Official Title of Study:

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

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STATISTICAL ANALYSIS PLAN

FOR

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

FINAL VERSION # 2.0

Revision History

Revision	Date	Revised By	Changes Made -- Reasons for the Change
1.0	11Feb2019		Original issue
2.0	28Aug2019	[redacted]	Added neutralizing antibody analysis and PK analysis excluding subjects with positive abatacept-induced ADA

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[redacted]

2 STUDY DESCRIPTION

2.1 Study Design

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

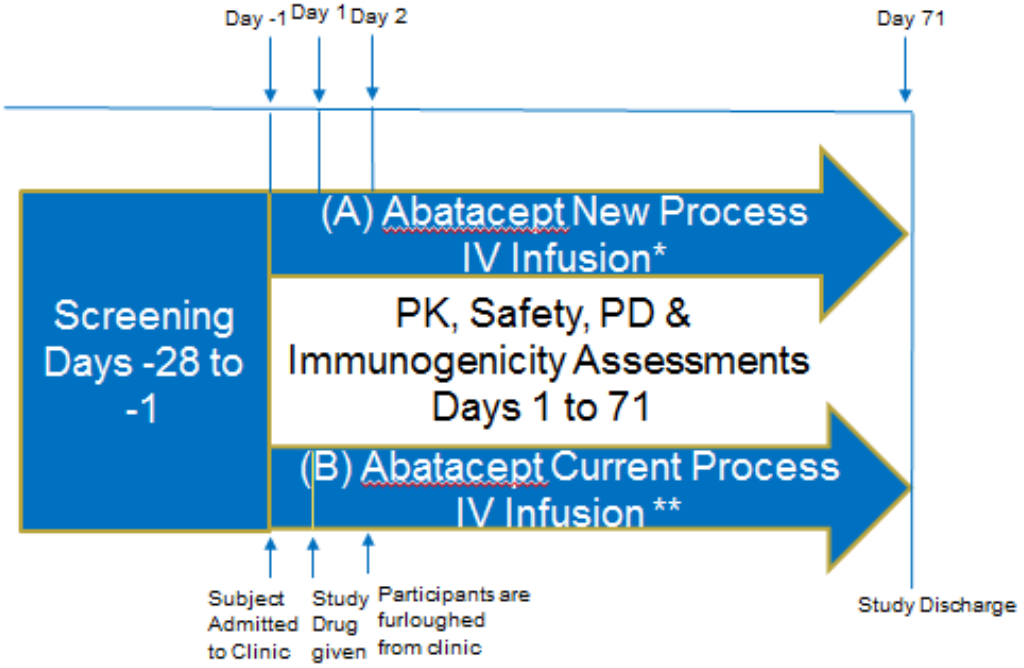
Participants will undergo screening evaluations to determine eligibility within 28 days prior to drug administration on Day 1. All participants are required to weigh between 60 and 100 kg, inclusive, and should be weighed using the same scale at each site.

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

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

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

Figure 2.1-1: Study Design Schematic



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

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical laboratory evaluations will be performed at selected times throughout the dosing interval.

Participants will be closely monitored for adverse events (AEs) throughout the study. Blood samples for PK analysis, immunogenicity, and PD assessments will be collected for up to 1680 hours (70 days) after study treatment administration. Approximately 260 mL of blood will be drawn from each participant during the study.

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

2.2 Treatment Assignment

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

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

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

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

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

Randomization numbers will be assigned prior to dosing.

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

2.3 Blinding and Unblinding

This is an open-label study.

2.4 Protocol Amendments

There has been one protocol amendment for this study. The first protocol amendment was issued on November 15, 2018 and includes the following updates:

- Exclusion criterion 3a was updated [redacted]
- Appendix 3 (Adverse Events and Serious Adverse Events, Definitions and Procedures for Recording, Evaluation, Follow Up and Reporting) was replaced with the most current version.
- In the schedule of activities, the collection of nonserious AEs on Day 1 was specified to begin at the start of study treatment.
- Terminology describing study patients was aligned (“subject” was replaced with “participant”).

- The Study Director's contact information was updated.

[redacted]

3 OBJECTIVES AND ENDPOINTS

Table 3-1: Objectives and Endpoints

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

4 SAMPLE SIZE AND POWER

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

Participants who drop out will be replaced to ensure that there will be at least 65 evaluable participants per treatment group. Sixty-five participants per treatment group will provide 86%

power to conclude that Treatment A is biocomparable to Treatment B if Treatment A increases abatacept exposure by 10% compared to Treatment B and 80% power if Treatment A decreases abatacept exposure by 10%.

These calculations assume that AUC(INF), and Cmax are log-normally distributed with between-participant standard deviation (SD) of 0.21 for Cmax and 0.27 for AUC(INF), as reported in the single dose IV study in healthy participants (IM101292) for manufacturing site transfer.[3]

5 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

5.1 Study Periods

- The pre-treatment period will be from the time the Informed Consent form is signed until dosing on Study Day 1 for all participants. The pretreatment period should be no longer than 28 days and will include all screening, enrollment, and Day -1 procedures.
- Study Period will be from the day of dosing on Study Day 1 until discharge visit on Study Day 71.

