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Clinical Protocol CA209923

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.

Revised Protocol Number: 01

Incorporates Amendment(s): 01

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	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.
Original Protocol	01-Sep-2016	Not Applicable

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1. SYNOPSIS

Protocol Title: 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.

Study Phase:

1b

[redacted]

Study Population:

Men and women ages ≥ 18 years old with severe sepsis or septic shock and sepsis-associated immunosuppression.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• 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	• Incidence rates of SAEs, AEs, immune-mediated AEs, AEs leading to discontinuation, deaths, and vital signs, ECG, or clinical laboratory abnormalities. • C_{max}, C_{min}, C_{avg}, T_{max}, AUC(0-T), CLT, V_d, $T_{1/2}$.
Secondary	
• 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	• 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, 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

Overall Design:

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.

Number of Participants:

Up to approximately 30 participants will be randomized and treated, in order to obtain a PK profile from at least 6 subjects per dose level.

Treatment Arms and Duration:

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 of nivolumab on Day 1, followed by clinical study assessments up to Day 90. AEs and SAEs will be collected up to Day 90.

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 Single dose nivolumab 960 mg (n=15)	Hospital discharge may occur prior to Day 90

Study treatment:

Study Drug for CA209923		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	10 mg/mL	IP

2. SCHEDULE OF ACTIVITIES

Table 2.-1: Screening Procedural Outline (CA209923)

Procedure	Screening [a] Visit	Baseline [b] Visit	Notes
Eligibility Assessments			
Informed Consent	X		A participant is considered enrolled only when a protocol specific informed consent is signed. Participants unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible.
Inclusion/Exclusion Criteria	X	X	
Medical History	X		Include any toxicities or allergy related to previous treatments. Include any chronic medical conditions (for example, hypertension, diabetes) and past surgeries.
Safety Assessments			
Physical Examination (PE)	X	X	If the screening PE is performed within 24 hours prior to dosing on Day 1 then a single exam may count as both the screening and predose evaluation.
Physical Measurements	X		Includes height, weight, and BMI.
Vital Signs	X	X	Includes body temperature, respiratory rate, blood pressure and heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes.
Electrocardiogram (ECGs)	X	X	ECGs should be recorded after the participant has been supine for at least 5 minutes.
Laboratory Tests			
Clinical safety laboratory tests	X	X	Includes blood and urine samples. See Section 9.4.4
Pregnancy Test	X	X	WOCBP only. See note in Section 9.4.4

Table 2.-1: Screening Procedural Outline (CA209923)

Procedure	Screening [a] Visit	Baseline [b] Visit	Notes
Follicle Stimulating Hormone (FSH)	X		Women only. Refer to Appendix 4 for applicability.
Thyroid function testing		X	See note in Section 9.4.4
Adverse Event Reporting			
Monitor for Serious Adverse Events (SAEs)	X	X	Collection of SAEs begins when the informed consent form is signed.
Clinical Drug Supplies			
Randomize		X	Randomization can occur either on Day -1 or Day 1.
Clinical Assessments			
SOFA Score		X	Pre-dose, after participant is admitted to the ICU
Ventilator Usage		X	Record Start date, if applicable
Vasopressor Usage		X	Record Start date, if applicable
Dialysis Usage		X	Record Start date, if applicable

[a] Screening assessments must be performed within 10 days prior to Day 1 administration of randomized study treatment. If screening assessments other than labs are within 24 hours of dosing, then assessments performed for screening can be counted as both screening and baseline. Screening labs within 48 hours prior to dosing can be counted as both screening and baseline.

[b] Baseline assessments excluding labs must be within 24 hours prior to dosing. Baseline labs can be within 48 hours prior to dosing.

Table 2.-2: On Treatment Procedural Outline (CA209923)											
Procedure	**WK 1 D1-7**	**WK2 D10**	**WK2 D14**	**WK3 D21**	**WK4 D28**	**WK6 D42**	**WK8 D56**	**WK10 D70**	**Index[a] Hospitalization Discharge**	**Study[b] Discharge D90**	**Notes**
Visit window		+/- 1 day	+/- 1 day	+/- 2 days	+/- 3 days	+/- 4 days	+/- 5 days	+/- 7 days		+/- 9 days	
Clinical Drug Supplies											
Randomize	X										Randomization can occur either on Day -1 or Day 1.
Study Drug Administration	X										Day 1.
Safety Assessments											
Physical Examination (PE)	X		X		X		X		X	X	Perform daily in Week 1, at Index Hospitalization Discharge, and at Study Discharge; Perform at other time points only if still hospitalized.
Physical Measurements									X	X	Weight only.
Vital Signs	X		X		X		X		X	X	Perform daily in Week 1, at Index Hospitalization Discharge, and at Study Discharge; Perform at other time points only if still hospitalized. See note in screening

