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Date:	14-Sep-2015
Revised Date:	27-Sep-2016

CLINICAL PROTOCOL IM103349

A Randomized, Open-label, Parallel-group, Single-dose, Biocomparability Study of the Pharmacokinetics of Belatacept Drug Products Using Active Pharmaceutical Ingredient Manufactured by Process E Relative to Active Pharmaceutical Ingredient Manufactured by Process C in Healthy Subjects

Revised Protocol Number: 02
Incorporates Amendment Number 01 and 02
Administrative Letter 01

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protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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 02	27-Sep-2016	Incorporates Amendment 02
Amendment 02	27-Sep-2016	The purpose of this protocol amendment is to add 30 replacement subjects who will be dosed. Audit and monitoring visits revealed major protocol deviations at Site 2. Due to the number and significance of these deviations, BMS does not believe that the data generated at this site should be included in the primary analysis.
Revised Protocol 01	06-Jan-2016	Incorporates Amendment 01 and Administrative Letter 01
Amendment 01	06-Jan-2016	The purpose of this protocol amendment is to fulfill the United States Food and Drug Administration (FDA) request to monitor subjects until titer and/or sero-status are judged to be stable by the investigator and to include an additional immunogenicity sample in the protocol. During review of this protocol for belatacept, the FDA requested that at the completion of the Day 71 visit, subjects that seroconvert will be asked to continue to participate until judged to be stable by the investigator and to add an immunogenicity sample on Day 15. In accordance with this, subjects who seroconvert will be asked to return for a visit approximately every 4 months after Day 71. These changes will apply to all current and future subjects after this amendment is approved.
Administrative Letter	06-Nov-2015	The purpose of this administrative letter was to clarify the units of measure for study drug dosage in Section 4 of the protocol, to clarify the subject numbers if replacement subjects are used in Section 4.4, and to update an inconsistency in Table 5.1-2 regarding the length of collection for nonserious adverse events (AEs) based on study duration. Both Treatment A and Treatment B will be dosed as 10 mg/kg, replacement subjects will be assigned the original subject's number plus 500, and all nonserious AEs will be collected through Day 71.
Original Protocol	14-Sep-2015	Not applicable

SYNOPSIS

Clinical Protocol IM103349

Protocol Title: A Randomized, Open-label, Parallel-group, Single-dose, Biocomparability Study of the Pharmacokinetics of Belatacept Drug Products Using Active Pharmaceutical Ingredient Manufactured by Process E Relative to Active Pharmaceutical Ingredient Manufactured by Process C in Healthy Subjects

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Each subject will be administered a single dose of Process E belatacept 10 mg/kg intravenous (IV) or Process C belatacept 10 mg/kg IV infused over 30 minutes according to a randomization schedule.

Study Phase: 1

Research Hypothesis: The pharmacokinetics (PK) of belatacept manufactured by Process E (Process E belatacept) and by Process C (Process C belatacept) are comparable in healthy subjects, based on exposure as measured by area under the serum concentration-time curve (AUC) from time zero extrapolated to infinite time (AUC[INF]) and maximum observed serum concentration (Cmax).

Objectives:

Primary:

The primary objective of this study is to compare the PK of Process E belatacept relative to Process C belatacept following a single-dose IV infusion of 10 mg/kg in healthy subjects.

Secondary:

The secondary objectives are as follows:

- To assess the safety of a single-dose IV infusion of 10 mg/kg Process E belatacept and 10 mg/kg Process C belatacept.
- To assess the immunogenicity of Process E belatacept and Process C belatacept.

Study Design: This is an open-label, randomized, parallel-group, single-dose, biocomparability study in healthy subjects. Due to a number of significant deviations that occurred at Site 2, 30 replacement subjects will be dosed. This protocol allows for replacement of subjects at sponsor discretion. The data from the 30 subjects who were enrolled and dosed at Site 2 will not be included in the primary analysis, and the data from the 30 replacement subjects to be dosed will be used for the primary analysis.

The initial plan was to dose approximately 146 subjects (approximately 73 in each cohort) in order to complete a minimum of 67 subjects per cohort. Given the protocol deviations at Site 2, the number of subjects dosed in this study has now increased to approximately 176 in order to ensure adequate sample size for the primary analysis. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to dosing on Day 1. To allow for possible dropouts, an adequate number of subjects will need to meet the inclusion/exclusion criteria at screening so that 73 subjects per arm will be dosed on Day 1.

Subjects will enter the study site on Day -1 and remain confined until completion of the Hour 72 PK sample collection on Day 4. On Day 1, subjects will be randomly assigned within stratified weight categories in a 1:1 ratio to receive either Process E belatacept or Process C belatacept 10 mg/kg, IV infused over 30 minutes. Subjects will return to the study site for PK blood sample collections after they are furloughed on Day 4 from the study site.

Blood samples for measurement of serum belatacept concentrations and immunogenicity will be obtained according to the schedule in Table 5.5.1-1.

Blood samples for immunogenicity assessments will be drawn prior to dosing and after dosing on Days 15, 29, 43, 57, and 71.

Subjects will be closely monitored for adverse events (AEs) throughout the study. Clinical laboratory tests, vital sign measurements, 12-lead electrocardiogram (ECG) measurements, and physical examinations will be performed at selected times following dosing. The approximate duration of the study is 99 days, including a 28-day screening period and a 71-day study period.

Subjects 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-belatacept antibodies approximately every 4 months until their titers and/or sero-status are judged to be stable by the investigator.

Subjects will undergo study procedures according to the study design schematic (Figure 1).

