Official Title of Study:

Randomized, Double-Blind, Parallel Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BMS-936558 (nivolumab) in Participants with Severe Sepsis or Septic Shock

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STATISTICAL ANALYSIS PLAN
FOR BMS-936558

RANDOMIZED, DOUBLE-BLIND, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF BMS-936558 (NIVOLUMAB) IN PARTICIPANTS WITH SEVERE SEPSIS OR SEPTIC SHOCK.

PROTOCOL CA209923

VERSION # 2.0

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2 STUDY DESCRIPTION

2.1 Study Design

CA209923 is a Phase 1b, randomized, double-blind, multi-center study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of a single dose of nivolumab in participants with severe sepsis or septic shock.

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

Figure 2.1-1: Study Design Schematic

Screening	Baseline	Treatment	On-Treatment Assessments
Day -10 to -1	Day -1	Day 1	Day 1 to Day 90
Determine eligibility	Randomize eligible participants (1:1 ratio)	Single dose nivolumab 480 mg (n=15) OR	Hospital discharge may occur prior to Day 90

		Single dose nivolumab 960 mg (n=15)	

The total duration of study for each participant is approximately 100 days, comprised of a screening period of up to 10 days, plus a single dose on Day 1, followed by clinical study assessments up to Day 90. AEs and SAEs will be collected up to Day 90.

Physical examinations, vital sign measurements, 12-lead electrocardiograms (ECG), and clinical safety laboratory assessments will be performed at selected times throughout the study. Participants will be closely monitored for adverse events throughout the study. Serial blood samples for PK, RO, PD, biomarker, and immunogenicity analyses will be collected predose and at selected time points postdose. Up to approximately 452 mL of blood will be drawn from each participant during the study (within any 7 day interval, no more than 180 mL may be drawn). Clinical parameters of organ dysfunction will be assessed predose and at selected time points postdose during participants' index hospitalization.

2.2 Treatment Assignment

Subjects will be randomized to receive either single dose nivolumab 480mg or single dose nivolumab 960mg according to a randomization scheme generated by an Interactive Response Technology (IRT). Before the study is initiated, each user will receive log in information and directions on how to access the IRT.

During the screening visit, the investigative site will contact the Interactive Response Technology (IRT) system to assign the participant identification number. Once it is determined that the participant meets the eligibility criteria following the screening visit, the investigative site will call the IRT to randomize the participant into the open dose panel.

2.3 Blinding and Unblinding

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

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

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

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

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

In case of an emergency, the investigator(s) has unrestricted access to randomization information via the Interactive Response Technology (IRT) and is capable of breaking the blind through the IRT system without prior approval from sponsor. Following the unblinding the Investigator shall notify the medical monitor and/or study director. For information on how to unblind in an emergency, consult the IRT manual.

Study participants and all clinical research site personnel, except the pharmacist, will be blinded. The pharmacist at the site and/or designee will be unblinded to the randomized treatment assignments in order to dispense treatment from bulk supplies, as needed.

Members of BMS Research and Development and their designees will be unblinded to study treatments to facilitate real-time analyses of PK, RO, and safety data in support of dose selection for future studies. No unblinded data will be communicated to Investigators or to other blinded clinical research site personnel. This unblinding is not expected to affect the integrity of the trial. PK and RO endpoints are objective assessments that should not be affected by unblinding, and BMS personnel will not communicate any trial results to the site to avoid any introduction of bias in safety assessments.

2.4 Protocol Amendments

This Statistical Analysis Plan (SAP) incorporates the Protocol Amendments below.

Document	Date of Issue	Summary of Change
Revised Protocol 01	03-Mar-2017	Incorporates Amendment 01
Amendment 01	03-Mar-2017	The number of participants in the study was clarified as being “up to approximately 30” to reflect the fact that 30 participants is the maximum number planned. A key objective of this study is to characterize the pharmacokinetics (PK) of nivolumab in participants with sepsis, with the goal to obtain a PK profile from at least 6 subjects per dose level. The body weight eligibility criteria was revised to (1) remove the word “ideal,” which was inadvertently included in the original protocol, and (2) align the upper limit of body weight with that studied in the nivolumab oncology development program. In the original protocol, members of BMS Research and Development are blinded; in the amended protocol, they will be unblinded to study treatment in order to facilitate real-time analyses of PK, RO, and safety data in support of dose selection for future studies. The unblinded data and the corresponding analysis/report will be included in documents for communication with regulatory authorities. The investigators, all study personnel with the exception of

		the pharmacist, and patients will remain blinded until the end of the study. The discrepancy between textual description of the schedule for thyroid function testing in Section 9.4.4 and the tabular presentation in Table 2-2 was corrected. A typographical error relating to time relative to dosing in hours at the Day 28 time point was corrected. The potential interim analysis was removed because, in the amended protocol, the BMS team is fully unblinded thus the interim analysis becomes unnecessary. The amendment applies to all subjects.

