NEW or MODIFIED **STATISTICAL ANALYSIS PLAN** APPROVAL PAGE

Study Specific SAP for 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

[redacted]

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STATISTICAL ANALYSIS PLAN
FOR

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

VERSION # FINAL V2.0

DATE: 18-JAN-2017

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REVISION HISTORY

Revision	Date	Revised By	Changes Made – Reasons for the Change
Version 2.0 Draft 1	[redacted]	[redacted]	Updated based on Protocol Amendment 02
Version 2.0 Draft 2	[redacted]	[redacted]	Updated based on BMS reviewers' comments
Version 2.0 Draft 3	[redacted]	[redacted]	Add clarification that the replacement subjects are enrolled in Site 1 and 3 and details of the inclusion/exclusion of subjects are specified in DPP, based on BMS suggestion
Version 2.0 Draft 4	[redacted]	[redacted]	30 subjects dosed at Site 2 will be excluded from all the populations; Add clarification of the protocol deviations at Site 2 and reasons for replacing these subjects.
Final Version 2.0	[redacted]	[redacted]	Add "persistent" ADA status. Final Version 2.0 based on the Protocol Amendment 02

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1 BACKGROUND AND RATIONALE

Background:

Renal transplantation is the most effective treatment for adults and pediatric patients of all ages with end stage renal disease. Compared with dialysis, kidney transplantation offers improved medical outcome, cognitive function, social adjustment, and quality of life.[1,2] Significant unmet medical needs remain in kidney transplantation, among which is the need for new therapies that can reduce the substantial toxicities associated with calcineurin inhibitor-based immunosuppressive regimens.

[redacted]

Study Rationale:

[redacted]

This will be an open-label, randomized, parallel-group, single-dose study to compare the PK of belatacept between 2 drug products manufactured by 2 different processes administered in healthy subjects. Parallel design was selected because the long half-life (T-HALF; approximately 10 days) would make it operationally challenging to washout and retain subjects, and the potential impact of immunogenicity response on PK in a crossover design. Previous studies have shown that there is a trend of higher clearance with increasing body weight.[4] Belatacept has linear PK from 1 to 20 mg/kg. This study will assess the most clinically applicable dose, 10 mg/kg, which is the highest approved dose. Belatacept has been given as single doses to normal healthy volunteers (NHVs) and shown to be safe and well tolerated.[5] There have been no deaths or serious adverse events (SAEs), and no subjects have discontinued from a study due to adverse events (AEs) in the pooled NHV population. A study in healthy volunteers is considered to be more sensitive in evaluating the product similarity because it is likely to produce less PK

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variability compared with that in patients with potentially confounding factors such as underlying and/or concomitant disease and concomitant medications.[6]

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).

Schedule of Analyses:

Final analysis will be performed following database lock according to agreed-upon reporting milestone(s), typically after all subjects have completed the study.

Exclusions of Site 2 Data Due to Major Protocol Deviations:

Prior to protocol amendment 02 (dated September 27, 2016), 146 subjects were dosed at 3 clinic sites: 60 at Site 1 (PPD), 30 at Site 2 (SNBL), and 56 at Site 3 (MRA). Audit and monitoring visits revealed major protocol deviations at Site 2 including but not limited to inclusion/exclusion criteria deviations, not providing HIPAA consent at screening visit, incomplete source documentation, failure to obtain laboratory tests within the pre-specified windows, failure to obtain protocol-specified laboratory tests, and incorrect handling of blood samples. Due to the number and significance of these deviations affecting the data of all subjects at Site 2, the 30 dosed subjects were not considered eligible for the analysis of the study endpoints.

Removing the data from the 30 dosed subjects at Site 2 from the analysis without replacing it would result in a total of 116 dosed subjects and under-power the study (approximately 74% power, assuming a true difference of 11%).

The protocol amendment 02 (dated September 27, 2016) was written to replace those 30 dosed subjects at Site 2 with 30 new subjects at Site 1 and Site 3, in order to maintain sufficient power. Randomization of the 30 new subjects was stratified by weight categories in the same way as for the originally planned subjects.

