serum quantitative results.
Adverse Event Reporting											
Monitor for Nonserious Adverse Events	X	X	X	X	X	X	X	X	X	X	All nonserious AEs must be collected at the start of study treatment on Day 1 through Day 71.
Monitor for Serious Adverse Events	X	X	X	X	X	X	X	X	X	X	See note in screening procedures.
Pharmacokinetic (PK) Assessments											
Blood PK Sampling	X	X	X	X	X	X	X	X	X	X	On Day 1, the blood sample should be drawn at predose. See Section 9.5.1.

Table 2-2: On Treatment Procedural Outline(IM101682)

Procedure	Day 1	Day 2	Day 4	Day 8	Day 15	Day 22	Day 29 ± 2 Days	Day 43 ± 2 Days	Day 57 ± 2 Days	Day 71 ± 2 Days Study Discharge[a]	Notes
Blood Sampling for Immunogenicity Assessment	X				X		X		X	X	On Day 1, the immunogenicity sample should be drawn at predose. See Section 9.8.2. Participants who seroconvert and continue to have a high titer at study discharge that is considered to be significantly increased versus baseline will be asked to return for follow-up assessment(s) for anti-abatacept antibodies approximately every 4 months until their titers and/or sero-status are judged to be stable by the investigator.
[redacted]	[redacted]		[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinical Drug Supplies											
Randomize	X										Participants will be randomized prior to dosing.
Study Treatment Administration[d]	X										Supplied by BMS.

[a] Evaluations performed prior to study discharge, or for participants who are prematurely discontinued.

[b] Measurements at predose, 30 minutes (end of infusion), and 60 minutes after the start of the infusion

[c] Prior to dosing and 3 hours after the start of the infusion

[d] Participants will be randomized to receive a 30-minute IV infusion of single dose (750 mg) abatacept drug product converted from drug substance by a new process (Treatment A), or a 30-minute IV infusion (750 mg) abatacept drug product converted from drug substance by the current process (Treatment B).

In the event that multiple procedures are required at a single time point, the ECG may be obtained up to 15 minutes earlier, vital signs may be obtained up to 10 minutes earlier or later, and clinical laboratory sample may be obtained up to 5 minutes earlier than the nominal time point, ensuring the pharmacokinetic (PK) samples can be collected on time.

For the predose assessments on Day 1 PK, immunogenicity, and PD samples, ECG, vital signs, and examinations may be obtained up to 60 minutes prior to study treatment administration.

[redacted]

[redacted]

[redacted] [27,28]

3.3 Benefit/Risk/Assessment

Abatacept is a fully human fusion protein representing a new class of therapeutic agent known as a selective costimulation modulator with potential for immunomodulatory activity. This expected activity should be taken into consideration in caring for human participants participating in clinical trials with abatacept. Investigators should be alert to signs of infection in participants, and participants should be cautioned to report any signs of infection, such as fever, sore throat, cough or unusual appearances of skin lesions (swelling, warmth, tenderness, or exudate) to their physician without delay. The risks of infection occurring in the currently proposed single dose study, however, are expected to be very low.

This study is in healthy participants, a population that would not receive any health benefit from participating in this study. Although this single dose study for normal healthy participants should not pose an unacceptable health risk to participants based on the established safety profile of abatacept, in order to minimize the overall risk to participants, this protocol has inclusion and exclusion criteria appropriate to the population and proposed dosing, exclusionary screening tests (tuberculosis testing, chest x-ray, medical history, physical examination), and specific follow-up safety assessments. Adverse events and SAEs will be reviewed on an ongoing basis by the BMS Medical Monitor and by the BMS Pharmacovigilance Department to look for trends and any safety issues.

Risks from the PK, immunogenicity, and clinical safety phlebotomy procedures are standard and include infection, bleeding, bruising, blood clot formation, discomfort at the injection site, and (rarely) fainting.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of abatacept may be found in the Investigator's Brochure[4], an addendum to the Investigator's Brochure[33], and the prescribing information.[1]

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary To compare the PK of the abatacept drug product converted from drug substance by a new drug substance process (Treatment A) relative to the current drug substance process (Treatment B) following a single dose (750 mg) IV infusion in healthy participants.	Cmax and AUC(INF) of abatacept
Secondary To assess the safety of a single dose (750-mg) IV infusion of the abatacept drug product converted from drug substance by a new drug substance process (Treatment A) versus drug substance by the current drug substance process (Treatment B).	Safety assessments will be based on medical review of AE reports, vital sign measurements, ECGs, physical examinations, and clinical laboratory tests.
To assess the immunogenicity of abatacept drug product converted from drug substance by a new drug substance process (Treatment A) versus drug substance by the current drug substance process (Treatment B).	Immunogenicity determination will be based on the incidence of laboratory-reported positive responses and titers of anti-abatacept antibodies specific for "CTLA4 and possibly Ig" and "Ig and/or Junction Region."
To characterize the PK of abatacept drug product converted from drug substance by a new drug substance process (Treatment A) versus drug substance by the current drug substance process (Treatment B).	Tmax, AUC(0-T), AUC(0-28 day), CLT, Vss, and T-HALF of abatacept

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

Abbreviations: AUC(0-28 day) = area under the serum concentration-time curve from time zero to 28 days after dosing; AUC(0-T) = area under the serum concentration-time curve from zero to the last time of the last quantifiable concentration; AUC(INF) = area under the serum concentration-time curve from time zero extrapolated to infinity; CD86 = cluster of differentiation 86; CLT = total body clearance; Cmax = maximum observed serum concentration; CTLA-4-T = cytotoxic T lymphocyte (T cell)-associated antigen 4; ECG = electrocardiogram; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; T-HALF = terminal phase elimination half-life in serum; Tmax = time of maximum observed serum concentration; Vss = volume of distribution at steady-state.