3 OBJECTIVES

3.1 Primary Objective

- To assess the safety and tolerability of a single dose of nivolumab 480 mg or 960 mg in participants with severe sepsis or septic shock
- To assess the pharmacokinetics of BMS-936558 in participants with severe sepsis or septic shock

3.2 Secondary Objective

- To assess receptor occupancy of nivolumab following single dose administration
- To assess the effect of a single dose of nivolumab on monocyte HLA-DR expression and absolute lymphocyte count
- To assess the immunogenicity of nivolumab following single dose administration

4 ENDPOINTS

4.1 Primary Endpoint

The primary objective (to assess the safety and tolerability) will be measured by the incidence rates of AEs, SAEs, AEs leading to discontinuation, immune-mediated AEs, and deaths. In addition, clinical laboratory tests, vital signs, and ECGs will be summarized.

The primary objective (to assess the pharmacokinetics of BMS-936558) will be measured by the following PK endpoints.

C_{max}	Peak nivolumab serum concentration
C_{min}	Trough nivolumab serum concentration
C_{avg}	Average nivolumab serum concentration
T_{max}	Time of maximum observed concentration
CLT	Total clearance
V_d	Volume of distribution
$T_{1/2.}$	Half-life
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration

4.2 Secondary Endpoints

- Receptor occupancy on T cells at baseline and after study treatment administration at planned sampling time points
- Baseline and post-dosing assessments of mHLA-DR expression on monocytes, and of absolute lymphocyte count
- Number and percentage of participants with detectable anti-nivolumab antibodies at baseline and following single dose administration of nivolumab and the relationship with other outcome measures

[redacted]

[redacted]

5 SAMPLE SIZE AND POWER

The number of participants is not based on statistical power consideration. Administration of nivolumab to up to approximately 15 participants in each arm provides an 80% probability of observing at least one occurrence of any adverse event that would occur with ≥ 10% incidence in the population from which the sample is drawn.

The overall purpose of Study CA209923 is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of two single doses of nivolumab in participants with severe sepsis or septic shock in order to inform feasibility and conduct of further studies of nivolumab in this population. Specifically, a key objective is to determine whether the exposures observed after a single dose of nivolumab in participants with severe sepsis or septic shock are comparable to the overall exposures observed at steady-state dosing with the nivolumab regimen approved in oncology indications. In order to achieve this goal, up to 15 subjects per dose level are estimated in order to obtain a PK profile from at least 6 subjects per dose level.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

This study consists two periods: pre-treatment and on-treatment.

The pre-treatment period begins with screening and extends until study drug administration on Day 1.

Measurements taken before Day 1 are considered pre-treatment for all data domains. In addition, measurements taken on Day 1 are considered pre-treatment for the following data domains: demography, SNP, medical history, physical measurements, inclusion/exclusion, and patient reported outcomes.

The on-treatment period begins with study drug administration on Day 1 and ends approximately 90 days after the dose date. It is expected that minimal drug exposure and undetectable drug levels will be present beyond 90 days post-dose.

Measurements taken after Day 1 through approximately Day 90 are considered on-treatment for all data domains. In addition, measurements taken on Day 1 are considered on-treatment for the following data domains: AEs, drug dispensation, exposure.

6.2 Treatment Regimens

The treatment group "as randomized" corresponds to the treatment group assigned by an Interactive Response Technology (IRT) system:

On Day 1, each subject will receive a single dose of nivolumab 480 mg or a single dose of nivolumab 960 mg in a double-blinded fashion. The time of initiation of dosing will be called "0" hour.

Treatment group "as treated": The treatment group "as treated" is defined as the study treatment actually received.

6.3 Populations for Analyses

All enrolled subjects: All subjects who have a signed informed consent form and are registered into the IRT.