Table 2.-2: On Treatment Procedural Outline (CA209923)											
Procedure	**WK 1 D1-7**	**WK2 D10**	**WK2 D14**	**WK3 D21**	**WK4 D28**	**WK6 D42**	**WK8 D56**	**WK10 D70**	**Index[a] Hospitalization Discharge**	**Study[b] Discharge D90**	**Notes**
											procedures.
Electrocardiogram (ECGs)	X		X		X		X		X	X	Perform at end of infusion on Day 1, at Index Hospitalization Discharge, and at Study Discharge; Perform at other time points only if still hospitalized.
Clinical safety laboratory tests	X	X	X	X	X		X		X	X	Days 1, 4 and 7 of week 1. See note in screening procedures and in Section 9.4.4
Pregnancy Test					X		X			X	WOCBP only. See note in Section 9.4.4.
Thyroid function testing							X		X	X	See note in Section 9.4.4
Adverse Event Reporting											
Monitor for Non-Serious Adverse Events	Collection of nonserious adverse events begins at initiation of study treatment. Adverse events must be collected up to Day 90.										
Monitor for Serious Adverse Events	See note in Screening procedures. SAEs must be collected up to Day 90.										
Other Assessments											

Table 2.-2: On Treatment Procedural Outline (CA209923)											
Procedure	**WK 1 D1-7**	**WK2 D10**	**WK2 D14**	**WK3 D21**	**WK4 D28**	**WK6 D42**	**WK8 D56**	**WK10 D70**	**Index[a] Hospitalization Discharge**	**Study[b] Discharge D90**	**Notes**
Ventilator Usage	In days counting from the day of study treatment administration during participant's index hospitalization.										
Vasopressor Usage	In days counting from the day of study treatment administration during participant's index hospitalization.										
Dialysis Usage	In days counting from the day of study treatment administration during participant's index hospitalization.										
Mortality	Date and primary cause of death.										
SOFA Score	Daily during the first week after study treatment administration, and weekly thereafter while participant is in ICU during participant's index hospitalization.										
Length of ICU stay During Index Hospitalization	ICU discharge date during index hospitalization.										
Length of Index Hospitalization	Hospital discharge date during index hospitalization.										
Pharmacokinetic (PK) and Immunogenicity Assessments	See Section 9.5 for details and collection schedule.										
Biomarker Assessments	See Section 9.8 for details and collection schedule.										
Exploratory Biomarker Assessments	See Section 9.8 for details and collection schedule.										
Additional Research Sampling	See Section 9.8.1										

[a] Index hospitalization discharge can occur at any time after dosing. Index hospitalization discharge assessments may be performed within 96 hours prior to hospital discharge. Study labs performed within 96 hours prior to hospital discharge can be counted for both the study day and hospital discharge visits.

[b] Study Discharge assessments should also performed for participants who are prematurely discontinued.