5 STUDY DESIGN

5.1 Overall Design

This is an open-label, randomized, parallel group, single-dose study in healthy participants following IV administration of abatacept.

Participants will undergo screening evaluations to determine eligibility within 28 days prior to drug administration on Day 1. All participants are required to weigh between 60 and 100 kg, inclusive, and should be weighed using the same scale at each site.

Participants will be admitted to the clinical facility the day prior to dosing (Day -1) and will be confined until at least 24 hours post-dose.

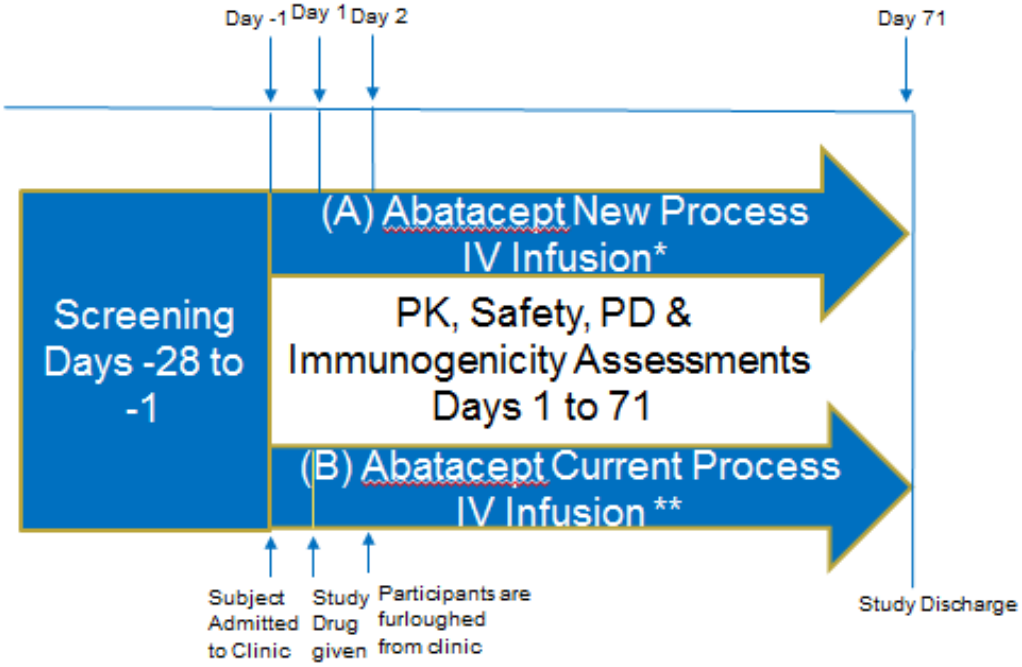
On Day 1, eligible participants will be randomized in a 1:1 ratio. The randomization will be stratified by weight categories: ≥ 60 to < 70 kg, ≥ 70 to < 80 kg, ≥ 80 to < 90 kg, and ≥ 90 to ≤ 100 kg. Within each weight category, participants will be randomly assigned to abatacept drug product converted from drug substance by a new drug substance process (Treatment A) or abatacept drug product converted from drug substance by the current drug substance process (Treatment B) in a 1:1 ratio. A minimum of 10 participants per treatment per weight category are planned to be randomized.

In order to decrease variability, the goal of the treatment group assignment is to match each participant 1:1 by weight category to a participant with the opposite treatment assignment. Randomization numbers will be sequential within each weight category, starting with 1001, 2001, 3001, and 4001 for ≥ 60 to < 70 kg, ≥ 70 to < 80 kg, ≥ 80 to < 90 kg, and ≥ 90 to ≤ 100 kg weight categories, respectively.

On Day 1, participants will receive a single IV infusion of either Treatment A or Treatment B at a dose of 750 mg over approximately 30 minutes using a calibrated, constant-rate infusion pump.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schematic



*Treatment A: IV infusion of single dose (750 mg) abatacept drug product converted from drug substance by a new process
**Treatment B: IV infusion of single dose (750 mg) abatacept drug product converted from drug substance by the current process
Abbreviations: IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval. Participants will be closely monitored for adverse events throughout the study. Blood samples for PK analysis, immunogenicity, [redacted] will be collected for up to 1680 hours (70 days) after study treatment administration. Approximately 260 mL of blood will be drawn from each participant during the study.

Participants will be closely monitored for AEs throughout the duration of the study. Participants will be discharged from the study following completion of evaluations on Day 71.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