Figure 1: Study Design Schematic

<table>
<tr><td>Days -28 to -1</td><td colspan="2">Day 1</td><td>Day 4</td><td>Days 5 to 71</td><td>Day 71</td></tr>
<tr><td rowspan="2">S, E</td><td rowspan="2">R[a]</td><td>10 mg/kg IV
Process E belatacept
OR
10 mg/kg IV
Process C belatacept</td><td rowspan="2">Furlough
after Hour 72 PK
sample</td><td rowspan="2">PK[b]: Days 8, 15, 22, 29, 36, 43, 57

IMG: Days 15, 29, 43, 57, 71</td><td rowspan="2">Discharge[c]</td></tr>
<tr><td>Serial PK sampling</td></tr>
</table>

Abbreviations: E = enrollment; IMG = immunogenicity; IV = intravenous; PK = pharmacokinetic; R = randomization; S = screening.

a Subjects randomly assigned within stratified weight categories in a 1:1 ratio.

b Subjects will return to the study site for collection of a single PK sample.

c Evaluations performed prior to study discharge, or for subjects who are prematurely discontinued.

Study Population: Healthy male and female subjects, including women of childbearing potential, ages 18 to 55 years inclusive, as determined by medical history, physical examination, vital signs, 12-lead ECGs, and clinical laboratory evaluations will be eligible to participate in the study. All subjects must weigh between 60.0 to 100.0 kg, inclusive.

Women of childbearing potential must not be breastfeeding or pregnant and must be using an acceptable method of contraception. Women of childbearing potential must have a negative pregnancy test within 24 hours prior to dosing with study drug.

Study Drug: Includes investigational products (IP).

Study Drug for IM103349

Medication	Potency	IP/Non-IP
Process E Belatacept	250 mg/vial	IP
Process C Belatacept	250 mg/vial	IP

Abbreviation: IP = investigational product.

Study Assessments:

- Safety Outcome Measures: Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests. The incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance.
- Pharmacokinetic Measures: PK parameters (Cmax, time of maximum observed serum concentration [Tmax], AUC from time zero to the time of last quantifiable concentration [AUC(0-T)], AUC(INF), total body clearance (CLT), volume of distribution at steady state (Vss) and terminal half-life [T-HALF]) will be derived from serum concentration versus time data.
- Immunogenicity Measures: Immunogenicity determination will be based on antibody specificity for anti-belatacept antibodies and their corresponding titers in serum over time.

Statistical Considerations:

Sample Size: The PK of Process E belatacept and Process C belatacept will be considered equivalent if the 90% confidence intervals (CIs) for the ratios of geometric means (Process E belatacept relative to Process C belatacept) are contained within the equivalence interval 0.80 to 1.25 for both AUC(INF) and Cmax. If there is no difference in the PK of belatacept between the 2 manufacturing processes, then 67 subjects per treatment group will provide at least 99% and 99% power with respect to AUC(INF) and Cmax, respectively, to conclude equivalence between the 2 manufacturing processes. The overall power to conclude equivalence for both AUC(INF) and Cmax in this case is also at least 99%.

If the PK of Process E belatacept is 11% greater or 10% less than the PK of Process C belatacept, then 67 subjects per treatment group will provide at least 96% and 84% power with respect to AUC(INF) and Cmax, respectively, to conclude equivalence between the 2 manufacturing processes. The overall power to conclude equivalence for both AUC(INF) and Cmax in this case is at least 81%.

These calculations assume that log(AUC[INF]) and log(Cmax) of belatacept are normally distributed with intersubject coefficients of variation no greater than 20% and 26%, respectively, based on the results of Study IM103024.

To allow for possible dropouts, an adequate number of subjects will need to meet the inclusion/exclusion criteria at screening so that a total of 176 subjects will be dosed including the originally planned 146 subjects (73 subjects per arm) and the 30 replacement subjects.

Endpoints: The primary endpoints are AUC(INF) and Cmax of belatacept. The secondary PK endpoints are Tmax, AUC(0-T), CLT, Vss, and T-HALF.

Safety endpoints include the occurrence of AEs, serious adverse events (SAEs), and AEs leading to discontinuation; results of clinical laboratory tests, vital sign measurements, ECG findings, and physical examinations; and marked abnormalities in clinical laboratory test results.

The immunogenicity endpoint includes the incidence of anti-belatacept antibodies.

Analyses:

The data from the 30 subjects who were enrolled and dosed at Site 2 will not be included in the primary analysis, and the data from the 30 replacement subjects to be dosed along with the data from the initial 116 subjects who were enrolled and dosed at the other sites will be used for the primary analysis. Details on handling of the data from the 30 subjects who were enrolled and dosed at Site 2 will be described in the statistical analysis plan.

Pharmacokinetic: A linear fixed effect model with treatment as a fixed effect will be fitted to the log-transformed PK parameters AUC(INF), Cmax, AUC(0-T) for use in estimation of effects and construction of CIs. To assess comparability of Process E belatacept to Process C belatacept, point estimates and the 2-sided 90% CIs for treatment differences on the log scale will be exponentiated to obtain estimates for ratios of geometric means and respective 90% CIs for belatacept AUC(INF), Cmax, and AUC(0-T) on the original scale. A sensitivity analysis comparing the PK between Process E and Process C may be performed by excluding patients who are positive for anti-belatacept antibodies. Biocomparability of Process E belatacept to Process C belatacept will be concluded if the 90% CIs for the ratios of geometric means for belatacept AUC(INF) and Cmax are contained within 80% to 125%.

All individual PK parameters will be listed for each analyte, including exclusions and reasons for exclusion from summaries. Summary statistics will be provided for each PK parameter by treatment, for belatacept. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-T), AUC(INF), CLT, and Vss by treatment group. Medians and ranges will be presented for Tmax by treatment group. Mean and standard deviation will be provided by treatment group for T-HALF.

Plots of individual AUC(INF), Cmax, and AUC(0-T) combined with corresponding geometric means will be provided versus treatment.

Immunogenicity: The incidence of positive response will be summarized in a table by study day and the corresponding titer values will be listed. The impact of anti-belatacept on PK parameters will also be evaluated in individual subjects.