All randomized subjects: All subjects who are randomized to any treatment group in the study.

All treated subjects: All subjects who receive at least one dose of study drug.

The pharmacokinetic data set includes all available concentration-time data from subjects who receive BMS-936558.

The pharmacodynamic data set includes all available data from subjects for whom pharmacodynamic measurements are available at baseline and at least one other time point.

The immunogenicity data set consists of all available immunogenicity data from subjects who receive BMS-936558 and have at least 1 post treatment immunogenicity measurement.

Analyses of safety and extent of exposure will be based on all treated subjects. The study conduct and study population will be based on all randomized subjects.

Subjects are grouped by arm "as randomized" for demography, baseline disease characteristics and by arm "as treated" for disposition, extent of exposure and safety.

7 STATISTICAL ANALYSES

7.1 General Methods

Continuous variables will be summarized using descriptive statistics, eg, medians, minimums, maximums, and means with standard deviations/standard errors of the mean. Categorical variables will be summarized by frequencies and percentages. Percentages will be rounded and may not always add up to 100%.

Summaries are presented by treatment unless mentioned otherwise. Also, in all statistical analysis or summary statistics described in this section, missing values due to death will be considered as missing values unless mentioned otherwise.

7.2 Study Conduct

Relevant protocol deviations are summarized by treatment and total for treated subjects. Relevant protocol deviations are those that are programmable and could potentially affect the interpretability of the study results, such as:[1]

- Certain inclusion or exclusion criteria;
- Incorrect dosing or study treatment assignment;

- Use of prohibited concomitant medications;
- Subjects remaining on treatment/in the study despite having met specified criteria for withdrawal.

A subject is considered to have a deviation of an inclusion or exclusion criterion only if all pre-treatment measurements fail the criterion. The consent date defines the beginning of enrollment. Appendix 1 describes the relevant protocol deviations that can be programmed from the database.

7.3 Study Population

7.3.1 Disposition of Subjects

Summaries are presented by treatment and total as described in Section 6.3, unless otherwise specified.

7.3.1.1 Pre-Treatment Subject Status and Accrual

Pre-treatment subject status is summarized for enrolled subjects. This presents the number of subjects enrolled, randomized, not randomized, treated and not treated. Reasons for not being randomized and not being treated are also included (e.g., AE, death, lost to follow-up).

Enrollment by country (as applicable) and investigative site is summarized for enrolled subjects and randomized subjects.

7.3.1.2 End of Treatment Subject Status

End of treatment subject status is summarized by treatment and total for treated subjects. This presents the number of subjects treated, completed the treatment period, did not complete the treatment period, reasons for not completing the treatment period (e.g. lack of efficacy, AE, death, lost to follow-up).

7.4 Demographics

Summaries are presented by treatment and total as described in Section 6.3, unless otherwise specified.

7.4.1 Demographics

- Age
- Age characterization (<65, ≥65)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity, for US only (Hispanic vs. Not Hispanic)
- Body weight
- Height
- Body Mass Index (BMI)

7.4.2 Baseline Characteristics

- Absolute lymphocyte count;
- Site of infection;
- Number of organ dysfunctions (0, 1, 2, 3, Organ dysfunctions: Hypotension, Acute respiratory failure, Acute kidney injury);
- Sequential Organ Failure Assessment (SOFA) score (continuous, total score and by category: Cardiovascular: 0-1 vs. 2-4; Respiratory: 0-1 vs. 2-4; Central Nervous System: 0-1 vs. 2-4; Renal: 0-1 vs. 2-4; Coagulation: 0-1 vs. 2-4; Liver: 0-1 vs. 2-4).

7.5 Extent of Exposure

7.5.1 Study Therapy

Dose Compliance

Subjects are considered dose compliant to study drug at the 95 level if dose infused is ≥95% of target dose. Number of subjects compliant to dose is summarized applying 95, 75 and 50 and < 50 cutoffs.

7.5.2 Concomitant Medications

Concomitant medications, as recorded on the "Previous and Concomitant Medications" CRF, are summarized by arm. Prior medications are medications other than those in the study therapy that are taken during the index hospitalization within 1 week before the 1st day on treatment period. Concomitant medications are medications other than those in the study therapy that are taken on or after the first day on treatment period. Medications are presented alphabetically by anatomic class, therapeutic class and generic name using the WHO dictionary.

The use of immune modulating concomitant medication will also be summarized.