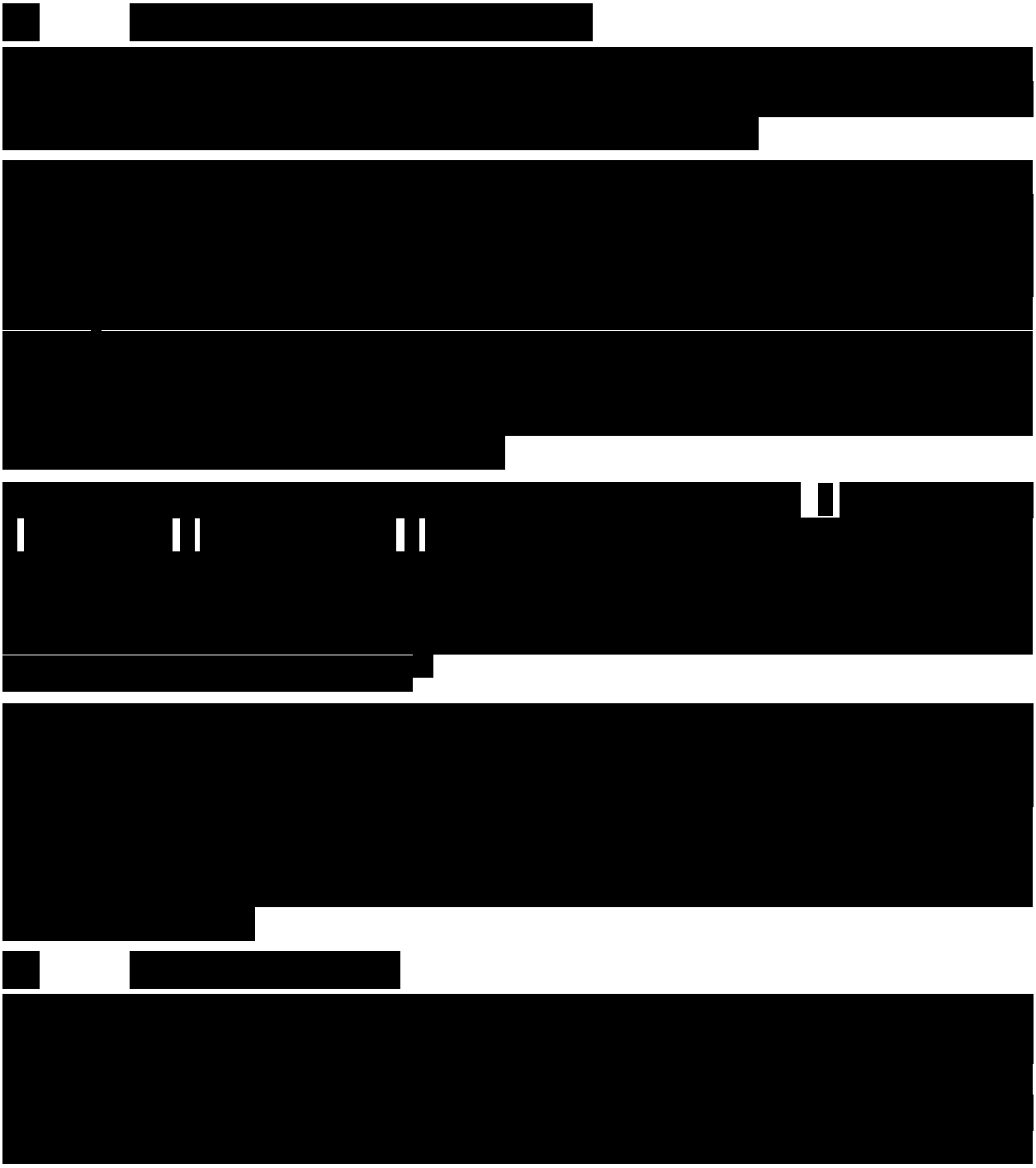
A sufficient number of participants will be screened to randomize approximately 140 participants into the study.

Approximately 70 participants will be assigned to each of the 2 treatment groups and will receive a single IV infusion of either Treatment A or Treatment B. Sample size determination is discussed in Section 10.1.

5.3 End of Study Definition

The start of the trial is defined as the first visit for the first participant screened. End of trial is defined as the last visit or last health status follow-up contact made to a participant discharged from the study. 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.

The approximate duration of the study for each participant will be 99 days which includes the 28-day screening period and the 71 day on-treatment period.



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6 STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Signed written informed consent must be obtained from the participants in accordance with requirements of the clinical facility's Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to the initiation of any protocol-required procedures.

2) Type of Participant and Target Disease Characteristics

a) Healthy participants as determined by no clinically significant deviation from normal in medical history, physical examination, vital signs, ECGs, and clinical laboratory determinations.

b) Body weight will be between 60 and 100 kg, inclusive.

3) Age and Reproductive Status

a) Males and Females, ages 18 or age of majority to 55 years, inclusive

b) Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 24 hours prior to the start of study treatment.

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with abatacept plus 5 half-lives of abatacept (85 days) plus 30 days (duration of ovulatory cycle) for a total of 115 days post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with abatacept plus 5 half-lives of abatacept (85 days) plus the duration of spermatogenesis (90 days) for a total of 175 days after the last dose of study treatment. In addition, male participants must be willing to refrain from sperm donation during this time.

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.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, (Appendix 4) which have a failure rate of < 1% when used consistently and correctly.

6.2 Exclusion Criteria

1) Medical Conditions

a) Participants who have a present malignancy or previous malignancy within the last 5 years prior to screening (except documented history of cured non-metastatic squamous or basal cell skin carcinoma or cervical carcinoma in situ). Participants who had a screening

procedure that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.

b) Participants at risk for tuberculosis (TB) defined as follows:
   i) Current clinical, radiographic, or laboratory evidence of active TB, even if currently being treated. Chest x-rays (posterior/anterior and lateral) obtained within the 6 months prior to screening and TB testing (IFN-α release assay or QuantiFERON_TB Gold) performed in the past month prior to screening will be accepted; however, a copy of the reports must be placed in the participant binder.
   ii) A history of active TB unless there is documentation that the participant had received prior anti-TB treatment that was appropriate in duration and type according to local health authority guidelines.
c) Participants with a history of herpes zoster
d) Any acute or chronic bacterial infection in the previous 12 weeks of dosing
e) Any recent infection requiring antibiotic treatment within 4 weeks of dosing
f) Known or suspected infection, including infection with human immunodeficiency virus (HIV), hepatitis B or C viruses
g) Presence of any factors that would predispose the participant to develop infection (eg, rectal fissures, poor dentition, open skin lesions)
h) Known or suspected autoimmune disorder
i) Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the participant's immune status
j) Any significant acute or chronic medical illness
k) Any major surgery within 4 weeks of study treatment administration
l) Donation of blood to a blood bank or in a clinical study (except a screening visit or follow-up visit) within 4 weeks of study treatment administration (within 2 weeks of study treatment administration for plasma only)
m) Blood transfusion within 4 weeks of study treatment administration
n) Inability to be venipunctured and/or tolerate venous access
o) Recent (within 6 months of study treatment administration) history of smoking or current smokers. This includes participants using electronic cigarettes or nicotine-containing products such as tobacco for chewing, nicotine patches, nicotine lozenges, or nicotine gum.
p) Recent (within 6 months of study treatment administration) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse (Appendix 5)
q) Any other sound medical, psychiatric and/or social reason as determined by the investigator

2) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7.

3) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG, or clinical laboratory determinations beyond what

is consistent with the target population. Estimated glomerular filtration rate (based on the MDRD equation) < 70 mL/min/1.73 m^2

b) Any of the following on 12-lead ECG prior to study treatment administration, confirmed by repeat
   i) PR ≥ 210 msec
   ii) QRS ≥ 120 msec
   iii) QT ≥ 500 msec
   iv) QTcF ≥ 450 msec for males, ≥ 470 msec for females

c) Any of the following clinical laboratory evaluation, at screening or Day -1, confirmed by repeat:
   i) Alanine aminotransferase (ALT) > ULN
   ii) Aspartate aminotransferase (AST) > ULN
   iii) Direct bilirubin > ULN
   iv) Total bilirubin > ULN
   v) LDH > ULN
   vi) Serum creatinine > ULN
   vii) Creatine kinase (CK) > 4 × ULN
   viii) Electrolytes (sodium, potassium, chloride, calcium, or phosphorus) outside of the reference range deemed to be clinically significant by the investigator
   ix) Complete blood count (including platelets) outside the reference range deemed to be clinically significant by the investigator

d) Positive urine screen for drugs of abuse including cotinine

e) Positive alcohol urine or breath test

f) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen (HBsAg), hepatitis B core antigen antibody (anti-HBc), or HIV-1 and -2 antibody

g) Clinically significant abnormal thyroid-stimulating hormone (TSH) at screening. A reflex test for free triiodothyronine (T3)/free thyroxine (T4) will be completed for TSH values out of the reference range to assist in the determination of clinical significance.

4) Allergies and Adverse Drug Reaction

a) History of allergy to abatacept or related compounds

b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)

5) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: under specific circumstances a person who has been imprisoned may be included as a participant. Strict conditions apply and Bristol-Myers Squibb approval is required.

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

c) Inability to comply with restrictions as listed in Section 6.3 Lifestyle Restrictions

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

- Participants are required to fast (nothing to eat or drink except water) for 1 hour prior to study treatment administration. Participants are required to continue to fast (nothing to eat or drink except water) for at least 1 hour after study treatment administration. Water may be consumed ad libitum at other times.
- Participants are required to fast (nothing to eat or drink except water) for 10 hours before blood laboratory evaluations.
- On Day 1:
  - A light breakfast (see Appendix 6) will be served approximately 1 hour post the end of the study treatment administration.
  - A standard lunch will be served approximately 4 hours post the end of study treatment administration.
  - A standard dinner will be served approximately 8 hours after post the end of study treatment administration.
  - A standard light snack will be served approximately 12 hours after post the end of study treatment administration.

6.3.2 Alcohol and Tobacco

- Participants are not permitted to consume alcohol-containing beverages from 3 days prior to dosing until release from the clinical facility on Day 2, and for 48 hours prior to study visits during which clinical laboratory assessments are scheduled.
- Participants are not permitted to smoke or use electronic cigarettes or any nicotine-containing products within 6 months prior to dosing on Day 1 until study discharge.

6.3.3 Activity

- Participants are to refrain from strenuous exercise, contact sports, and sunbathing from screening to end of the study.
- Participants are required to remain in the clinical facility for at least 24 hours after dosing.
- Participants should remain in a seated or reclined position during IV infusion of abatacept and for a minimum of 1 hour after the end of the infusion. Participants must be under direct observation for 1 hour after the end of the infusion.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently randomized in the study/included in the analysis population. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious AEs.

6.4.1 Retesting During Screening or Lead-In Period

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

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).

The most current result prior to Randomization is the value by which study inclusion will be assessed, as it represents the participant's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 2-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified participants. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

7 TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device intended to be administered to a study participant according to the study randomization or treatment allocation.

- Investigational products: abatacept (new drug substance process), abatacept (current drug substance process)

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-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
- Other drugs administered as part of the study that are critical to claims of efficacy (eg, background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

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.

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.

Table 7-1: Study treatments for IM101682					
Product Description / Class and Dosage Form	**Potency**	**IP/ Non-IMP**	**Blinded or Open Label**	**Packaging / Appearance**	**Storage Conditions (per label)**
Abatacept for IV infusion, 250 mg/vial	250 mg/vial	IP	Open Label	Vial	Refer to the label on the container

Abbreviation: IP = investigational product

7.1 Treatments Administered

The selection and timing of dose for each participant is as follows:

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)/Dosage level(s)	Dosage formulation Frequency of Administration	Route of Administration
A	750 mg	Single 30-minute infusion on Day 1	IV
B	750 mg	Single 30-minute infusion on Day 1	IV

Abbreviations: A = IV infusion of single dose (750 mg) abatacept drug product converted from drug substance by a new process; B = IV infusion of single dose (750 mg) abatacept drug product converted from drug substance by the current process; IV = intravenous

In the morning on Day 1, after fasting for at least 1 hour, each participant will receive a single IV dose of abatacept.