Safety: All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical

examination findings, ECG recordings, and clinical laboratory results will be listed. The number and percentage of subjects with marked laboratory abnormalities will be summarized. Electrocardiogram recordings will be evaluated by the investigator and abnormalities, if present, will be listed. All SAEs reported though Day 101 after the dose of the study drug will be included in the SAE summary table. All nonserious AEs that are reported though Day 71 after the dose of the study drug will be included in the AE summary table. Data from any safety related procedure after Day 71 or nonserious AEs will continue to be collected in the source documents, but not captured in the electronic case report form.

TABLE OF CONTENTS

1. INTRODUCTION AND STUDY RATIONALE

[redacted]

1.1 Study Rationale

[redacted]

[redacted]

1.2 Research Hypothesis

The PK of belatacept manufactured by Process E (Process E belatacept) and by Process C (Process C belatacept) are comparable in healthy subjects, based on exposure as measured by area under the serum concentration-time curve (AUC) from time zero extrapolated to infinite time (AUC[INF]) and maximum observed serum concentration (Cmax).

1.3 Objectives

1.3.1 Primary Objective

The primary objective of this study is to compare the PK of Process E belatacept relative to Process C belatacept following a single-dose IV infusion of 10 mg/kg in healthy subjects.

1.3.2 Secondary Objectives

The secondary objectives are as follows:

- To assess the safety of a single-dose IV infusion of 10 mg/kg Process E belatacept and 10 mg/kg Process C belatacept
- To assess the immunogenicity of Process E belatacept and Process C belatacept

1.3.3 Exploratory Objectives

Not applicable.

1.4 Product Development Background

An extensive description of the nonclinical and clinical belatacept studies is available in the Investigator Brochure (IB), Section 4 and Section 5, respectively.[5]

1.4.1 Pharmacology

Belatacept (NULOJIX) represents a new class of therapeutic agents that target the blockade of CD28-B7 (CD80, CD86) interactions, key costimulatory signals required for T-cell activation. Belatacept is approved for the prophylaxis of organ rejection in adult kidney transplant recipients. [redacted]

1.4.2 Toxicity

[redacted]

1.4.3 Preclinical Metabolism and Pharmacokinetics

[redacted]

1.4.4 Clinical Pharmacology and Safety

[redacted]

1.4.4.1 Pharmacokinetics of Belatacept

[redacted]

No studies of the metabolism of belatacept in humans were conducted. Generally, therapeutic proteins are cleared through their interactions with specific receptors, as well as interactions with the FcgR1 receptors. Proteins are also cleared nonspecifically through proteolysis in the Kupffer cells in the liver and macrophage activity in the spleen. These nonspecific mechanisms of clearance are the presumed primary expected routes of elimination for belatacept.

1.4.4.2 Safety of Belatacept in Healthy Subjects

[redacted]

Overall, the percentage of healthy subjects that developed antibodies to belatacept can be high after receiving a single dose of belatacept, up to 100% with most subjects (67%) having neutralizing anti-belatacept antibodies. However, these findings are not clinically relevant because the incidence of drug-specific antibody formation in kidney transplant recipients is low when belatacept is a component of multi-dose, multi-drug immunosuppressive regimes.

A summary of the results of these studies is available in Section 5.5.1 of the IB.[5]

1.5 Overall Risk/Benefit Assessment

Belatacept represents a new class of therapeutic agents that target the blockade of CD28-B7 (CD80, CD86) interactions, key costimulatory signals required for T-cell activation. Belatacept is approved for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. Overall, the data in the belatacept clinical development program, including 36-month results of Phase 3 trials, support a favorable risk-benefit profile for belatacept.

This study is in healthy male and female subjects, a population that would not receive any health benefit from participating in this study.

Although this single-dose study in healthy subjects should not pose an unacceptable health risk to participants (Section 1.4.4.2 includes a discussion of the safety of belatacept in healthy subjects), in order to minimize the overall risk to participating subjects, this protocol has inclusion and exclusion criteria appropriate to the population and proposed dosing, exclusionary screening tests (12-lead ECG, medical history, physical examination, and clinical laboratory assessments), and specific safety assessments at study discharge.

2. ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

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

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

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

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

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

2.2 Institutional Review Board/Independent Ethics Committee

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

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

2.3 Informed Consent

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

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

BMS or its designee will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form(s) (ICF) which will include all elements required by the ICH harmonised tripartite guideline E6(R1): Good Clinical Practice and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

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

subject's willingness to continue participation in the study. This communication should be documented.

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

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

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

3. INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label, randomized, parallel-group, single-dose, biocomparability study in healthy subjects. Due to a number of significant deviations that occurred at Site 2, 30 replacement subjects will be dosed. Section 4.4 allows for replacement of subjects at sponsor discretion. The data from the 30 subjects who were enrolled and dosed at Site 2 will not be included in the primary analysis, and the data from the 30 replacement subjects to be dosed will be used for the primary analysis.

The initial plan was to dose approximately 146 subjects (approximately 73 in each cohort) in order to complete a minimum of 67 subjects per cohort. Given the protocol deviations at Site 2, the number of subjects dosed in this study has now increased to approximately 176 in order to ensure adequate sample size for the primary analysis. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to dosing on Day 1. To allow for possible dropouts, an adequate number of subjects will need to meet the inclusion/exclusion criteria at screening so that 73 subjects per arm will be dosed on Day 1.

Subjects will enter the study site on Day -1 and remain confined until completion of the Hour 72 PK sample collection on Day 4. On Day 1, subjects will be randomly assigned within stratified weight categories in a 1:1 ratio to receive either Process E belatacept or Process C belatacept, 10 mg/kg, IV infused over 30 minutes. Subjects will return to the study site for PK blood sample collections after they are furloughed on Day 4 from the study site. Blood samples will be collected through Day 57 (approximately 5-6 half-lives) for PK analysis and through Day 71 (approximately 7-8 half-lives) for assessment of immunogenicity when drug concentrations are low and unlikely to interfere with analysis of anti-drug antibodies.