The 30 dosed subjects at Site 2 will not be included in the analysis and 30 replacement subjects dosed at Site 1 and Site 3 will be included in the analysis. A total of 176 subjects will be dosed including the originally planned 146 subjects and the 30 replacement subjects.

In addition, the data from the subjects who were enrolled at Site 2 will only be presented in the listings and be excluded from any summaries or statistical analyses.

2 STUDY DESCRIPTION

2.1 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. The data from the 30 subjects who were enrolled and dosed at Site 2 will

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not be included in the analysis, and the data from the 30 replacement subjects to be dosed will be included in the analysis.

The initial plan was to dose approximately 146 subjects (approximately 73 in each treatment group) in order to complete a minimum of 67 subjects per treatment group. Given the protocol deviations at Site 2, the number of subjects dosed in this study has increased to approximately 176 in order to ensure adequate sample size for the analysis for the primary objective. 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 approximately 88 subjects (73 initial planned and 15 replacements) per treatment group 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 serum samples will be collected at selected times throughout the study. Serum samples for immunogenicity will be obtained prior to dosing and after dosing on Days 29, 43, 57, and 71.

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic

<table>
<tr><th>Days -28 to -1</th><th colspan="2">Day 1</th><th>Day 4</th><th>Days 5 to 71</th><th>Day 71</th></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 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.

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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.

2.2 Treatment Assignment

Subjects will be randomly assigned to Process E belatacept or Process C belatacept in 1:1 ratio according to a computer-generated randomization scheme, stratified by weight categories: 60 to < 70 kg, 70 to < 80 kg, 80 to < 90 kg, and 90 to 100 kg. Randomization numbers will be assigned prior to dosing.

2.3 Blinding and Unblinding

This is an open-label study.

2.4 Protocol Amendments

This analysis plan reflects all protocol amendments through Amendment #2, dated 27-Sep-2016.

3 OBJECTIVES

3.1 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.

3.2 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.

3.3 Exploratory Objective

There are no exploratory objectives.

4 ENDPOINTS

4.1 Efficacy Endpoints

There are no planned efficacy endpoints.

4.2 Safety Endpoints

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.

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4.3 Pharmacokinetic Endpoints

Pharmacokinetic parameters of belatacept will be derived from serum concentration versus time data by collection interval. Individual PK parameter values will be derived by noncompartmental methods by a validated PK analysis program using actual times.

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

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

Table 4.3-1: PK Parameters, Naming Conventions and Definitions

Parameter	Definition
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
T-HALF	Terminal serum half-life
CLT	Total body clearance
Vss	Volume of distribution at steady state

4.4 Biomarker Endpoints

There are no planned biomarker endpoints.

4.5 Exploratory Biomarker Endpoints

There are no planned exploratory biomarker endpoints.

4.6 Immunogenicity Endpoints

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

5 SAMPLE SIZE AND POWER

[redacted]

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[redacted]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

The pre-treatment period will be from the time the Informed Consent Form (ICF) is signed until just prior to dosing on Day 1 for all subjects. The pre-treatment period will be no longer than 28 days and will include all screening, Day -1, pre-dose on Day 1 and randomization procedures.

Treatment period will be from the time of doing on Day 1 until the subject is discharged on Day 71 (or until premature discontinuation after dosing on Day 1)

Any data collected at study discharge and afterwards will be assigned to the post-treatment period.

6.2 Treatment Regimens

Treatment A = belatacept 10 mg/kg IV, Process E belatacept

Treatment B = belatacept 10 mg/kg IV, Process C belatacept

6.3 Populations for Analyses

The exclusion of the subjects from Site 2 due to major protocol deviations is described in the footer of planned outputs in the Data Presentation Plan (DPP) as appropriate.

- 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 a 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.

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- The PK Population is a subset of the Treated Population. The PK population includes all treated subjects who had any available concentration-time data and did not have any protocol deviations which were determined to affect PK parameters.
- The Evaluable PK Population is a subset of the PK Population. The Evaluable PK Population includes all subjects who have adequate PK profiles. All available derived PK parameter values will be included in the PK data set and reported, but only subjects with adequate PK profiles will be included in the summary statistics and statistical analysis.
- The Immunogenicity Analysis Population: All treated subjects with at least 1 post-baseline immunogenicity result reported will be included in immunogenicity analysis.