7.6 Efficacy

7.6.1 Exploratory Efficacy

Summary statistics will be provided for the following assessments by treatment and periodic time points. Listings will also be provided.

- Duration of mechanical ventilation, vasopressor use, or dialysis use separately during the index hospitalization.
- Sequential organ failure assessment (SOFA) scores at baseline and post-dosing time points, and change from baseline of SOFA scores during the index hospitalization.
- Length of ICU and hospital stay during index hospitalization.

7.7 Safety

Safety endpoints are assessed by treatment and total, unless otherwise specified.

All recorded AEs will be listed and tabulated by system organ class, preferred term, treatment and total. Summaries of AEs will include AEs, AEs by intensity, and AEs by relationship.

The investigators determine the intensity (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03.) of AEs and the relationship of AEs to study therapy. The investigators' terms are coded and grouped by system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) in production at BMS.

AEs are presented by system organ class and preferred term, each in descending order of frequency, unless otherwise specified.

Summaries of AEs include both SAEs and non-serious, unless otherwise specified. If a subject had an AE with different intensities during the study period, then only the worst grade is reported for a study period, unless otherwise specified.

Laboratory toxicities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The laboratory value during the study period with the worst grade will be reported for each test.

7.7.1 Death

All reported deaths after a subject is enrolled (i.e., has signed the informed consent) will be listed by subject. All-cause mortality and primary cause of death will be tabulated by treatment group and total.

7.7.2 Serious Adverse Events

SAEs are summarized by system organ class and preferred term, by treatment and total for on treatment period. The standard layouts are used:

- SAEs on-treatment
- Drug-related SAEs on-treatment

A listing of all SAEs, regardless of study period, is provided based on all treated subjects.

Two types of summaries are produced, one for subjects with grade 1-5 SAEs and a second restricted to subjects with grade 3-4 & grade 5 SAEs.

7.7.3 Adverse Events Leading to Discontinuation

AEs that lead to discontinuation during the on-treatment period are summarized by system organ class and preferred term. This analysis is presented by treatment and total for the on treatment period regardless of onset.

7.7.4 Overall Adverse Events

AE are summarized by descending frequency of SOC and preferred term within SOC. The tables will follow the standard layouts.

The following AE summaries will be produced:

- Adverse events on-treatment
- Drug-related adverse events on-treatment
- Adverse events on-treatment occurring in ≥ 5% of subjects*
- Drug-related adverse events on-treatment occurring in ≥ 5% of subjects*

* The 5% criterion cutoff refers to 5% in any column.

Two types of summaries are produced, one for subjects with grade 1-5 AEs and a second restricted to subjects with grade 3-4 & grade 5 AEs.

7.7.5 Immune-Mediated Adverse Events

In order to further characterize AEs of special clinical interest, an analysis of immune-mediated AEs (IMAEs) will be conducted. Immune-mediated AEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, endocrine (adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis), and other specific events, considered potential immune-mediated events by investigator, that meet the definition summarized below:

- those occurring within 90 days of the dose,
- regardless of causality,
- treated with immune-modulating medication (of note, endocrine Adverse events such as adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis are considered IMAEs regardless of immune-modulating medication use, since endocrine drug reactions are often managed without immune-modulating medication).

For the most recent immune-oncology studies, the data collection for IMAE was modified to also collect data on investigator assessment of potential IMAE including evidence of immune mediated etiology. For these studies, an additional criteria accounting for immune mediated etiology or immune mediated component is also to be considered:

- with no clear alternate etiology based on investigator assessment, or with an immune-mediated component

The list of MedDRA preferred terms used to identify Immune-Mediated adverse events is revisited quarterly and updated accordingly. The preferred terms used for the selection at the time of the database lock by categories will be provided.

IMAEs will be summarized by treatment group for each immune mediated category / PT using the 90-day safety window:

- Overall summary of AEs (subjects with grade 1-5 AEs) presented by immune mediate Category / PT. This summary includes all AEs that are qualified for IMAE preferred terms list, without requirement of either usage of immune modulating medications or accounting for immune mediated etiology or immune mediated component.

- Overall summaries of IMAEs [(subjects with grade 1-5 AEs) and (restricted to subjects with grade 3-4 & grade 5 AEs)] where immune modulating medication was initiated presented by Category / PT.
- Overall summaries of endocrine IMAEs [(subject with grade 1-5 AEs) and (restricted to subjects with grade 3-4 & grade 5 AEs)] presented by Category / PT.