The PK and immunogenicity blood sample schedule is shown in Table 5.5.1-1. Blood samples for immunogenicity will be obtained prior to dosing and after dosing on Days 15, 29, 43, 57, and 71.

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

Figure 3.1-1: Study Design Schematic

<table>
<tr><td>Days -28 to -1</td><td colspan="2">Day 1</td><td>Day 4</td><td>Days 5 to 71</td><td>Day 71</td></tr>
<tr><td rowspan="2">S, E</td><td rowspan="2">R[a]</td><td>10 mg/kg IV
Process E belatacept
OR
10 mg/kg IV
Process C belatacept</td><td rowspan="2">Furlough
After Hour 72 PK sample</td><td rowspan="2">PK[b]: Days 8, 15, 22, 29, 36, 43, 57

IMG: Days 15, 29, 43, 57, 71</td><td rowspan="2">Discharge[c]</td></tr>
<tr><td>Serial PK sampling</td></tr>
</table>

Abbreviations: E = enrollment; IMG = immunogenicity; IV = intravenous; PK = pharmacokinetic; R = randomization; S = screening.

[a] Subjects randomly assigned within stratified weight categories in a 1:1 ratio.

[b] Subjects will return to the study site for collection of a single PK sample.

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

Physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the study. Subjects will be closely monitored for AEs throughout the study. Approximately 200 mL of blood will be drawn from each subject during the study.

The approximate duration of the study is a 28-day screening period, 71 study days per subject for a total of up to 99 days.

Subjects 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-belatacept antibodies approximately every 4 months until their titers and/or sero-status are judged to be stable by the investigator.

3.2 Post Study Access to Therapy

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

3.3 Study Population

For entry into the study, the following criteria MUST be met prior to dosing on Day 1. No exceptions will be granted.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Signed written informed consent must be obtained from the subjects in accordance with requirements of the study center's IRB/IEC prior to the initiation of any protocol-required procedures.

2. Target Population

a) Healthy male and female subjects, including women of childbearing potential (WOCBP), as determined by no significant deviation from normal in history, physical examination, vital signs, ECGs, and clinical laboratory determinations.

b) Must weigh between 60.0 to 100.0 kg, inclusive.

c) Must have body mass index (BMI) of 18.0 to 30.0 kg/m^2, inclusive; BMI=weight (kg)/[height (m)]^2.

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

3. Age and Reproductive Status

a) Males and females, ages 18 to 55 years, inclusive.

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of belatacept (50 days) plus 30 days (duration of ovulatory cycle) for a total of 80 days following treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of the belatacept (50 days) plus 90 days (duration of sperm turnover) for a total of 140 days following treatment completion.

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

g) Men must be willing to refrain from sperm donation for 140 days after dosing.

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

At a minimum, subjects must agree to the use of 1 method of highly effective contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP

subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug

- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with active tuberculosis (TB) requiring treatment; subjects with a history of active or latent TB without documented adequate therapy; subjects with current clinical, radiographic, or laboratory evidence of active or latent TB. All subjects will be required to have a negative QuantiFERON-TB Gold test at the screening visit. A QuantiFERON-TB Gold test performed within 4 weeks of dosing on Day 1 will be acceptable provided there is documentation of a negative result. All subjects will be required to have a negative chest x-ray [posterior-anterior and lateral views] for TB at the screening visit. A chest x-ray performed within the past 6 months will be acceptable provided written documentation of negative results is available.

b) History of malignancy or strong family history of malignancy.

c) History of herpes zoster.

d) Any acute or chronic bacterial infection in the previous 12 weeks.

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 subject 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 subject's immune status.

2. Medical History and Concurrent Diseases

a) Any significant acute or chronic medical illness.

b) History of clinically relevant hypertension that requires treatment.

c) Any major surgery within 4 weeks of study drug administration.

d) Donation of blood to a blood bank or in a clinical study (except a screening or follow-up visit) within 4 weeks of study drug administration (within 2 weeks for plasma only).

e) Blood transfusion within 4 weeks of study drug administration.

f) Inability to tolerate IV medication.

g) Inability to be venipunctured and/or tolerate venous access.

h) Smoking within less than 6 months of study drug administration.

i) Recent (within 6 months of study drug administration) drug or alcohol abuse as defined in DSM IV, Diagnostic Criteria for Drug and Alcohol Abuse[7] (Appendix 1).

j) Any other sound medical, psychiatric, and/or social reason as determined by the investigator.

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.

b) Any of the following on 12-lead ECG prior to study drug administration, confirmed by a repeat test.

i) PR ≥ 210 msec

ii) QRS ≥ 120 msec

iii) QT ≥ 500 msec

iv) QT interval corrected with Fridericia's method ≥ 450 msec

c) Screening or Day 1 predose systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg, confirmed by repeat assessment.

d) Positive urine screen for drugs of abuse.

e) Positive blood screen for hepatitis C antibody, hepatitis B surface antigen, or HIV-1 or -2 antibody.

f) Positive urine screen for cotinine.

g) Positive alcohol screening test.

h) Any of the following laboratory results outside of the range specified below prior to study drug administration, confirmed by repeat test

i) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > upper limit of normal (ULN)

ii) Total bilirubin > ULN

iii) Hemoglobin < 0.9 × lower limit of normal

iv) Creatinine > ULN

4. Allergies and Adverse Drug Reaction

a) History of allergy to belatacept or related compounds.

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

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated.

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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4.

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

3.3.3 Women of Childbearing Potential

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

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

- 1 week minimum for vaginal hormonal products (eg, 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.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study drug administration in the study are described below. Medications taken within 4 weeks prior to study drug administration must be recorded on the case report form (CRF).