7 STATISTICAL ANALYSES

SAS® version 9.2 or higher will be used for statistical analyses, tabulations, and graphical presentations.

7.1 General Methods

The data from the subjects who were enrolled at Site 2 will not be included in any summaries or statistical analyses. These data will only be presented in the listings. Details of the data presentation are specified in the DPP. The data from the 30 replacement subjects along with the data from the initial 116 subjects who were enrolled and dosed at the other sites will be used for analyses.

All data recorded on case report forms will be listed by subject. Descriptive summaries will be presented for continuous variables using number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. Geometric mean and coefficient of variation (CV%) will also be presented for sample serum concentration-time data and PK parameters. Descriptive summaries for categorical variables will utilize counts and percentages.

For all treatment comparisons, a linear fixed effect model with treatment as a fixed effect will be fitted to the log-transformed PK parameters Cmax, AUC(0-T) and AUC(INF) for use in estimation of effects and construction of CIs. Point estimates and 90% CIs for differences on the log-scale will be exponentiated to obtain estimates for ratios of geometric means and respective 90% confidence intervals on the original scale. The SAS procedure (PROC MIXED) will be used to derive all inter-subject variances, and for the estimation of test to reference ratios and respective confidence intervals.

Adverse events and medical history will be coded according to the most recent Medical Dictionary for Regulatory Activities (MedDRA) version. Previous and concomitant medications will be coded using the BMS Drug Dictionary.

7.2 Study Conduct

Relevant deviations from the study protocol, protocol amendments and administrative changes will be documented and accounted for in presenting the data summaries, listings and descriptive statistical analyses. Deviations of protocol-specified inclusion and exclusion criteria, and protocol deviations as recorded on a log maintained by the clinical monitors, will be listed. Any

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changes from planned protocol-specified analysis, if any, will be defined in the SAP and reported in the clinical study report (CSR).

7.3 Study Population

7.3.1 Subject Disposition

Subject disposition will be listed. Summary tables reflecting the number of subjects who are enrolled, who are randomized, reasons for not being randomized, who are treated, and who completed the study will be presented as overall.

The number of subjects who do not complete the study, both overall and according to reasons for discontinuation from the study, will be summarized for all treated subjects, as overall and by treatment.

7.3.2 Demographic Characteristics

Demographic characteristics such as gender, age, race and ethnicity will be listed for all treated subjects. Demographic characteristics will also be summarized for all treated subjects, as overall and by treatment.

7.3.3 Physical Measurements

Physical measurements such as body weight, height and body mass index (BMI) will be listed for all treated subjects. Measurements will also be summarized by nominal visit for all treated subjects, as overall and by treatment.

7.3.4 Medical History and Previous Medications

Medical history and previous medications taken prior to dosing will be listed for all treated subjects.

7.4 Extent of Exposure

No analysis regarding extent of exposure is planned. Study drug administration, randomization schedule, and batch numbers will be documented as per subject listings. Any non-study medications taken by subjects, any conducted non-study medical treatment procedures, and any utilized non-study diagnostic procedures will also be listed.

7.5 Efficacy

There are no efficacy assessments in the study.

7.6 Safety

Analysis of all safety data will follow the BMS guideline of analysis of safety data[7].

The evaluation of safety is based on clinical AEs, vital signs, ECG results, clinical laboratory results, and physical examination findings reported during the study. Unless otherwise specified, all safety presentations will utilize the treated population as described in Section 6.3.

All recorded AEs will be listed and tabulated by system organ class (SOC), preferred term (PT), treatment and overall. Any physical examination findings will be listed. ECG, vital signs and clinical laboratory test results and corresponding change from baseline values will be listed and

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summarized by treatment and visit. Values for ECG, vital signs and clinical laboratory test results outside the pre-specified criteria will also be listed and summarized. Electrocardiogram readings will be evaluated by the investigator and abnormalities, if present, will be listed.

Where appropriate, baseline is defined as the last non-missing result with a collection date-time less than the date-time of the first active dose of study medication, for laboratory results, vital signs, and ECG results.

7.6.1 Deaths

All reported deaths after a subject is enrolled (i.e., has signed the informed consent) will be listed separately by subject.