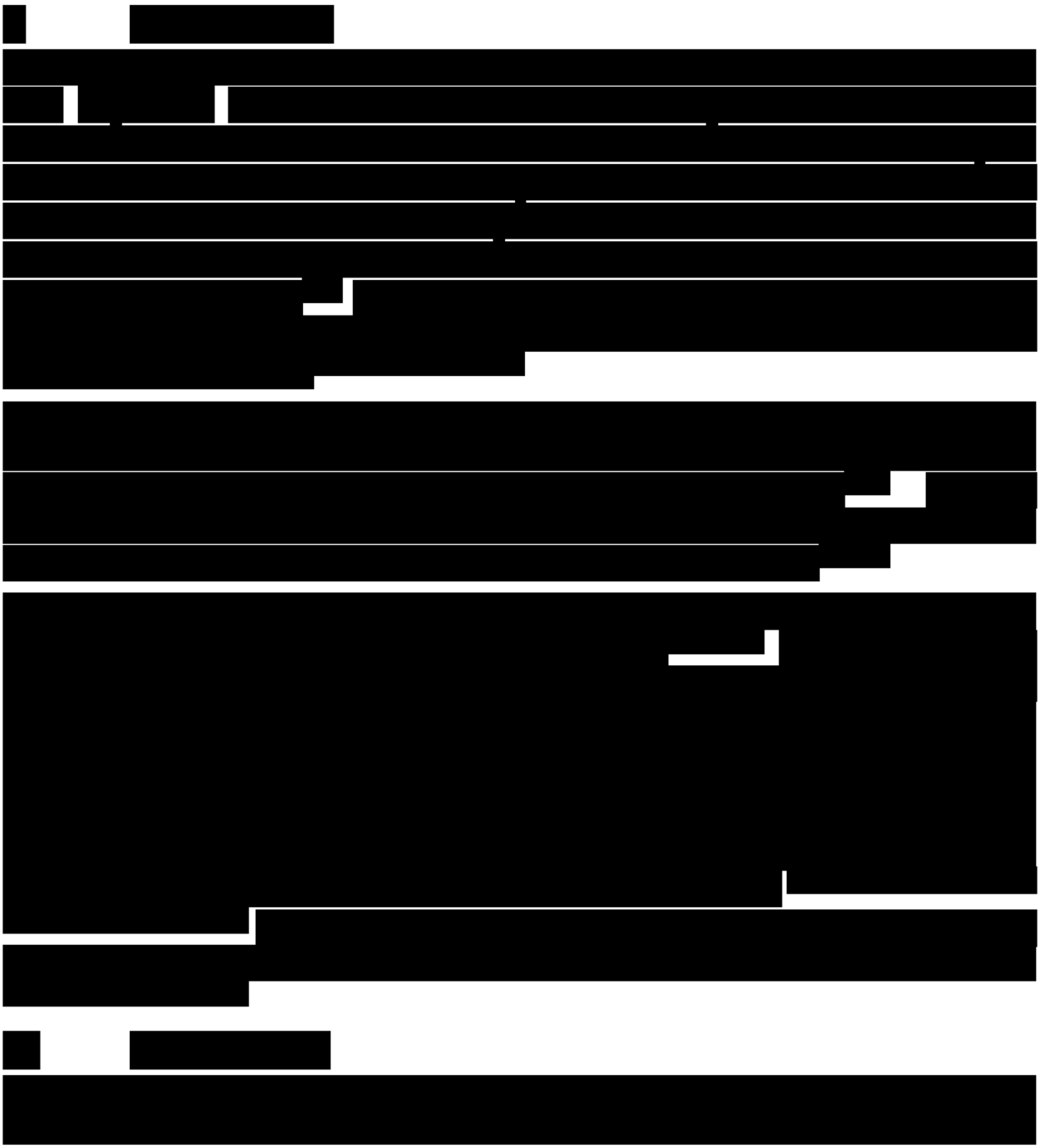
Abbreviations: D=Day

In the event that multiple samples are to be collected at a single time point, the following is the order in which samples should be collected:

Pharmacokinetic (PK) samples

Receptor occupancy (RO) samples

Clinical safety laboratory samples



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3.2 Background

PD-1 is a member of the CD28 family of T-cell signaling receptors that also includes CD28, CTLA 4, ICOS, and BTLA.[67] PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression has also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes.[68] These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors.

In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ±1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both

proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[69]

Nivolumab is approved in multiple oncology indications. The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience, as of May-2015, in approximately 12,300 oncology clinical trial subjects.[70] Details on the safety profile of nivolumab in oncology subjects are available in the Investigator Brochure and will not be repeated here.[70] Study CA209923 is the first clinical trial of nivolumab in sepsis.

The single-dose and multiple dose pharmacokinetics of nivolumab were previously well-characterized in oncology subjects and are known to be linear and dose-proportional in the range of 0.1 to 10 mg/kg. The geometric mean (% CV) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Nivolumab accumulation following every 2 weeks administration in oncology subjects was in the range of 2.9 to 3.3 based on AUC(TAU), 2.0 to 2.4 based on C_{max}, and 3.1 to 4.8 based on C_{min}. There was no dose-related trend in the accumulation index of AUC(TAU), C_{max}, or C_{min}. There was no meaningful change in cytokines known to have indirect effects on CYP enzymes across all studied dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment.[70] This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction. Nivolumab is an IgG4 monoclonal antibody, which is likely eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system). These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab. The immunogenic potential of nivolumab was minimal with low titers, low persistent positive rates, low incidences of neutralizing antibodies and no impact of immunogenicity on safety or PK.[70]

A detailed description of the chemistry, pharmacology, efficacy, and safety of nivolumab is provided in the Investigator Brochure.[70]

3.3 Benefit/Risk Assessment

As described below, the risk profile for evaluation of a single dose of nivolumab in participants with severe sepsis or septic shock is acceptable.