5.2 Treatment Regimens

In the morning on Day 1, after fasting for at least 1 hour, each participant will receive a 30-minute IV infusion of a single dose (750 mg) abatacept drug product converted from drug substance by a new process or a 30-minute IV infusion of a single dose (750 mg) abatacept drug product converted from drug substance by the current process.

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

5.3 Populations for Analyses

For purposes of analysis, the following populations are defined:

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

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

Pharmacokinetic listings and PK parameter calculations will be based on the PK population. All available derived PK parameter values will be included in the PK data set and reported, but only

participants in the Evaluable PK Population will be included in the summary statistics and statistical analysis.

6 STATISTICAL ANALYSES

SAS®, version 9.3 or higher, will be used for statistical analyses, tabulations, and graphical presentations.

6.1 General Methods

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

Where appropriate, baseline is defined as the last nonmissing result with a collection date-time less than the date-time of the first dose of study treatment.

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 World Health Organization (WHO) Drug Dictionary.

6.2 Study Conduct

Deviations from the study protocol, and administrative changes will be documented. In general, relevant protocol deviations are a subset of the significant protocol deviations that could potentially affect the interpretability of study results. In this healthy volunteer study there are no relevant protocol deviation criteria specified.

6.3 Study Population

6.3.1 Participant Disposition

Participant disposition will be listed. Summary tables reflecting the number of subjects who are enrolled, who are randomized, who are not randomized, who are treated, and reasons for not being randomized and not entering treatment period will be presented as overall.

The number of participants who complete the study, who do not complete the study, and reasons for not completing the study, will be summarized for all treated participants, overall and by treatment.

6.3.2 Demographic Characteristics

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

6.3.3 Physical Measurements

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

6.3.4 Medical History and Previous Medications

Medical history and previous/concomitant medications taken prior to dosing or during the course of the trial will be listed for all treated participants.

6.4 Extent of Exposure

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

6.5 Efficacy

There are no efficacy assessments in the study.

6.6 Safety

Analysis of all safety data will follow the BMS guideline of analysis of safety data. The evaluation of safety is based on clinical AEs, vital signs, ECG results, and clinical laboratory results reported during the study.

All data collected from the sampling outside the scheduled visits will only be included in the listing and will be excluded from the summary tables.

6.6.1 Deaths

All reported deaths after a participant is enrolled (ie, has signed the informed consent) will be listed by participant.

6.6.2 Serious Adverse Events

All reported serious adverse events (SAEs) will be listed for all enrolled participants.

6.6.3 Adverse Events

Adverse events that occur on or after the administration of study treatment will be tabulated. Events occurring after discharge will be assigned to the study treatment received for up to 56 days after the termination of study drug. The proportion of participants having an AE will be calculated as the number of participants having the event in the specific treatment interval, divided by the total number of participants receiving study treatment during that treatment interval.

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. The AE listing of all AEs will also include those AEs that occurred beyond 56 days after the termination of study drug. Additional listings will be provided for AEs leading to discontinuation and AEs without recorded resolution.

All AEs will be summarized by system organ class, preferred term, treatment and overall for all treated participants. Summaries of AEs will include AEs, AEs by intensity and AEs related to study drug.

Additional summaries will be provided for acute peri-infusional and postinfusional AEs that occurred during the 30-minute infusion period and the 24-hour post-infusion period, respectively, after the start of the abatacept infusion.

AE Counting Rules:

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

When a participant 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

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

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

6.6.4 Injection Site Reaction

Injection site reaction data will be listed per participant and time point.

6.6.5 Clinical Laboratory Evaluations

The results of all protocol-specified clinical laboratory tests and corresponding change from baseline values will be listed by subject for all treated participants. Laboratory measurements and corresponding change from baseline values will be summarized by treatment and scheduled nominal visit for each laboratory test.

The criteria used for classifying laboratory test results as markedly abnormal will be listed.

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

Laboratory results for participants with any marked laboratory abnormality (scheduled and unscheduled) will be listed. This listing will include all observations for the specific laboratory test and participant, not only the marked laboratory abnormality measurements. The frequency of participants with any marked laboratory abnormality, based on pre-specified criteria, will be presented.

6.6.6 Electrocardiograms

All recorded electrocardiograms (ECGs) will be listed for all treated participants.

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

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

If QTcB is not available in the database, QTcB will not be calculated.

Summaries of ECG parameters (HR, QT (QT, QTcB, QTcF), PR, and QRS intervals) will be tabulated by study day and treatment. Summaries of ECG parameters will include change from baseline at Day 1, 3 hours after the start of infusion, and Day 71 (at discharge). Baseline will be considered as Day 1 pre-dose measurement.

Participants with ECG intervals outside of a pre-specified range and investigator identified ECG abnormalities will also be listed.