7.7.6 Clinical Laboratory Evaluations

7.7.6.1 Laboratory Abnormalities

Laboratory abnormalities are determined from laboratory measurements analyzed at the central or local laboratory.

Three types of laboratory summaries are produced by treatment and total for on-treatment period:

- Worst grade of laboratory value on treatment (0, 1, 2, 3, 4, 3-4),
- Treatment emergent abnormalities (not emergent, 1, 2, 3, 4, 3-4),
- Change from baseline to worst grade on treatment (0, 1, 2, 3, 4, and not reported, for baseline and on-study).

Worst grade of emergent laboratory abnormalities are summarized by treatment and total for on-treatment period. Treatment emergent abnormalities are abnormalities that worsened relative to baseline (including missing baseline). The "not emergent" category in this table is for subjects whose laboratory grades did not increase from baseline.

Laboratory abnormalities are further summarized by baseline toxicity grade: "0," "1-2, "3-4" or "Not reported" versus worst on-study grade "0," "1-2,""3-4" or "Not Reported." These analyses are done by treatment.

Commonly collected laboratory tests with CTCAE grades may include, but are not limited to, the following:

- Hematology: hemoglobin, Hematocrit, WBC count with differential to calculate absolute lymphocyte count, platelets; CD4+, CD8+ T-Cell Count and CD4+/CD8+ ratio
- Serum Chemistry: Sodium, Potassium, Chloride, Bicarbonate, Blood Urea Nitrogen (BUN), Creatinine, Glucose, ALT, AST, total bilirubin (reflex to Direct bilirubin), Alkaline phosphatase, Lactate dehydrogenase (LDH), Total Protein, Albumin, Calcium, Phosphorus, Magnesium, Amylase and Lipase
- Thyroid Function Test: TSH (reflex to Free T3 and Free T4)

A by-subject listing of these laboratory parameters will be provided. Laboratory abnormality criteria and laboratory results outside of normal range will be listed.

7.7.6.2 Laboratory Tests over Time

Laboratory values are summarized at baseline and each scheduled visit week on treatment for treated subjects using observed values. This summary is done by treatment group and total. A similar analysis is done for change from baseline laboratory values. Commonly collected laboratory tests may include, but are not limited to, the following:

- Hematology: hemoglobin, Hematocrit, WBC count with differential to calculate absolute lymphocyte count, platelets, , CD4+, CD8+ T-Cell Count and CD4+/CD8+ ratio
- Serum Chemistry: Sodium, Potassium, Chloride, Bicarbonate, Blood Urea Nitrogen (BUN), Creatinine, Glucose, ALT, AST, total bilirubin (reflex to Direct bilirubin), Alkaline phosphatase, Lactate dehydrogenase (LDH), Total Protein, Albumin, Calcium, Phosphorus, Magnesium, Amylase and Lipase
- Thyroid Function Test: TSH (reflex to Free T3 and Free T4)

7.7.6.3 Select Laboratory Test Results

The number of subjects who meet the following laboratory-defined criteria for potential drug induced liver injury (pDILI) during on-treatment period will be summarized by treatment and total:

- AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
  AND
- Concurrent Total bilirubin > 2 times ULN. Concurrent is defined as elevation of total bilirubin within 3 days of the AT elevation.

7.7.7 Vital Signs and other Safety Evaluation

7.7.7.1 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 for each scheduled visit.

ECG

All recorded ECGs values will be listed.

If QTcF is not available in the database, QTcF will be calculated using the reported uncorrected

QT Interval and Heart Rate, and the following formula:

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

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 listed time points.

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

QTcF (msec): Value > 450 or change from baseline > 30

QTcF (msec): Value > 500 or change from baseline > 60

Physical examination

Physical examination findings will be listed.

7.7.8 Immunogenicity

ADA Status of a Sample:

- ADA Positive Sample: ADA is detected
- ADA Positive Relative to Baseline Sample: After initiation of treatment, (1) an ADA positive sample in a participant who is baseline ADA negative or missing but with sample confirmed as specific against nivolumab (2) an ADA positive sample with ADA titer to be at least 4-fold or greater (≥) than baseline positive titer
- ADA Negative Sample: No ADA detected.