Potential risks of nivolumab

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials in oncology with no MTD reached at any dose

tested up to 10 mg/kg Q2W. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level. Based on dosing simulations, the proposed 480 mg and 960 mg single-dose regimens in CA209923 provide comparable or higher exposures as steady-state levels of the approved 3 mg/kg Q2W regimen and the projected exposures are within the safety margins of the previously studied 10 mg/kg Q2W regimen.

In clinical trials of nivolumab monotherapy in oncology, select AEs thought to be due to the effects of inflammatory cells on specific tissues have been identified which include, but are not limited to, pneumonitis, diarrhea/colitis, hepatitis, endocrinopathies, rash, and nephritis. Potential safety concerns and recommended management guidelines regarding pulmonary toxicities, GI toxicities, hepatotoxicities, endocrinopathies, dermatologic toxicities, and other toxicities of concern are summarized in the Investigator Brochure.[70] In clinical trials of nivolumab monotherapy, most high-grade immune-mediated AEs were manageable with the use of corticosteroids or hormone replacement therapy (for endocrinopathies). Use of corticosteroids or hormone replacement therapy to manage immune-mediated AEs is not expected to present an undue risk to a patient with severe sepsis or septic shock.

Potential benefit of nivolumab in severe sepsis

As described earlier, the data from a mouse model of sepsis and from patients with sepsis suggests a role for the PD-1/PD-L1 pathway in sepsis. Taking these data together with evidence of an immunosuppressive phase in severe sepsis associated with poor clinical outcomes, interventions with the potential to improve host immune function, such as nivolumab, may benefit patients with severe sepsis.

Risk mitigation approaches in CA209923

Eligibility criteria. In CA209923, the target population is patients with severe sepsis/septic shock and sepsis-associated immunosuppression. As such, the eligibility criteria are written in order to avoid enrolling participants in the early, predominantly pro-inflammatory phase of sepsis and rather to enroll participants in the immunosuppressive phase. To achieve this, in CA209923 participants with severe sepsis or septic shock must have the onset of organ dysfunction at least 24 hours prior to study treatment administration and immunosuppression as assessed by a depressed absolute lymphocyte count. The rationale for this approach is that pro-inflammatory cytokines are typically high in the early stages of severe sepsis and septic shock, generally peaking between 3 and 36 hours and diminishing over subsequent hours.[71]

Single-dose administration and dose levels to be studied. In the current study only single-dose administration will be studied and in any potential future clinical development program for nivolumab in severe sepsis only short-term administration is anticipated. Using a population pharmacokinetic (PPK) model, nivolumab concentration-time profiles were predicted for the proposed 480 mg and 960 mg single-dose regimens in CA209923 and the profiles were compared to the steady state levels of the approved 3 mg/kg Q2W regimen and the 10 mg/kg Q2W regimen, previously studied in oncology. Based on dosing simulations, it is anticipated that

the exposures achieved with the doses to be studied in CA209923 will not exceed the exposures that have been observed in patients with cancer.

Safety monitoring. Given the complicated clinical course of critically ill patients with sepsis, monitoring safety in sepsis trials is complex; however, there is a long history of monitoring safety in such trials. Monitoring safety in the CA209923 study of nivolumab will include routine safety monitoring as well as any special monitoring precautions, tests, observations, and stopping rules outlined in the protocol. The current study will include education of site personnel about the potential for, and recommended management of, infusion reactions and immune-mediated adverse events. The proper means of recording and reporting adverse safety information will follow procedures outlined in the protocol.

4. OBJECTIVES AND ENDPOINTS

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
Primary • 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	• Incidence rates of SAEs, AEs, immune-mediated AEs, AEs leading to discontinuation, deaths, vital signs, ECG, or clinical laboratory abnormalities • C_{max}, C_{min}, C_{avg}, T_{max}, AUC(0-T), CLT, V_d, $T_{1/2}$.
Secondary • 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	• 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, 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]

Table 4.-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	[redacted]

5. STUDY DESIGN

5.1 Overall 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 5.1-1.

Figure 5.1-1: 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 Single dose nivolumab 960 mg (n=15)	Hospital discharge may occur prior to Day 90

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.

5.1.1 Data Monitoring Committee and Other External Committees

Not applicable.