1) Prior exposure to abatacept and/or belatacept or leukocyte-depleting agents (eg, rituximab).
2) Exposure to any investigational drug within 4 weeks of study drug administration.
3) Use of any prescription drugs within 4 weeks prior to study drug administration except those medications cleared by the PPD medical monitor after consultation with the BMS clinical/medical monitor.
4) Use of any other drugs, including over-the-counter medications (OTC) and herbal preparations, including St John's wort, within 1 week or 5 half-lives, whichever is longer, prior to study drug administration except those medications cleared by the PPD medical monitor after consultation with the BMS clinical/medical monitor.

5) Administration of oral polio vaccine or live varicella vaccine to subjects or household contacts during the course of the study.
6) Vaccination with any live vaccine within the past 4 weeks prior to dosing and for 71 days post dosing.

No concomitant medications (prescription, OTC, or herbal) are to be administered during the study unless they are prescribed by the investigator for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

3.4.2 Other Restrictions and Precautions

1) Subjects are to refrain from strenuous exercise, contact sports, and sunbathing for the duration of the study.
2) Subjects are not permitted to consume alcohol-containing beverages from 3 days prior to first dose until clinic furlough.
3) Subjects are required to remain in the clinical facility at least 72 hours after dosing until furloughed.
4) Subjects are required to fast (nothing to eat or drink except water) for 4 hours before until 2 hours after study drug administration.
5) On Day 1, all subjects will receive identical meals.
   - A standard light breakfast will be served approximately 2 hours postdose.
   - A standard lunch will be served approximately 4 hours postdose.
   - A standard dinner will be served approximately 8 hours postdose.
   - A standard light snack will be served approximately 12 hours postdose.

   The food content of meals may vary on Days 2 through 4.
6) Subjects should maintain an upright (seated or reclining) position for at least 4 hours postdose on Day 1.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment and/or participation in the study
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Unblinding a subject for any reason (emergency or nonemergency)
- Inability to comply with protocol
- Discretion of the investigator
- Pregnancy

In the case of pregnancy, the PPD medical monitor or designee must immediately notify the BMS medical monitor or designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible

favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor or designee must occur.

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

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

3.6 Post Study Drug Follow-up

Subjects who discontinue study drug may continue to be followed.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 3 documented phone calls, faxes, texts, or emails as well as lack of response by subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

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

4. STUDY DRUG

Study drug includes both investigational [medicinal] product (IP/IMP) and non-investigational [medicinal] product (Non-IP/Non-IMP) 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: (eg, glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

After at least a 4-hour fast, on Day 1 each subject will receive a single 10 mg/kg IV dose of either belatacept Process E or belatacept Process C infused over 30 minutes according to a randomization schedule:

- Treatment A: belatacept 10 mg/kg IV, Process E belatacept
- Treatment B: belatacept 10 mg/kg IV, Process C belatacept

Belatacept process E (Treatment A) or belatacept process C (Treatment B) will be administered intravenously, at a dose of 10 mg/kg using a calibrated, constant-rate infusion pump. The continuous infusion solution must be filtered upon administration using an in-line, sterile, nonpyrogenic, low-protein binding filter with a pore size of 1.2 microns. Belatacept infusion should be administered over a period of 30 minutes, in a fixed volume of 100 mL, using 0.9% sodium chloride (normal saline) as diluent, to produce a final infusion concentration of 2 mg/mL to 10 mg/mL. If normal saline cannot be obtained sites may use 5% dextrose in water as an acceptable alternative.

The time at the start of the infusion will be called “0” hour. The IV infusion of study drug will be administered with the subject in the seated or reclining position. At the end of the infusion, the line must be flushed per the belatacept pharmacy manual for this study. Any unused portion of the infusion solution should not be stored for reuse.

Belatacept infusion must be completed within 24 hours of reconstitution of the lyophilized powder, If not used immediately the infusion solution may be stored under refrigerated conditions: 2°C to 8°C (36°F to 46°F) and protected from light for up to 24 hours (4 of these hours may be at room temperature, 20°C to 25°C [68°F to 77°F], and normal light).

Product description and storage information is described in Table 4-1.

Table 4-1: Study Drugs for IM103349

Product Description Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/Appearance	Storage Conditions (per label)
Belatacept for IV infusion, 250 mg/vial (Process C)	250 mg vial	IP	Open label	White to off white, whole or fragmented cake in a vial.	Store refrigerated, 2°C-8°C (36°F-46°F); Protect from light.
Belatacept for IV infusion, 250 mg/vial (Process E)	250 mg vial	IP	Open label	White to off white, whole or fragmented cake in a vial.	Store refrigerated, 2°C-8°C (36°F-46°F); Protect from light.

Abbreviations: IP=investigational product; IV=intravenous.

4.1 Investigational Product

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

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

4.2 Non-investigational Product

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

4.3 Storage and Dispensing

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

Study drug not supplied by BMS will be stored in accordance with the package insert. Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets). Specific instructions for preparation, stability and administration of the IP will be provided in a separate document.

4.4 Method of Assigning Subject Identification

Enrolled subjects, including those not dosed, will be assigned sequential subject numbers starting with 00001, (eg, 00001, 00002, 00003.... 00010). Those enrolled subjects meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

Previous studies indicate that in subjects who take belatacept, there is a trend in higher clearance with increasing body weight.[4] In this study, 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, subjects will be randomly assigned to Process E belatacept or Process C belatacept in 1:1 ratio. Randomization numbers will be sequential within each weight category, starting with 1001, 2001, 3001, and 4001 for each weight category, respectively.

Subjects will not be replaced if they are discontinued from the study secondary to an AE unless the AE can be determined to be unrelated to treatment. If a subject is replaced after dosing then the replacement subject will be assigned the original subject's number plus 500. The replacement subject will receive the same treatment as the subject being replaced but a new randomization number will be assigned to him or her. For example, Subject 4 would be replaced by Subject 504.