7.6.2 Serious Adverse Events

All reported SAEs will be listed and summarized for all enrolled subjects.

7.6.3 Adverse Events

All AEs will be coded and grouped into PT by SOC, using MedDRA. Listings and summaries will be based on the resulting SOCs and PTs.

Adverse events which occur on or after the first dose of study treatment will be tabulated. Events will be assigned to the study treatment administered to the subject. Events occurring after discharge will be assigned to the study treatment received for SAEs reported through Day 101 after the dose of the study drug and non-serious AEs that are reported through Day 71 after the dose of the study drug. The proportion of subjects having an AE will be calculated as the number of subjects experiencing the event, divided by the total number of subjects receiving study treatment.

All AE listings will indicate the unique subject identifier, age, gender, current treatment, the date of onset, the date of resolution, day of onset relative to the start of treatment, action taken, investigator's assessment of severity and relationship to study drug. Additional listings will be provided for AEs leading to discontinuation and AEs without recorded resolution. Summaries of AEs will include AEs, AEs by intensity and AEs by relationship.

Where a subject has the same AEs, based on preferred terminology, reported multiple times in a single analysis period, the subject will only be counted once at the preferred terminology level in AE frequency tables.

Where a subject has multiple AEs within the same SOC in a single analysis period, the subject will only be counted once at the SOC level in AE frequency tables.

When a subject has the same AE, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Relationship to study medication
- Intensity of event
- Onset date and time

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When reporting AEs by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- Intensity of event
- Onset date and time

Subjects will only be counted once in the 'Total' at their maximum intensity, regardless of SOC or PT.

7.6.4 Clinical Laboratory Evaluations

The results of all protocol-specified clinical laboratory tests, as well as laboratory results outside of the normal range, will be listed. Scheduled laboratory measurements and corresponding change from baseline values will be summarized by treatment and nominal visit for each laboratory test. Laboratory evaluations will be reported both in conventional units and in SI units.

Laboratory results will be classified as markedly abnormal based on sponsor-defined criteria. The criteria will be listed.

Laboratory results for subjects with any marked laboratory abnormality (scheduled and unscheduled) will be listed. This listing will include all observations for the specific laboratory test and subject, not only the marked laboratory abnormalities. The frequency of subjects with any marked laboratory abnormality as well as hematology, serum chemistry, and urinalysis marked abnormalities, based on pre-specified criteria, will be presented.

Laboratory results will be listed for subjects with ALT results greater than 3 times of upper limit of normal (ULN) and total bilirubin results greater than 2 times of ULN on the same date. This listing will include all observations for ALT, total bilirubin, AST, and alkaline phosphatase for the above mentioned subjects.

Pregnancy results will be listed.

7.6.5 Electrocardiograms

All recorded ECGs will be listed. The investigator identified ECG abnormalities will be listed.

If QT interval corrected for heart rate using the Fridericia formula (QTcF) is not available in the database, QTcF will be calculated using the reported uncorrected QT interval and heart rate, and the following formula:

$$QTcF = \frac{QT}{(60/HEART\ RATE)^{1/3}}$$

If QT corrected for heart rate using the Bazett formula (QTcB) is not available in the database, QTcB will not be calculated.

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Summaries of ECG parameters (heart rate (HR), QT (QT, QTcF), PR and QRS intervals) will be tabulated by study day and treatment. Summaries of ECG parameters will include change from baseline at end of study.

Subjects with ECG intervals outside of a pre-specified range will also be listed.

The following criteria will be used to determine ECG results that are outside of a pre-specified range:

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

7.6.6 *Vital Signs*

Vital signs parameters (systolic blood pressure (BP), diastolic BP, heart rate, respiratory rate, and body temperature) will be listed. Summaries of vital sign parameters will be provided for each vital sign parameter at corresponding visits by treatment and respective changes from baseline.

Subjects with vital signs outside of a pre-specified range will also be listed.

The following criteria will be used to determine vital sign results that are outside of a pre-specified range, where changes from baseline are based on matched postural positions and are calculated as parameter value - baseline parameter value:

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

7.6.7 *Physical Examination Findings*

All physical examination abnormal findings will be listed per subject and visit.