ADA Status of a Participant:

- Baseline ADA Positive Participant without on treatment boost: A participant with baseline ADA positive sample with no titer increase ≥ 4 fold following initiation of treatment
- ADA Positive Participant: Participant is counted as ADA positive if after initiation of treatment, has a ADA positive relative to baseline sample. The samples in the following definitions below refer to post-dose samples only
- Persistent Positive Participant: ADA positive relative to baseline sample at 2 or more sequential time points, where the first and last ADA positive relative to baseline samples are at least 8 weeks apart.
- Only the Last Sample Positive Participant: Not persistent but ADA positive relative to baseline sample in the last sampling time point
- Other Positive Participant: Not persistent but some ADA positive relative to baseline samples with the last sample being not ADA positive relative to baseline sample
- ADA Negative Participant: A participant with no ADA positive sample at any time

The number and percentage of participants with positive ADA samples in each of the ADA Positive Participant subgroups will be summarized by treatment and by time. A by-participant listing will be provided with corresponding antibody titer values.

A summary table for the incidence of different types of ADA positive participants will be provided by treatment.

7.8 Pharmacokinetics

Pharmacokinetics parameters as defined in the primary endpoint section (Section 4.1) will be derived using serum concentration versus time, as data allow.

Individual subject pharmacokinetic parameter values will be derived by non compartmental methods using a validated pharmacokinetic analysis program. Actual times will be used for the analyses.

Subject serum concentration-time profiles will be listed and summarized by treatment and nominal collection time. Plots of individual serum concentration profiles over time will be provided. Overlays of individual serum concentration profiles over time will be provided by treatment. Plots of mean (+SD) serum concentration profiles versus nominal time will be presented, and both treatments will be superimposed on the same plot.

All individual PK parameters will be listed including any exclusions and reasons for exclusion from summaries. Summary statistics will be tabulated for each PK parameter by treatment. Geometric means and coefficients of variation will be presented for Cmax, Cmin, Cavg, AUC(0-T), CLT, and Vd. Median and range will be presented for Tmax. Mean and standard deviation will be presented for $T_{1/2}$. Scatter plots of Cmax, Cmin Cavg and AUC(0-T) versus dose will be provided.

7.9 Biomarker Analyses

Summary statistics of PD-1 receptor occupancy levels will be tabulated by treatment and time. Profile plots will be provided.

Summary statistics for pharmacodynamic marker (mHLA-DR expression, absolute lymphocyte count) assessments and corresponding changes (or percent changes) from baseline will be tabulated by treatment and time. Possible association between changes in pharmacodynamic measures of interest and nivolumab exposure may be explored graphically, when appropriate.

[redacted]

8 CONVENTIONS

Presentations follow BMS general global standards for all data domains.[2] This document is available upon request.

8.1 Visit Window

Windows are constructed for each visit in order to slot data. Labels for study periods and visits appear in listings and datasets.

Time is measured from the dose date of study therapy. For longitudinal summaries of data, windows around planned measurement times are based on the midpoint between planned study visits unless specified otherwise. [2]

Study day is defined as the difference between the measurement date and dose date of study therapy. [2]

Visits are defined below in Table 8.1-1. Windows are constructed for each visit in order to slot data. Labels for study periods and visits appear in listings and datasets.

Table 8.1-1: Visit Definitions

Study Period Label		Visit Label	Visit Number	Target Day from Start of Study Period	Visit Window
PRE-TREAT		PRE-TREAT	1	1	< 1 day[a]
ON-TREAT		DAY 1	2	1	1 - 4 days[b] or 1-2 days[c] or day 1[d]
		DAY 2	3	2	day 2[d]
		DAY 3	4	3	day 3[d]
		DAY 4	5	4	day 4[d] or 3-5 days[c]
		DAY 5	6	5	day 5[d]
		DAY 6	7	6	day 6[d]
		DAY 7	8	7	day 7[d] or 6-8 days[c]
		WEEK 2- DAY 10	9	10	5 - 11 days[b] or 9-11 days[e] or 8 -11 days[d]
		WEEK 2- DAY 14	10	14	12 - 17 days
		WEEK 3 - DAY 21	11	21	18 - 24 days
		WEEK 4 - DAY 28	12	28	25 - 35 days
		WEEK 6 - DAY 42	13	42	36 - 49 days
		WEEK 8 - DAY 56	14	56	50 - 63 days
		WEEK 10 - DAY 70	15	70	64 - 80 days
		INDEX HOSPITALIZATION DISCHARGE	16	-	-
		STUDY DISCHARGE - DAY 90	17	90	≥ 81 days

[a] See Section 6.1, Study Periods, for classification of measurements on Day 1 (active study therapy) as pre-treatment or on-treatment depending on the data domain.