5.2 Number of Participants

Up to approximately 30 participants will be randomized in a 1:1 ratio into one of two treatment groups, in order to obtain a PK profile from at least 6 subjects per dose level.

Refer to Section 10.1 for sample size rationale.

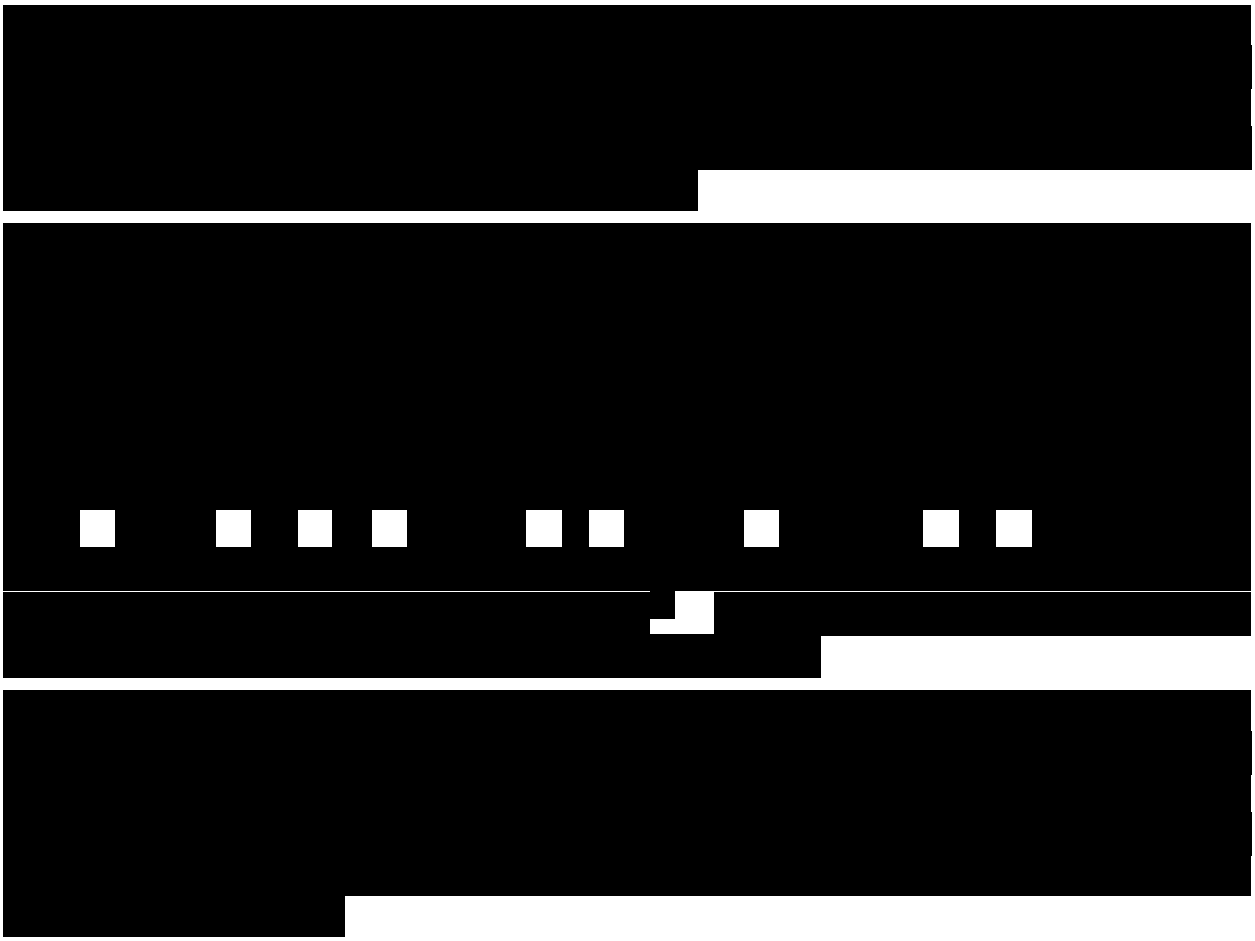
5.3 End of Study Definition

The start of the trial is defined as the first visit for first participant screened.

The last visit is defined as the last scheduled visit in the Table of Procedures, Section 2.

The end of study is defined as the date of the last visit.