7.7 Pharmacokinetics

The PK population will be used for all listings. Evaluable PK population will be used for summary statistics and statistical analyses. Analysis will include all analyte data in the PK dataset for belatacept.

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Subject serum concentration-time data will be listed and summarized by treatment and nominal collection time for belatacept. Details of T-HALF derivation and the harmonic mean of terminal slope by treatment will also be presented. Plots of individual serum concentration profiles over time will be provided. Overlay of individual serum concentration profiles over time will be provided by treatment. Plots of mean (+SD) serum concentration profiles versus time will be presented for belatacept, and both treatments will be superimposed on the same plot.

All individual PK parameters will be listed for belatacept including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and CV% will be presented for Cmax, AUC(0-T), AUC(INF), CLT, and Vss. Medians and ranges will be presented for Tmax. Arithmetic mean and standard deviation will be presented for T-HALF. Decimal place specifications for summary statistics are described in Section 7.10.

Separately by antibody status (negative antibody status with respect to baseline as defined in Section 7.9) and overall, a linear fixed effect model with treatment as a fixed effect will be employed. Kenward-Rogers degrees of freedom will be specified in the model. Point estimates and 90% CIs for treatment differences on the log-scale will be exponentiated to obtain point estimates and 90% CIs for the ratios of geometric means 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. The following SAS code will be implemented, where A is the Process E belatacept, and B is the Process C belatacept.

[redacted]

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

In addition, the impact of anti-belatacept antibody status on PK parameters will also be evaluated in individual subjects. Summary statistics may be tabulated for each PK parameter by antibody status for each treatment. Plots of individual PK parameters versus treatment by antibody status may be provided. Refer to Section 7.9 for the definition of positive antibody status for each subject.

7.8 Biomarkers

No biomarker assessments are scheduled for this study.

7.9 Immunogenicity

[redacted]

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[redacted]

7.10 Conventions

Enhanced Biometric Analysis & Reporting Capability (EmBARC) standard time windowing, imputation rules, and counting rules will be applied.

7.10.1 Decimal Places

The number of decimal places displayed in efficacy, safety, and biomarker listings will be determined by the number of decimal places in the raw data.

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, one more decimal place for the mean and median, and two more decimal places for the standard deviation. The adjusted geometric mean, geometric mean ratio and the lower and upper limits of CI will be displayed to three decimal places.

7.10.2 Pharmacokinetic Summaries

In-text Tables

For in-text PK tables, CV% will be reported as integers. For other statistics except for standard deviations, values of 100 or higher will be presented as integers, values of 10 - <100 will be displayed to one decimal place, and values of 1 - < 10 will be displayed to two decimal places.

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Values less than 1 will be displayed to three decimal places. Ratios will also be displayed to three decimal places. Standard deviations will be reported to a precision of 1 decimal place more than the mean.

Handling of Non-Quantifiable Concentrations[8]

For the summaries of serum concentration-time data, concentrations that are less than the lower limit of quantification (LLOQ) should be displayed as "< LLOQ" in the listings and be treated as missing in summary tables and plots. For the purpose of calculating PK parameters, pre-dose concentrations that are less than LLOQ and concentrations prior to the first quantifiable concentration that are less than LLOQ will be set to zero, and all other concentrations less than LLOQ will be set to missing.

All available serum concentration-time data and derived PK parameter values will be included in the PK data set and listed accordingly.

Treatment of Outliers

Individual serum concentrations, if deemed to be anomalous, may be excluded from the analysis following a review of available documentation (e.g., bioanalytical report, clinical data). Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Entire serum concentration-time profiles for a subject may be excluded following review of available documentation (e.g., bioanalytical report, clinical data). However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

PK Exclusions[8]

PK Analysis, Reporting, and Exclusion criteria should following the BMS PK Harmonization document Version 3.0. Specific guideline for exclusionary criteria for half-life and how other PK parameters are affected for exclusion is under section 6.2 of the BMS PK Harmonization document.

8 CONTENT OF REPORTS

Statistical components for the clinical study report will be based on the content of this statistical analysis plan (SAP). Details of the tables, listings, and figures to be prepared for the final CSR will be included in a study-specific DPP.

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9 REFERENCES

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