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

PR (msec):	Value > 200
QRS (msec):	Value > 120
QT (msec):	Value > 500 or change from baseline > 30
QTcB (msec):	Value > 450 or change from baseline > 30
QTcF (msec):	Value > 450 or change from baseline > 30

6.6.7 Vital Signs

Vital signs parameters (systolic blood pressure, diastolic blood pressure, 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.

Participants 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 calculated as parameter value - baseline parameter value:

Heart Rate (bpm)	Value > 100 and change from baseline > 30, or Value < 55 and change from baseline < -15
Systolic BP (mmHg)	Value > 140 and change from baseline > 20, or Value < 90 and change from baseline < -20
Diastolic BP (mmHg)	Value > 90 and change from baseline > 10, or Value < 55 and change from baseline < -10
Respiration (breaths/min)	Value > 16 or change from baseline > 10
Temperature (°C)	Value > 38.3°C or change from baseline > 1.6°C

6.6.8 Physical Examination Findings

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

6.7 Pharmacokinetics

The Pharmacokinetic (PK) population will be used for all listings. Evaluable PK population will be used for summary statistics and statistical analyses. Statistical analyses will be repeated excluding subjects with positive abatacept induced ADA responses. Analysis will include all valid analyte data for BMS-188667.

Subject serum concentration-time profiles will be listed and summarized by treatment and nominal collection time. Plot 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 the first 24 hours and separately for the entire study duration on both linear and log-linear scale and both treatments will be superimposed on the same plot. Scatter plots of PK parameters for Cmax, T-HALF, CLT, Vss, AUC(0-28 day), AUC(0-T), and AUC(INF) will be produced for each treatment.

All individual PK parameters will be listed including any exclusions and reasons for exclusion. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and coefficients of variation will be presented for Cmax, AUC(INF), AUC(0-T), AUC(0-28 day), CLT and Vss. Medians and ranges will be presented for Tmax. Means and standard deviations will be presented for other PK parameters (i.e., T-HALF). Decimal place specifications for summary statistics are described in Section 6.9.

To assess comparability of Treatment A (new drug substance process) to Treatment B (current drug substance process), an ANCOVA model will be fitted with treatment as a fixed effect and adjusted for baseline body weight. Point estimates and 90% CIs for treatment differences on the log scale for AUC(INF) and Cmax will be exponentiated to express the results as ratios of geometric means and the corresponding 90% CIs on the original scale. Biocomparability of Treatment A to Treatment B will be concluded if the 90% CIs for the ratios of geometric means for abatacept Cmax and AUC(INF) are contained within 80% to 125%.

[redacted]

In addition, the adjusted geometric mean ratios (GMRs) and corresponding 90% CIs for AUC(INF) and Cmax will be summarized in forest plots overall and by baseline weight class. These estimates will be obtained from a model with treatment and baseline body weight class as fixed effects.

[redacted]

A listing of subjects excluded from the Evaluable PK Population along with reasons for exclusion will be provided.

[redacted]

6.8.1 Immunogenicity

On Day 1, the immunogenicity sample should be drawn at predose.

Participants who seroconvert and continue to have a high titer at study discharge that is considered to be significantly increased versus baseline will be asked to return for follow-up assessment(s) for anti-abatacept antibodies approximately every 4 months until their titers and/or sero-status are judged to be stable by the investigator.

Lack of immunogenicity is defined as the absence of a positive antibody response generated against abatacept. A participant is considered to have a positive abatacept-induced immunogenicity for "CTLA4 and possibly immunoglobulin (Ig)" and "Ig and/or Junction Region" if one of the following criteria are met:

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

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

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

The incidence of laboratory-reported positive responses and the corresponding titer values will be listed by participant and by study day. The frequency and percentage of positive, abatacept-induced immunogenicity response will be summarized by treatment.

Titer will be listed.

The number and percentage of subjects with a positive neutralizing antibody response will be summarized by treatment group and study day. The summary will include all subjects with a positive abatacept-induced immunogenicity response.

Neutralizing antibody data will be listed.

[redacted]

6.9 Conventions

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

6.9.1 Decimal Places

The number of decimal places displayed in all 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 the CI will be displayed to three decimal places.

One decimal place for percent change from baseline data and 3 decimal places for ratio will be used for data presentation.

6.9.2 Pharmacokinetic Summaries

In-text Tables

For in-text pharmacokinetic tables, coefficient of variation (%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. 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

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 pharmacokinetic 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

PK Analysis, Reporting, and Exclusion criteria should following the BMS PK Harmonization document Version 2.0. Specific guideline for exclusionary criteria for half-life and how other PK parameters are affected for exclusion is under section 9.2 of the BMS PK Harmonization document.

Exclusion of one or more parameters or the entire dataset may be considered due to incomplete profile such as AUC(INF) or when T-HALF cannot be reliably calculated, or there is no sample around the suspected Cmax. In addition, subjects may be excluded from the analysis if they missed dosing.

7 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 Data Presentation Plan (DPP).

[redacted]