[redacted]



5.5 Justification for Dose

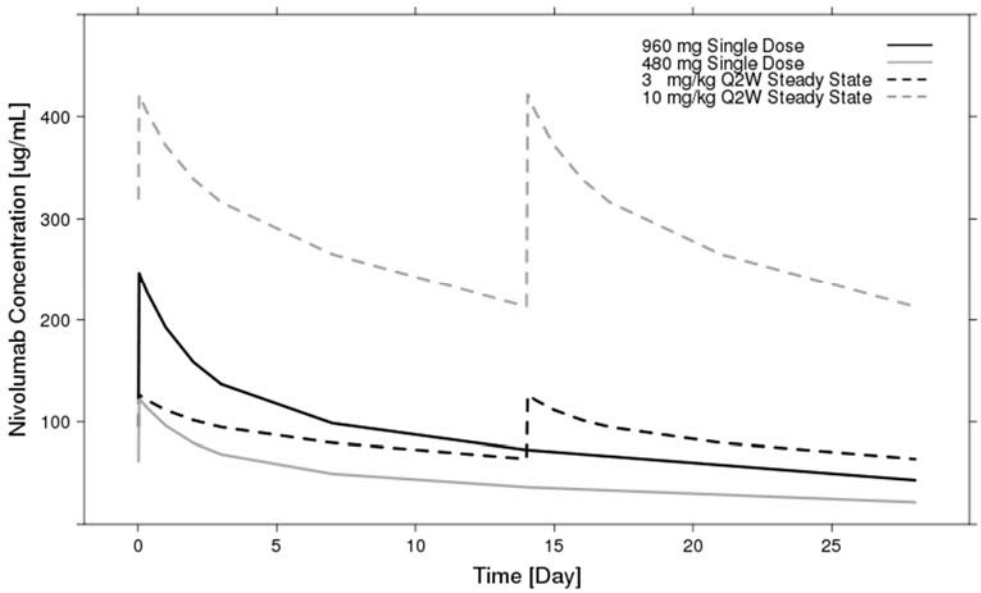
As stated above, the goal of the current study is to determine whether the PK exposures attained after a single dose of nivolumab in participants with severe sepsis or septic shock are comparable to the PK exposures observed at steady state dosing of nivolumab in participants with cancer. In the current study, single dose administration of either 480 mg or 960 mg nivolumab will be evaluated in participants with severe sepsis or septic shock. The pharmacokinetics and safety of nivolumab monotherapy up to dose levels of 10 mg/kg Q2W and 10 mg/kg Q3W were previously well-characterized across multiple tumor types. Nivolumab 3 mg/kg Q2W is currently approved and indicated for the treatment of several cancers, including melanoma, squamous and non-squamous non-small cell lung carcinoma, renal cell carcinoma, and classical Hodgkin lymphoma.

Nivolumab concentration-time profiles were predicted for the proposed 480 mg and 960 mg single-dose regimens and compared to the steady state levels of the approved 3 mg/kg Q2W regimen using a population pharmacokinetic model (PPK). In the PPK model, the disposition of nivolumab was well-described by a linear 2-compartment model, which incorporates time-varying clearance. The model was developed with data from 1895 participants with solid tumors who received 0.3 to 10.0 mg/kg nivolumab in 11 clinical trials during the course of nivolumab development across multiple tumor types.[70] A full covariate model was developed to assess

covariate effects on pharmacokinetic parameters. The only potentially clinically relevant (>20%) covariate was baseline body weight; such that participants with higher baseline body weight have higher baseline clearance and central volume of distribution.