The start time of the IV dose administration will be called "0" hour.

Restrictions related to food and fluid intake are described in Section 6.3.

7.2 Method of Treatment Assignment

Participants will be randomized on Day 1 in a 1:1 ratio to either Treatment A or Treatment B groups. The randomization will be stratified by weight categories: ≥ 60 to < 70 kg, ≥ 70 to < 80 kg, ≥ 80 to < 90 kg, and ≥ 90 to ≤ 100 kg according to a computer generated randomization scheme prepared by ICON.

Within each weight category, participants will be randomly assigned to abatacept drug product converted from drug substance by a new drug substance process (Treatment A) or abatacept drug product converted from drug substance by the current drug substance process (Treatment B).

In order to decrease variability, the goal of the treatment group assignment is to match each participant 1:1 by weight category to a participant with the opposite treatment assignment. A minimum of 10 participants per treatment per weight category are planned to be randomized.

Randomization numbers will be sequential within each weight category, starting with 1001, 2001, 3001, and 4001 for ≥ 60 to < 70 kg, ≥ 70 to < 80 kg, ≥ 80 to < 90 kg, and ≥ 90 to ≤ 100 kg weight categories, respectively. A copy of the randomization listing will be provided to the pharmacist prior to study initiation.

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with 00001 (eg, 00001, 00002, 00003.... 00010). Sequential numbering may restart at 00001 for each participating site as the distinct patient identification number (PID) will ultimately be comprised of the site number and participant number, (eg, 0002-00001). Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

Participants will not be replaced if they are discontinued from the study secondary to an adverse event unless the adverse event can be determined to be unrelated to treatment. If a participant is replaced after dosing, the replacement participant will be identified from the same site and from the same weight category to the discontinued participant. The replacement participant will receive the same treatment as the participant that was discontinued but a new randomization number will be assigned to him or her. The new randomization number will be the original randomization number plus 4000. For example, Participant 1004 would be replaced by Participant 5004.

7.3 Blinding

Not applicable.

7.4 Dosage Modification

Not applicable.

7.5 Preparation/Handling/Storage/Accountability

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 Participants. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study treatment 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 treatment arise, the study treatment should not be dispensed and contact BMS immediately.

Study treatment 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).

For study drugs not provided by BMS and obtained commercially by the site, storage should in accordance with the product label.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2 as specified by the study team.

7.5.1 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.5.2 Retained Samples for Biocomparability

At the time of receipt of the investigational product by the investigator or designee, BMS will specify the appropriate number of containers or units to select for retention, the conditions of sample storage, required duration of sample retention, and provisions for returning or disposing of the investigational product. When samples are selected, containers or units should be placed in packaging with a tamper evident seal either provided by BMS, or sourced by the site. Package

labeling should clearly identify the contents as biocomparability samples and state that the investigational product should be stored in the restricted area with limited access.

7.6 Treatment Compliance

Study treatment will be administered in the clinical facility.

[redacted]

[redacted]

7.8 Treatment After the End of the Study

At the end of the study, BMS will not continue to provide BMS supplied study treatment to participants/investigators unless BMS chooses to extend the study. The investigator should ensure that the participant receives appropriate standard of care to treat the condition under study.

8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information
- 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 participant
- 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. (Note: Under specific circumstances, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
- Pregnancy
- Inability to comply with the protocol
- Discretion of the investigator
- The infusion of study medication should be immediately discontinued if there is any sign of anaphylaxis

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets 1 of the conditions outlined in Section 9.2.7 or if the investigator believes that it is in best interest of the participant.

Refer to the Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed

In the case of pregnancy, the investigator must immediately notify within 24 hours of awareness of the pregnancy, the BMS Medical Monitor/designee of this event. In most cases, the study treatment will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety). Refer to Section 9.2.5 Pregnancy.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including posttreatment study followup or loses the

ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.

- Participants 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 treatment 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 participant 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.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain 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 participant's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant'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 participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

9.1 Efficacy Assessments

Not applicable.

9.2 Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue before completing the study.

Contacts for SAE reporting specified in Appendix 3.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting.

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures and within 101 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 treatment or protocol-specified procedure (eg, a follow-up skin biopsy).

All nonserious AEs must be collected at the start of study treatment until the timepoints specified in the Schedule of Activities (Section 2).

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the appropriate section of the eCRF module.
- All SAEs will be recorded and reported to Sponsor or designee within 24 hours, as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of evaluating, and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AE and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known adverse events, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment 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.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.

- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting AEs 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.

9.2.5 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant 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 Appendix 3.

If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, or re-initiation of study treatment, a discussion between the investigator and the BMS Medical Monitor/designee must occur. If, for whatever reason, the pregnancy has ended, confirmed by negative serum pregnancy test, treatment may be resumed (at least 3 weeks and not greater than 6 weeks after the pregnancy has ended), following approvals of participant /sponsor /IRB/EC, as applicable.

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 Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic, as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

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

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

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

9.2.7 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 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

3) 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.

9.2.8 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.

9.3 Overdose

For this study, any dose of abatacept greater than the protocol-required amount will be considered an overdose.

All occurrences of overdose must be reported as an SAE (see Section 9.2).

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.1.1 Medical Photography

Initial and subsequent photographs may be taken of any areas of rash and/or of the IV injection site (for any local reaction such as redness, swelling, or rash) that may develop after the start of the infusion.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

Investigators must document their review of each laboratory safety report.

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

Results of clinical laboratory tests performed on Day -1 must be available and reviewed prior to dosing.