[b] For measurements to be assessed only on Day 1 during the first week.

[c] For measurements to be assessed on Day 1, Day 4 and Day 7 during the first week.

[d] For measurements to be assessed daily during the first week.

[e] For measurements to be assessed on Day 10, Day 14, Day 21 and Day 28 during Week 2 - Week 4.

8.2 Domain Derivations

Refer to BMS internal documents for additional conventions, such as on date imputation and on derivation of parameters, across study periods for standard data domains: AEs, demography, ECGs, laboratory test results, non-study medications, physical measurements, subject status, and vital signs.[3,4,5,6,7,8,9,10,11,12,13] These documents are available upon request.

Duration of organ support

1) Rules to calculate vasopressor use

Following vasopressors are recorded

a) Dopamine
b) Epinephrine
c) Norepinephrine (Levophed)
d) Vasopressin
e) Phenylephrine (NeoSynephrine)

Dobutamine is not a vasopressor for this determination. If a patient receives any of the 5 vasopressors listed above on a calendar day, then it is counted as a vasopressor day.

2) Rules for duration of Mechanical Ventilation (MV)

a) We define MV as invasive ventilation only; it does not include non-invasive techniques such as continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) mask ventilation.
b) Duration of MV is the number of consecutive* days of invasive mechanical ventilation that a subject requires.
   i) *If a subject is free of MV for < 48hrs (or 2 days when hours are not recorded) these days are counted as part of the overall duration of MV should the participant be assisted with MV.
      (1). If free of MV for < 48 hrs, this will count as part of one episode, however if free for > 48 hrs, this will count as an independent episode
      References: http://www.trialsjournal.com/content/12/1/79
      http://www.nejm.org/doi/full/10.1056/NEJMoa1005372#t=articleTop
   ii) Use calendar day for all calculations. If a subject receives MV for a few hours (intubated late at night or extubated early in the morning), each calendar day is included in the calculation.

3) Rules for Renal Replacement Therapy (RRT)

a) Types of renal replacement therapy (RRT) in this measurement include peritoneal dialysis, continuous renal replacement therapy (CRRT), and hemodialysis (HD).
b) Duration of RRT is defined as the amount of consecutive* days that a subject requires RRT.

i) *If a subject is free of RRT for < 72hrs (or 3 days when hours are not recorded) these days are counted as part of the duration of RRT

c) "Duration of renal support will be defined as the number of days from initiation of RRT to final dialysis treatment. Duration of renal support will be censored if the patient is still dialysis dependent at the time of death" or hospital discharge.

d) Reference: http://www.nejm.org/doi/full/10.1056/NEJMoa0802639

e) The duration of dialysis is recorded as 0 if subjects received chronic dialysis prior to hospital admission.

9 CONTENT OF REPORTS

9.1 Planned Analyses

- The final analysis will be performed after all subjects have completed Day 90 on treatment.

9.2 Listings

Reports also contain listings described in the Data Presentation Plan (DPP). Listings are sorted by Subject ID, as applicable. Select listings display dosing status according to the GBS standard temporal dosing model.[14]

10 CONTENT OF REPORTS

The analyses described in this SAP will be included in clinical study report.

APPENDIX 1 RELEVANT PROTOCOL DEVIATIONS

The relevant protocol deviations that can be programmed from the database are identified below.

The list would be updated as appropriate if, in the course of monitoring the study, additional protocol deviations are found and considered relevant.

- Age < 18 years;
- Patient does not have documented or suspected infection prior to study drug administration;
- Patient does not have at least 1 new organ dysfunction prior to study drug administration;
- Patient does not have absolute lymphocyte (ALC) values </= 1100 cells/uL prior to study drug administration;
- Patient is not in ICU at time of study drug administration;
- Medical history of autoimmune disease;
- Medical history of bone marrow or solid organ transplant;
- Body Weight ≤ 50 kg or ≥ 180 kg;
- Exposure to nivolumab or to an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (#);
- Exposure to GM-CSF (Granulocyte-macrophage colony-stimulating factor; Sargramostim; Leukine) within 4 weeks or 5 half-lives (whichever is longer) of study treatment administration;
- Incorrect dosing or study treatment assignment.