4.5 Selection and Timing of Dose for Each Subject

Each subject will receive a single IV dose of either 10 mg/kg belatacept Process E or 10 mg/kg belatacept Process C infused over 30 minutes on Day 1.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

Study drug will be administered intravenously in the study site under the supervision of study personnel.

4.8 Destruction of Study Drug

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, (ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the monitor to review throughout the clinical trial period.

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

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

4.9 Return of Study Drug

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

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

4.10 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

5. STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Study assessments and procedures are presented in Table 5.1-1 and Table 5.1-2.

Table 5.1-1: Screening Procedural Outline (IM103349)

Procedure	Screening Visit Day -28 to Day -2	Day -1 Visit	Notes
Eligibility Assessments			
Informed Consent	X		A subject 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. Screening medical history evaluation may occur on Day -1 if the screening physical examination occurs on Day -1 (See "Physical Examination" note below).
Admit to Clinical Facility		X	
Safety Assessments			
Physical Examination	X	X	If the screening physical examination is performed within 24 hours prior to dosing on Day 1 then a single examination may count as both the screening and prior to dosing evaluation.
Physical Measurements	X	X	Height and weight at screening; weight only Day -1. Body mass index will be calculated at screening and 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 subject has been resting quietly for at least 5 minutes. Day -1 vital sign measurements must be reviewed prior to dosing on Day 1.
12-Lead ECGs	X	X	ECGs should be recorded after the subject has been supine for at least 5 minutes. Results must be reviewed prior to dosing on Day 1.
Chest X-ray	X		A posterior-anterior and lateral chest x-ray will be performed at enrollment. A chest x-ray performed within the past 6 months will be acceptable provided written documentation of negative results is available.
Laboratory Tests	X	X	Includes blood and urine samples. Subjects are required to fast for at least 10 hours prior to the collection of specimens for clinical laboratory tests. All clinical laboratory assessment must be available and reviewed by the investigator prior to dosing on Day 1.

Table 5.1-1: Screening Procedural Outline (IM103349)

Procedure	Screening Visit Day -28 to Day -2	Day -1 Visit	Notes
Serology	X		Includes hepatitis C antibody, hepatitis B surface antigen, and HIV-1 and -2 antibodies. Results must be available and reviewed prior to dosing on Day 1.
QuantiFERON-TB Gold Test	X		A QuantiFERON-TB Gold test performed within 4 weeks of dosing on Day 1 will be acceptable.
Urine Drug Test (including cotinine)	X	X	Results must be available and reviewed prior to dosing on Day 1.
Alcohol Test	X	X	A urine alcohol test will be performed. Results must be available and reviewed prior to dosing on Day 1.
Pregnancy Test	X	X	For WOCBP only; serum pregnancy test at screening and Day -1. Serum or urine pregnancy test at all subsequent time points during the study. Results must be reviewed prior to dosing on Day 1.
Follicle-stimulating Hormone			Women only. Refer to Section 3.3.3.
Adverse Event Reporting			
Monitor for Serious Adverse Events	X	X	All SAEs must be collected from the date of subject's written consent until 30 days after discontinuation of dosing or completion of the subject's participation in the study if the last scheduled visit occurs at a later time.

Abbreviations: ECG = electrocardiogram; HIV = human immunodeficiency virus; SAEs = serious adverse events; WOCBP = women of childbearing potential.

Table 5.1-2: On Treatment Procedural Outline (IM103349)

Procedure[a]	Day 1	Day 2	Day 4[b]	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 57	Day 71[c]	Notes
Safety Assessments												
Physical Examination			X								X	
Physical Measurements											X	Weight only
Vital Signs	X		X		X		X		X		X	Vital signs will be measured predose and within 30 minutes postdose on Day 1. Day 4 vital signs will be measured prior to furlough from study site. See note in screening procedures.
12-Lead ECG											X	See note in screening procedures.
Laboratory Tests			X		X			X			X	See note in screening procedures and Section 5.3.2.
Pregnancy Test			X				X			X	X	
Adverse Event Reporting												
Monitor for Nonserious AEs	X	X	X	X	X	X	X	X	X	X	X	AEs will be reported from after dose of study drug through Day 71.
Monitor for SAEs	X	X	X	X	X	X	X	X	X	X	X	SAEs will be reported from subject's written consent through Day 101.
Pharmacokinetic (PK) Assessments												
Serial Blood PK Sampling for Belatacept	X	X	X	X	X	X	X	X	X	X		See Table 5.5.1-1.

Table 5.1-2: On Treatment Procedural Outline (IM103349)

Procedure[a]	Day 1	Day 2	Day 4[b]	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 57	Day 71[c]	Notes
Immunogenicity Assessments												
Blood Sampling	X				X		X		X	X	X	Prior to dosing on Day 1. See Table 5.5.1-1. Subjects 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-belatacept antibodies approximately every 4 months until their titers and/or sero-status are judged to be stable by the investigator.
Clinical Drug Supplies												
Randomize	X											
Study Drug Administration	X											Supplied by BMS.

Abbreviations: AE = adverse event; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event.

[a] The window for Days 8 and 15 is ± 1. The window for Days 22, 29, 36, 43, and 57 is ± 2. The window for Day 71 is -2 days.

[b] Subjects will be furloughed from the clinic site after the Hour 72 PK sample on Day 4.