Hematology	
Hemoglobin Hematocrit Total leukocyte count, including differential Platelet count	
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	Total Protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase (screening only)
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 (HBsAg), hepatitis B core antigen antibody (anti-HBc), HIV-1 and -2 antibodies will be conducted (screening only)	
Other Analyses	
Urine test for drugs of abuse including cotinine (screening and Day -1) Urine or breath alcohol test (screening and Day -1)	
Thyroid-stimulating hormone (TSH) with reflex to free triiodothyronine (T3) and free thyroxine (T4) as applicable (screening only)	
QuantiFERON-TB Gold test (screening only)	
Pregnancy test (quantitative results) (WOCBP only): screening, on Day -1, Day 15, Day 29, Day 57, and Day 71 (study discharge).	
Follicle stimulating hormone (FSH) (screening only for women only)	

9.4.5 Suicidal Risk Monitoring

Not applicable.

9.4.6 Imaging Safety Assessment

Not applicable.

9.4.7 Chest X-ray

A posterior-anterior and lateral chest x-ray, performed during screening, is required for all participants. All participants must have a chest x-ray negative for TB to be entered in this study. The chest x-ray result will be recorded on the appropriate page of the CRF.

9.5 Pharmacokinetics

Pharmacokinetics of abatacept will be derived from serum concentration versus time data. The PK parameters to be assessed include:

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
AUC(0-28 day)	Area under the serum concentration-time curve from time zero to 28 days after dosing
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the serum concentration-time curve from time zero extrapolated to infinite time
T-HALF	Terminal phase elimination half-life in serum
CLT	Clearance
Vss	Volume of distribution at steady-state

Individual participant PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

9.5.1 Pharmacokinetics: Blood Collection and Processing

Table 9.5.1-1 lists the sampling schedule to be followed for the assessment of PK. The capture of precise PK sampling times relative to the actual dosing time is integral to the PK analysis and must be accurately recorded on the eCRF. The date and time of sample collection must be recorded so that compliance with the sampling schedule can be confirmed.

Table 9.5.1-1: Pharmacokinetic Sampling Schedule for Abatacept

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of Abatacept) Hour: Min	Blood Sample for Serum Abatacept
1	predose	00:00	X
1		00:15	X
1	EOI[a]	00:30	X
1		01:00	X
1		02:00	X
1		06:00	X
1		12:00	X

Table 9.5.1-1: Pharmacokinetic Sampling Schedule for Abatacept

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of Abatacept) Hour: Min	Blood Sample for Serum Abatacept
2		24:00	X
4		72:00	X
8		168:00	X
15		336:00	X
22		504:00	X
29		672:00	X
43		1008:00	X
57		1344:00	X
71		1680:00	X

[a] EOI=End of Infusion, This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly.

The serum samples will be analyzed for abatacept by a validated enzyme-linked immunosorbent assay (ELISA).

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

[redacted]

9.8.2 Immunogenicity Assessments

Table 9.8.2-1 lists the sampling schedule to be followed for immunogenicity assessments. Blood samples for determination of antibodies to abatacept and time-matched PK samples will be collected on Days 1, 15, 29, 57, and 71. Participants who seroconvert and continue to have a high titer at study discharge that is considered to be significantly increased versus baseline will be asked to return for follow-up assessment(s) for anti-abatacept antibodies approximately every 4 months until their titers and/or sero-status are judged to be stable by the investigator.

Table 9.8.2-1: Immunogenicity Sample Schedule

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of Abatacept Hour: Min	Blood Sample for Immunogenicity
1	predose	00:00	X
15		336:00	X
29		672:00	X
57		1344:00	X
71		1680:00	X

A validated, sensitive, electrochemiluminescence assay (ECL) method will be used to detect anti-abatacept-antibodies with specificities to "CTLA4 and possibly Ig" and "Ig and/or Junction Region".[34]

Samples that are confirmed positive with specificity to "CTLA4 and possibly Ig" antibodies with the ECL immunogenicity assay will be further analyzed with a validated, in vitro, cell-based bioassay to determine whether the anti-abatacept-antibodies have neutralizing activity.

Record the date and time of sample collection so that compliance with the sampling schedule can be confirmed. Detailed instructions for the immunogenicity blood collection, labeling, processing, storage, and shipping will be provided to the site in the procedure manual.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

Biocomparability of Treatment A to Treatment B will be concluded if the 90% CIs for the ratios of geometric means for abatacept Cmax and AUC(INF) are contained within 80% to 125%. Seventy participants per treatment group (Treatment A or Treatment B) will provide 88% power to conclude that Treatment A is biocomparable to Treatment B if Treatment A increases abatacept exposure by 10% compared to Treatment B; if Treatment A decreases abatacept exposure by 10%, 70 participants per treatment group will provide 83% power to conclude that Treatment A is biocomparable to Treatment B.

Participants who drop out will be replaced to ensure that there will be at least 65 evaluable participants per treatment group. Sixty-five participants per treatment group will provide 86% power to conclude that Treatment A is biocomparable to Treatment B if Treatment A increases abatacept exposure by 10% compared to Treatment B and 80% power if Treatment A decreases abatacept exposure by 10%.

These calculations assume that AUC(INF), and Cmax are log-normally distributed with between-participant standard deviation of 0.21 for Cmax and 0.27 for AUC(INF), [redacted]

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Enrolled Participants	All participants who sign informed consent
All Treated Participants	All participants who receive study treatment
Pharmacokinetic Population	All participants who receive abatacept and have any available concentration-time data.
Evaluable Pharmacokinetic Population	All participants in the PK Population with adequate PK profiles for accurate estimation of PK parameters. All available derived PK parameter values will be included in the PK data set and reported, but only participants with evaluable PK will be included in the summary statistics and statistical analysis.