Non-study medications marked above with # are identified by a BMS physician prior to database lock.

APPENDIX 2 IMMUNE MEDIATED ADVERSE EVENTS DEFINITION AND CONVENTIONS

Immune-Mediated Adverse Event Definition

Category	Preferred Terms
ADRENAL INSUFFICIENCY	ADRENAL INSUFFICIENCY HYPOTHALAMIC PITUITARY ADRENAL AXIS SUPPRESSION SECONDARY ADRENOCORTICAL INSUFFICIENCY
DIABETES MELLITUS	DIABETES MELLITUS DIABETIC KETOACIDOSIS FULMINANT TYPE 1 DIABETES MELLITUS LATENT AUTOIMMUNE DIABETES IN ADULTS TYPE 1 DIABETES MELLITUS
DIARRHEA/COLITIS	AUTOIMMUNE COLITIS COLITIS COLITIS ULCERATIVE DIARRHOEA ENTERITIS ENTEROCOLITIS
HEPATITIS	ACUTE HEPATIC FAILURE ACUTE ON CHRONIC LIVER FAILURE ALANINE AMINOTRANSFERASE INCREASED ASPARTATE AMINOTRANSFERASE INCREASED AUTOIMMUNE HEPATITIS BLOOD BILIRUBIN INCREASED DRUG-INDUCED LIVER INJURY HEPATIC FAILURE HEPATITIS HEPATITIS ACUTE HEPATOTOXICITY HYPERBILIRUBINAEMIA TRANSAMINASES INCREASED
HYPERSENSITIVITY	ANAPHYLACTIC REACTION ANAPHYLACTIC SHOCK HYPERSENSITIVITY INFUSION RELATED REACTION

Immune-Mediated Adverse Event Definition

Category	Preferred Terms
HYPERTHYROIDISM	BASEDOW'S DISEASE HYPERTHYROIDISM PRIMARY HYPERTHYROIDISM
HYPOPHYSITIS	HYPOPHYSITIS HYPOPITUITARISM LYMPHOCYTIC HYPOPHYSITIS
HYPOTHYROIDISM	AUTOIMMUNE HYPOTHYROIDISM HYPOTHYROIDISM PRIMARY HYPOTHYROIDISM
HYPOTHYROIDISM/THYROIDITIS	ATROPHIC THYROIDITIS AUTOIMMUNE HYPOTHYROIDISM AUTOIMMUNE THYROIDITIS HYPOTHYROIDISM PRIMARY HYPOTHYROIDISM THYROIDITIS THYROIDITIS ACUTE
NEPHRITIS AND RENAL DYSFUNCTION	ACUTE KIDNEY INJURY AUTOIMMUNE NEPHRITIS BLOOD CREATININE INCREASED CREATININE RENAL CLEARANCE DECREASED HYPERCREATININAEMIA NEPHRITIS NEPHRITIS ALLERGIC PARANEOPLASTIC GLOMERULONEPHRITIS RENAL FAILURE RENAL TUBULAR NECROSIS TUBULOINTERSTITIAL NEPHRITIS
PNEUMONITIS	INTERSTITIAL LUNG DISEASE PNEUMONITIS
RASH	AUTOIMMUNE DERMATITIS

Immune-Mediated Adverse Event Definition

Category	Preferred Terms
RASH	DERMATITIS
	DERMATITIS ALLERGIC
	DERMATITIS EXFOLIATIVE
	DRUG ERUPTION
	ERYTHEMA MULTIFORME
	EXFOLIATIVE RASH
	FIXED DRUG ERUPTION
	NODULAR RASH
	RASH
	RASH ERYTHEMATOUS
	RASH GENERALISED
	RASH MACULAR
	RASH MACULO-PAPULAR
	RASH MORBILLIFORM
	RASH PAPULAR
	RASH PRURITIC
	RASH VESICULAR
	STEVENS-JOHNSON SYNDROME
	TOXIC EPIDERMAL NECROLYSIS
	TOXIC SKIN ERUPTION
THYROIDITIS	ATROPHIC THYROIDITIS
	AUTOIMMUNE THYROIDITIS
	THYROIDITIS
	THYROIDITIS ACUTE