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

In the event multiple procedures are required at a single time point, the following is a list of procedures from highest priority to low:

1) PK sampling

2) Safety (ECG)

3) Safety (clinical laboratory tests)

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single screening or lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

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

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

5.2 Study Materials

The site will provide all required materials for the tests performed locally (ie, relevant clinical laboratory tests and urine drug screens). The site will have available a well-calibrated scale for recording body weight, a 12-lead ECG machine, and a calibrated sphygmomanometer and thermometer for vital signs assessments. A current and fully-stocked advanced cardiac life support cart will be immediately available on the premises. The site will have, a refrigerated centrifuge, a monitored and alarmed refrigerator, and freezer (-20°C [-68°F] or below), as well as containers and dry ice for shipment and storage of blood samples. The site will provide all materials required for accurate source documentation of study activities and for housing the subjects during the study. The site will source marketed product from a single commercial lot.

BMS or designee will provide a BMS-approved protocol and any amendments or administrative letters (if required), and IB. Case report forms (electronic or hard copy) will be provided by BMS or designee. BMS or the clinical facility will provide labels and tubes for the collection of blood samples for PK and immunogenicity analysis.

5.3 Safety Assessments

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance found on a chest x-ray that are not directly associated with the objectives of the protocol should be evaluated and handled by the study investigator as per standard medical/clinical judgment.

5.3.2 Laboratory Test Assessments

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 prior to dosing.

The following clinical laboratory tests will be performed:

Hematology

Hemoglobin
Hematocrit
Total leukocyte count, including differential
Platelet count

Serum Chemistry

AST
ALT
Total bilirubin
Direct bilirubin
Alkaline phosphatase
Lactate dehydrogenase
Creatinine
Blood urea nitrogen
Uric acid
Fasting glucose
Total protein
Albumin
Sodium
Potassium
Chloride
Calcium
Phosphorus
Magnesium

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, HIV-1 and -2 antibody (screening only)

Other Analyses

Test for drugs of abuse, including cotinine (urine or serum) (screening and Day -1)
Alcohol screening (urine) (screening and Day -1)
FSH (if necessary for confirmation of menopause at screening; see Section 3.3.3).
Pregnancy test (WOCBP only: screening, Day -1, Days 4, 29, 57, and 71)
QuantiFERON-TB Gold test (screening only)

Results of all laboratory tests required by this protocol must be provided to BMS, either recorded on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and BMS (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units. Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF (See Section 6.3).

5.4 Efficacy Assessments

Not applicable.

5.4.1 Primary Efficacy Assessment

Not applicable.

5.4.2 Secondary Efficacy Assessments

Not applicable.

5.5 Pharmacokinetic Assessments

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

Cmax	Maximum observed serum concentration
Tmax	Time of maximum observed serum concentration
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
Vss	Volume of distribution at steady state
CLT	Total body clearance
T-HALF	Half-life

Individual subject PK parameter values will be derived by noncompartmental methods by a validated PK analysis program. Actual times will be used for the analyses.

5.5.1 Pharmacokinetics and Immunogenicity: Collection and Processing

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

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule for Belatacept

Study Day of Sample Collection[a]	Event	Time (Relative To The Start of Belatacept Infusion) Hour: Min	PK Blood Sample for Belatacept	Immunogenicity Blood Sample
1	predose	00:00	X	X
		00:15	X	
	EOI[b]	00:30	X	
		01:00	X	
		02:00	X	
		06:00	X	
		12:00	X	
2		24:00	X	
4		72:00	X	
8		168:00	X	
15		336:00	X	X
22		504:00	X	
29		672:00	X	X
36		840:00	X	
43		1008:00	X	X
57		1344:00	X	X
71		1680:00		X

[a] The window for Days 8 and 15 is ± 1. The window for Days 22, 29, 36, 43, and 57 is ± 2. The window for Day 71 is -2 days.

[b] 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.

5.5.2 Pharmacokinetic Sample Analyses

The serum samples will be analyzed for belatacept by a validated ligand binding assay using a validated enzyme-linked immunosorbent assay platform. The lower limit of quantification is 3 ng/mL.

5.5.3 Labeling and Shipping of Biological Samples

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

5.6 Biomarker Assessments

Not applicable.

5.7 Exploratory Biomarker Assessments

Not applicable.

5.8 Outcomes Research Assessments

Not applicable.

5.9 Other Assessments

5.9.1 Immunogenicity Sample Analysis

[redacted]

5.9.2 Immunogenicity Labeling and Shipping of Biological Samples

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

The blood sampling schedule to be followed for the assessment of immunogenicity is shown in Table 5.5.1-1.

5.10 Additional Research Collection

Not applicable.

6. ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

6.1 Serious Adverse Events

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

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

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

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

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

NOTE:

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

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

- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg,-routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the IB represent the Reference Safety Information to determine expectedness of SAEs for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 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 drug or protocol-specified procedure.

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS or designee within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the electronic case report form (eCRF). The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS medical monitor or designee using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

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

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

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

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

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

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

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (See Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury

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

Potential DILI is defined as:

1) Aminotransaminases (ALT or AST) elevation > 3 times 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 aminotransaminase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

7. DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8. STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

[redacted]

8.2 Populations for Analyses

- The Enrolled Population includes all subjects who sign an ICF.
- The Randomized Population is a subset of the Enrolled Population including only subjects who were randomly assigned to a treatment. When using the Randomized Population, subjects will be presented in the treatment group they were randomly assigned to, even when the treatment they received was different.
- The Treated Population is a subset of the Enrolled Population including only subjects who received at least 1 dose of study medication. All analyses using the Treated Population will be presented by randomized treatment group, except in cases where information was available which indicated that a subject received a different treatment for the entire course of their participation in the study. In this case, the safety data and PK data for those subjects will be presented by the treatment actually received.
- The PK Population is a subset of the Treated Population. The PK population includes all subjects who received at least 1 dose of study medication and had any available concentration-time data.

- The Evaluable PK Analysis Set is a subset of the PK Population. The Evaluable PK Analysis Set includes all subjects who have adequate PK profiles. All available concentration-time data and derived PK parameters will be reported, however only subjects with adequate PK profiles will be included in the summary statistics and statistical analyses.
- The Immunogenicity Analysis Population: All treated subjects with at least 1 post-baseline immunogenicity result reported will be included in immunogenicity analysis.