All participants who receive study treatment will be included in the safety data set.

10.3 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

A description of the participant population will be included in the statistical output reported, including subgroups of age, gender, and race.

No efficacy analyses will be performed.

Below is a summary of planned statistical analyses of the primary and secondary endpoints.

10.3.1 Pharmacokinetic Analyses

Pharmacokinetic results will be listed for the PK population; descriptive summary statistics will use the evaluable PK population.

Endpoint	Statistical Analysis Methods
Primary Cmax and AUC(INF)	Summary statistics by treatment will be tabulated for serum concentrations and PK parameters of abatacept. Geometric means and coefficients of variation (CV%) will be presented for Cmax and AUC(INF). To assess comparability of Treatment A to Treatment B, point estimates and the two-sided 90% confidence intervals (CIs) will be constructed for the ratios of geometric means of abatacept AUC(INF) and Cmax based on analyses of covariance on log(AUC(INF)) and log(Cmax) adjusted for baseline body weight. Biocomparability of Treatment A to Treatment B will be concluded if the 90% CIs for the ratios of geometric means for abatacept Cmax and AUC(INF) are contained within 80% to 125%.
Secondary Tmax, AUC(0-T), AUC(0-28 day), CLT, Vss, and T-HALF	Summary statistics by treatment will be tabulated for PK parameters of abatacept. Geometric means and coefficients of variation (CV%) will be presented for AUC(0-T), AUC(0-28 day), CLT, and Vss. Medians and ranges will be presented for Tmax. Means and standard deviations (SDs) will be presented for T-HALF.

10.3.2 Safety Analyses

All safety analyses will be performed on the All Treated Participants Population.

Endpoint	Statistical Analysis Methods
The occurrence of nonserious AEs, SAEs, AEs leading to study discontinuation or death; results of clinical laboratory tests, vital sign measurements, ECGs, and physical examinations; and marked abnormalities in clinical laboratory test results	All AEs will be listed and summarized by system organ class and preferred term for all treated participants. Vital signs, ECGs, and laboratory test results will be listed and summarized by time point. Any significant physical examination findings and marked abnormal clinical laboratory test results will be listed. Electrocardiogram recordings will be evaluated by the investigator and abnormalities, if present, will be listed. Acute peri-infusional and postinfusional AEs will be tabulated for the 30-minute infusion period and the 24-hour postinfusion period, respectively, after the start of the abatacept infusion.

10.3.3 Other Analyses

10.3.3.1 Immunogenicity

Endpoint	Statistical Analysis Methods
anti-abatacept antibodies antibodies specific for “CTLA4 and possibly Ig” and “Ig and/or Junction Region”	The incidence of laboratory-reported positive responses and the corresponding titer values will be listed by participant and by study day. The frequency and percentage of positive abatacept-induced immunogenicity response will be summarized by treatment.

Lack of immunogenicity is defined as the absence of a positive antibody response generated against abatacept.

A participant is considered to have a positive abatacept-induced immunogenicity for ‘CTLA4 and possibly Ig’or ‘Ig and/or Junction Region’ if 1 of the following criteria are met:

A missing baseline immunogenicity measurement and a positive laboratory-reported immunogenicity response after baseline.

- A negative laboratory-reported baseline immunogenicity response and a positive laboratory-reported immunogenicity response after baseline.
- A positive laboratory-reported baseline immunogenicity response and a positive laboratory-reported immunogenicity response after baseline that has a titer value strictly greater than the baseline titer value.

This definition will be applied for each antibody-reactivity separately. All other ECL immunogenicity measurements will be classified as negative.

[redacted]

10.3.4 Interim Analyses

Not applicable.

12 APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
anti-HBc	hepatitis B core antigen antibody
APC	antigen presenting cell
AUC	area under the serum concentration-time curve
AUC(0-28 days)	area under the serum concentration-time curve from time zero to 28 days after dosing
AUC(INF)	area under the serum concentration-time curve from time zero extrapolated to infinity
AUC(0-T)	area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration
BCG	Bacillus Calmette-Guerin
BMI	body mass index
BMS	Bristol-Myers Squibb
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CLR	renal clearance
CLT	total body clearance
Cmax	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form, paper or electronic
CRO	Contract Research Organization
CTLA-4	cytotoxic T-lymphocyte (T-cell)-associated antigen 4
CV%	coefficient of variation
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
FDA	Food and Drug Administration

Term	Definition
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
JIA	juvenile idiopathic arthritis
MS	multiple sclerosis
MTX	methotrexate
PD	pharmacodynamics
PE	physical examination
PK	pharmacokinetic
PPK	population PK
PK	pharmacokinetic(s)
RA	rheumatoid arthritis
SAE	serious adverse event
SC	subcutaneous
TB	tuberculosis
T-HALF	terminal plasma half-life
Tmax	time of maximum observed concentration
TNF	tumor necrosis factor
Treatment A	abatacept drug product converted from drug substance by a new drug substance process
Treatment B	abatacept drug product converted from drug substance by the current drug substance process

Term	Definition
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
USA	United States (of America)
Vss	volume of distribution at steady-state
WOCBP	women of childbearing potential

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The term 'Participant' is used in the protocol to refer to a person who has consented to participate in the clinical research study. The term 'Subject' used in the eCRF is intended to refer to a person (Participant) who has consented to participate in the clinical research study.

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical GuidelinesGood Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

The study will be conducted in compliance with the protocol. The protocol and any amendments and the participant informed consent will receive approval/favorable opinion by Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable local regulations prior to initiation of the study.