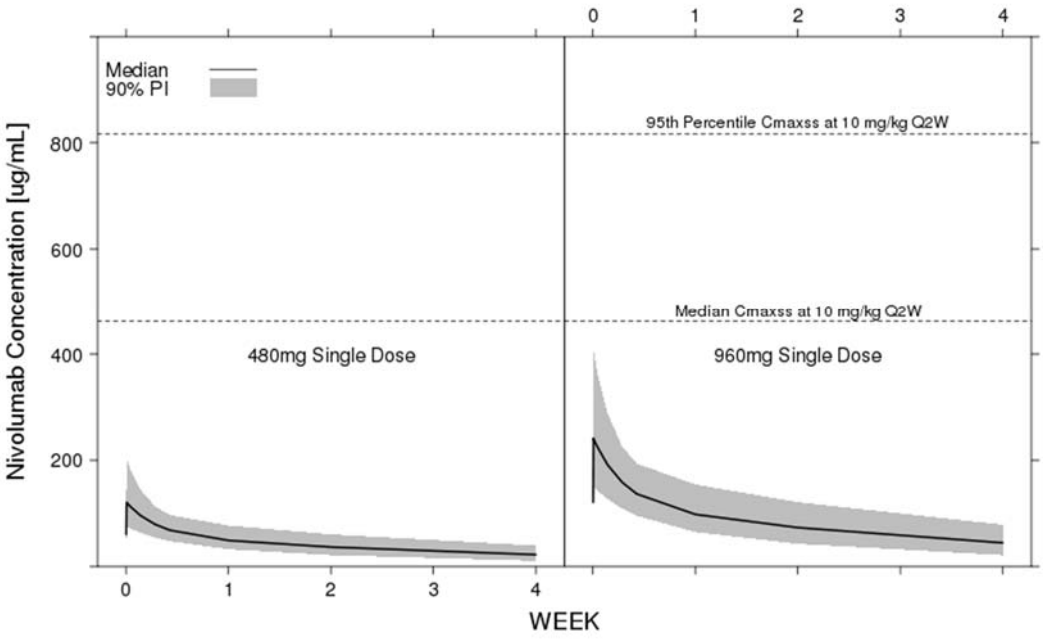
Simulations performed using the PPK model showed that C_{max} values produced by the proposed 480 mg and 960 mg dosing regimens are either equivalent to, or higher than those of the steady state levels of approved 3 mg/kg Q2W regimen but lower than the steady state levels of 10 mg/kg Q2W regimen (see Figure 5.5-1). C_{avg} values produced by the proposed 480 mg and 960 mg dosing regimens are either equivalent to (at 960 mg), or lower (at 480 mg) than those of the steady state levels of approved 3 mg/kg Q2W regimen and lower than the steady state levels of 10 mg/kg Q2W regimen. Whereas C_{min} values produced by the proposed regimens were comparable or lower than that of the 3 mg/kg Q2W approved regimen and significantly lower than the 10 mg/kg Q2W regimen (Table 5.5-1). Based on previous studies, steady-state C_{max} (C_{maxss}) and C_{min} at Day-28 (C_{mind28}) were identified as the exposure measures most likely to impact safety and efficacy of nivolumab, respectively. The C_{max} of the proposed 960 mg dose was higher than that of the approved 3 mg/kg Q2W dose but lower than the 10 mg/kg Q2W dose (see Figure 5.5-2). The safety data accumulated for nivolumab up to steady state dose levels of 10 mg/kg Q2W in multiple tumor types provide a wide safety margin. C_{max} values produced by a single dose of up to 960 mg will be lower than the 10 mg/kg Q2W dose (see Figure 5.5-2). Thus based on dosing simulations, 480 mg and 960 mg dosing regimens will provide comparable or higher overall exposures as the steady state levels of 3 mg/kg Q2W regimen, and will be within the safety margins of 10 mg/kg Q2W regimen at steady-state.

Figure 5.5-1: Predicted nivolumab geometric mean concentration vs time profile for a single dose of 480 mg and 960 mg compared with steady state multiple dose of 3 mg/kg and 10 mg/kg



Analysis directory source: /global/pkms/data/CA/209/923/prd/ppk/final
PPK model: Analysis directory/nm/a-2202-3p1.ctl

Figure 5.5-2: Simulated nivolumab exposure for a single dose of 480 mg and 960 mg



The solid lines and shaded band represent the simulation-based median and 90% prediction intervals. The dotted lines and values represent median and 95th percentile.

Analysis directory source: /global/pkms/data/CA/209/923/prd/ppk/final
PPK model: Analysis directory/nm/a-2202-3p1.ctl

Table 5.5-1: Comparisons of C_{min}, C_{max}, and C_{avg} for geometric mean and median of 3mg/kg Q2W steady state and 480 mg and 960 mg single dosing regimens