8.3 Endpoints

8.3.1 Primary Endpoints

The primary endpoints are AUC(INF) and Cmax of belatacept.

8.3.2 Secondary Endpoints

- The secondary PK endpoints are Tmax, AUC(0-T), CLT, Vss, and T-HALF of belatacept.
- Safety endpoints include the occurrence of AEs, SAEs, and AEs leading to discontinuation; results of clinical laboratory tests, vital sign measurements, ECG findings, and physical examinations; and marked abnormalities in clinical laboratory test results.
- The immunogenicity endpoint includes the incidence of anti-belatacept antibodies.

8.3.3 Exploratory Endpoint(s)

Not applicable.

8.4 Analyses

The data from the 30 subjects who were enrolled and dosed at Site 2 will not be included in the primary analysis, and the data from the 30 replacement subjects to be dosed along with the data from the initial 116 subjects who were enrolled and dosed at the other sites will be used for the primary analysis. Details on handling of the data from the 30 subjects who were enrolled and dosed at Site 2 will be described in the statistical analysis plan.

8.4.1 Demographics and Baseline Characteristics

Frequency distributions of gender and race will be tabulated. Summary statistics for age, body weight, height, and BMI will be tabulated.

8.4.2 Efficacy Analyses

Not applicable.

8.4.3 Safety Analyses

All recorded AEs will be listed and tabulated by system organ class, preferred term, and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, ECG recordings, and clinical laboratory results will be listed. The number and percentage of subjects with marked laboratory abnormalities will be summarized. Electrocardiogram recordings will be evaluated by the investigator and abnormalities, if present, will be listed. All SAEs reported though Day 101 after the dose of the study drug will be included in the SAE summary table. All nonserious AEs that are reported though Day 71 after the dose of the study drug will be included in the AE summary

table. Data from any safety related procedure after Day 71 or nonserious AEs will continue to be collected in the source documents, but not captured in the eCRF.

8.4.4 Pharmacokinetic Analyses

A linear fixed effect model with treatment as a fixed effect will be fitted to the log-transformed PK parameters AUC(INF), Cmax, AUC(0-T) for use in estimation of effects and construction of CIs. To assess comparability of Process E belatacept to Process C belatacept, point estimates and the 2-sided 90% CIs for treatment differences on the log scale will be exponentiated to obtain estimates for ratios of geometric means and respective 90% CIs for belatacept AUC(INF), Cmax, and AUC(0-T) on the original scale. A sensitivity analysis comparing the PK between Process E and Process C may be performed by excluding patients who are positive for anti-belatacept antibodies. Biocomparability of Process E belatacept to Process C belatacept will be concluded if the 90% CIs for the ratios of geometric means for belatacept AUC(INF) and Cmax are contained within 80% to 125%.

All individual PK parameters will be listed for each analyte, including exclusions and reasons for exclusion from summaries. Summary statistics will be provided for each PK parameter by treatment, for belatacept. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-T), AUC(INF), CLT, and Vss by treatment group. Medians and ranges will be presented for Tmax by treatment group. Mean and standard deviation will be provided by treatment group for T-HALF.

Plots of individual AUC(INF), Cmax, and AUC(0-T) combined with corresponding geometric means will be provided versus treatment.

8.4.5 Biomarker Analyses

Not applicable.

8.4.6 Exploratory Biomarker Analyses

Not applicable.

8.4.7 Outcomes Research Analyses

Not applicable.

8.4.8 Immunogenicity Analyses

[redacted]

[redacted]

8.5 Interim Analyses

Not applicable.

9. STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

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

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

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

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study and BMS will notify the investigator when the study records are no longer needed.

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

9.2.2 Study Drug Records

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

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS

- retained samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form

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

9.2.3 Case Report Forms

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

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

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

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

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

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

9.3 Clinical Study Report and Publications

For this single site protocol, the principal investigator for the site will sign the clinical study report.

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study require approval by BMS prior to publication or presentation and must adhere to BMS's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to BMS at the earliest practicable time for review, but

at any event not less than 30 days prior to submission or presentation unless otherwise set forth in the CTA. BMS shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10. GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If 1 form of contraception is required, complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If 2 forms of contraception are required, complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. Expanded definition Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, postovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

11. LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
AUC(INF)	area under the serum concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the serum concentration-time curve from time zero to time of the last quantifiable concentration
BMI	body mass index
BMS	Bristol-Myers Squibb
CFR	Code of Federal Regulations
CI	confidence interval
CLT	total body clearance
Cmax	maximum observed serum concentration
CRF	case report form, paper or electronic
CTA	clinical trial agreement
DILI	drug induced liver injury
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
ECG	electrocardiogram
ECL	electrochemiluminescence
eCRF	electronic case report form
eg	exempli gratia (for example)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation

Term	Definition
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	Investigational New Drug
IP	investigational product
IRB	Institutional Review Board
IU	International Unit
IUD	intrauterine device
IV	intravenous
L	liter
mg	milligram
mL	milliliter
mm Hg	millimeters of mercury
ng	nanogram
NHV	normal healthy volunteer
OTC	over the counter
PK	pharmacokinetic(s)
SAE	serious adverse event
TB	tuberculosis
T-HALF	half-life
Tmax	time of maximum observed serum concentration
ULN	upper limit of normal
Vss	volume of distribution at steady state
WOCBP	women of childbearing potential

12. REFERENCES

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6 Department of Health and Human Services, Food and Drug Administration (US). Guidance for industry: Clinical pharmacology data to support a demonstration of biosimilarity for a reference product. May 2014.

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APPENDIX 1 DIAGNOSTIC CRITERIA FOR DRUGS 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 three (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 (e.g., current cocaine use despite recognition of cocaine-induce 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. 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 (e.g., 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