All potential serious breaches must be reported to Sponsor or designee immediately. A breach of the conditions and principles of Good Clinical Practice (GCP) (occurring in any country) in connection with that trial or the protocol related to the trial which is likely to affect to a significant degree the safety or physical or mental integrity of 1 or more subjects of the trial or the scientific value of the trial.

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).

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, participant 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, Sponsor or designee 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.

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) 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 relevant approval/favorable opinion(s) the deviation or change will be submitted, as soon as possible to:

- IRB/IEC
- Regulatory Authority(ies), if applicable by local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and if applicable, also by local health authority must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the participant: (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).

FINANCIAL DISCLOSURE

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

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 participant volunteers to participate.

Sponsor or designee 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 participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant'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 participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant'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 participant 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.

SOURCE DOCUMENTS

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.

STUDY TREATMENT RECORDS

Records for study treatments (whether supplied by BMS, its vendors, or the site) must substantiate study treatment integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors):	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 participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., 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.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study treatment integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy.

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

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 Sponsor or designee 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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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, 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. Subinvestigators in Japan may not be delegated the CRF approval task. 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 Sponsor or designee training requirements and must only access the BMS electronic data capture tool using the unique user account provided by Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

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

In addition, the study may be evaluated by Sponsor or designee 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 Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) 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 or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) 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, study site, IRB). Notice of such transfer will be given in writing to BMS or designee.

RETURN OF STUDY TREATMENT

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

If..	Then
Study treatments supplied by BMS (including its vendors	Any unused study treatments supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study treatments containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics). If study treatments will be returned, the return will be arranged by the responsible Study Monitor.
Study treatments sourced by site, not supplied by BMS (or its vendors) (examples include study treatments sourced from the sites stock or commercial supply, or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal, 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. The following minimal standards must be 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.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study treatments provided by BMS (or its vendors). Destruction of non- study treatments sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

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:

Other criteria (as determined by the study team)

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

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW UP AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment 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 treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant 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) 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 (e.g., 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 (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) • admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
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 participant or may require intervention [e.g., 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 9.2.7 for the definition of potential DILI.)

Pregnancy and potential drug induced liver injury (DILI) must follow the same transmission timing and processes to BMS as used for SAEs (see section 9.2.5 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy should be reported as SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

EVALUATING AES AND SAES

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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 treatment or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the eCRF.
  - The paper SAE Report Form is only intended as a back-up option when the electronic data capture (EDC) system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile (fax) transmission
    - When paper forms are used, the original paper forms are to remain on site
- Pregnancies must be recorded on a paper Pregnancy Surveillance Form and transmitted via email or confirmed facsimile (fax) transmission

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state 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 > 40 mIU/mL to confirm menopause.

Note: 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.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

Any one of the approved methods of contraception (highly effective and/or less than highly effective) listed below is required during study duration and for 115 days after treatment has been discontinued.

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Intrauterine device (IUD)[c] • Intrauterine hormone-releasing system (IUS)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of >1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 85 days after the end of treatment plus an additional 90 days for a total of 175 days.
- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure defined as 85 days after the end of treatment in the male participant.

- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 175 days after the end of treatment.
- Refrain from donating sperm for the duration of the study treatment and for 85 days after the end of treatment for a total of 175 days.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5 and the Appendix for Adverse Events and Serious Adverse Events Definitions and procedures for Evaluating, Follow-up and Reporting.

APPENDIX 5 DIAGNOSTIC CRITERIA FOR DRUG AND ALCOHOL ABUSE

The following is taken from DSM-IV:

Diagnostic Criteria for Psychoactive Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as manifested by 3 (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect,
   b) Markedly diminished effect with continued use of the same amount of the substance.
2. Withdrawal, as manifested by either of the following:
   a) The characteristic withdrawal syndrome for the substance,
   b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (eg, visiting multiple doctors or driving long distances), use the substance (eg, chain-smoking) or recover from its effects.
6. Important social, occupational or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurring physical or psychological problem that is likely to have been caused or exacerbated by the substance (eg, current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption.)

Criteria for Severity of Psychoactive Substance Dependence:

Mild: Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others.

Moderate: Symptoms or functional impairment between “mild” and “severe”.

Severe: Many symptoms in excess of those required to make the diagnosis, and the symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others.

In Partial Remission: During the past six months, some use of the substance and some symptoms of dependence.

In Full Remission: During the past six months, either no use of the substance, or use of the substance and no symptoms of dependence.

Diagnostic Criteria for Psychoactive Substance Abuse

A. A maladaptive pattern of psychoactive substance use, leading to clinically significant impairment or distress as manifested by one (or more) of the following, occurring at any time in the same 12-month period:

   1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (eg, repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school, neglect of children or household).
   2. Recurrent substance use in situations in which it is physically hazardous (eg, driving an automobile or operating a machine when impaired by substance use).
   3. Recurrent substance-related legal problems (eg, arrests for substance-related disorderly conduct).
   4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (eg, arguments with spouse about consequences of intoxication, physical fights).

B. The symptoms have never met the criteria for substance dependence for this class of substance.

APPENDIX 6 REPRESENTATIVE LIGHT BREAKFAST

Food Item	Calories (kcal)	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices of white bread	128	1.8	24.0	4.0
1 teaspoonful low fat margarine	26	2.9	Trace	Trace
1 tablespoon jam	56	Trace	13.8	Trace
5 oz apple juice	71	0.2	17.5	0.2
5 oz skim (nonfat) milk	54	0.3	7.5	53
Total grams (g)	-	5.2	62.8	9.5
Total calories (kcal)	335	47	251	38
% of total calories	100	14	75	11

[redacted]