Summary Exposure	3 mg/kg Q2W Steady State GM [μg/mL] (%CV)	480 mg Single Dose GM [μg/mL] (%CV)	% Difference in GMs	3 mg/kg Q2W Steady State Median [μg/mL] (5th, 95th percentile)	480 mg Single Dose Median [μg/mL] (5th, 95th percentile)
C_{min}	63.9 (62.5)	21.6 (39)	-66.2	66.4 (27.9 , 120)	22.3 (10.6 , 39.3)
C_{max}	126 (51.2)	123 (85.4)	-2.38	126 (74.9 , 202)	121 (74.7 , 204)
C_{avg}	83.5 (51.3)	42.7 (28.5)	-48.9	85.1 (42.7 , 143)	42.8 (27 , 67.7)
Summary Exposure	3 mg/kg Q2W Steady State GM [μg/mL] (%CV)	960 mg Single Dose GM [μg/mL] (%CV)	% Difference in GMs	3 mg/kg Q2W Steady State Median [μg/mL] (5th, 95th percentile)	960 mg Single Dose Median [μg/mL] (5th, 95th percentile)
C_{min}	63.9 (62.5)	43.2 (39)	-32.4	66.4 (27.9 , 120)	44.6 (21.2 , 78.6)
C_{max}	126 (51.2)	246 (85.4)	95.2	126 (74.9 , 202)	242 (149 , 408)
C_{avg}	83.5 (51.3)	85.4 (28.5)	2.28	85.1 (42.7 , 143)	85.6 (54 , 135)

C_{min}: Trough nivolumab serum concentration, C_{max}: Peak nivolumab serum concentration, C_{avg}: Average nivolumab serum concentration, GM: Geometric mean, CV: Coefficient of variation

Analysis directory source: /global/pkms/data/CA/209/923/prd/ppk/final
PPK model: Analysis directory/nm/a-2202-3p1.ctl

6. STUDY POPULATION

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

6.1 Inclusion Criteria

1) Signed Written Informed Consent

a) The informed consent form signed by the participant or the participant's legally acceptable representative

2) Type of Participant and Target Disease Characteristics

a) Men and women ages ≥ 18 years old

b) Participant has documented OR suspected infection

i) Documented infection is infection confirmed with a microbiologic diagnosis

ii) Suspected infection is infection being treated with ongoing antimicrobial therapy at the time of study treatment administration

c) Participant has the onset of severe sepsis or septic shock at least 24 hours prior to study treatment administration based on having at least 1 of the 3 organ dysfunction criteria below. Organ dysfunction must be new and thought to be due to sepsis.

i) Hypotension defined as the need for treatment with any vasopressor(s) for at least 6 hours to maintain a systolic pressure ≥ 90 mmHg or a mean arterial pressure ≥70 mmHg
OR

ii) Acute respiratory failure defined as the need for invasive mechanical ventilation for at least 24 hours to support pulmonary function
OR

iii) Acute kidney injury defined as creatinine > 2.0 mg/dL (from a creatinine that was within the normal reference range prior to onset of sepsis) OR urine output < 0.5 mL/kg/hr for > 2 hours despite adequate fluid resuscitation. In the presence of pre-existing impairment of renal function (defined as a serum creatinine concentration >2 times the upper limit of the normal reference range prior to the onset of sepsis), the participant should meet 1 of the other 2 organ dysfunction criteria above.

d) Participant has sepsis- associated immunosuppression based on an absolute lymphocyte count ≤ 1100 cells/μL on at least one assessment within the 96 hours prior to study treatment administration

e) Participant is in an intensive care unit at the time of study treatment administration and, based on their medical condition, there are no plans to discharge from the ICU in the next 24 hours

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

3) Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatment

b) Women must not be breastfeeding

c) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab (the terminal half-life of nivolumab is up to 25 days) plus 30 days (duration of ovulatory cycle) for a total of 5 months post-treatment completion (See Appendix 4).

d) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception (Appendix 4) for the duration of treatment with nivolumab plus 5 half-lives of nivolumab plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time (See Appendix 4).

e) Azoospermic males are exempt from contraceptive requirements.

f) WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements but still must undergo pregnancy testing as described in this section.

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

6.2 Exclusion Criteria

1) Medical Conditions

a) Previous episode of severe sepsis or septic shock with ICU admission during the current hospitalization

b) Active, known, or suspected autoimmune disease **NOTE**: Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

c) History of solid organ or bone marrow transplant.

d) Known history of malignancy and has undergone treatment for such within 6 weeks prior to study treatment administration.

e) Known history of infection with HIV and not on antiretroviral therapy prior to the current hospitalization or CD4 ≤ 200 cells/mm3 or AIDS-defining illness in the past year.

f) Known history of chronic HBV infection and not on treatment with an HBV nucleos(t)ide analogue prior to the current hospitalization or HBV DNA > 100 IU/mL.

g) Known history of infection with HCV and currently undergoing treatment for HCV infection or has detectable HCV RNA.

h) Known active illicit drug use disorder (defined as illicit drug use on 5 or more days in the past 30 days) OR known active alcohol use disorder (defined as drinking 5 or more alcoholic drinks on the same occasion on 5 or more days in the past 30 days)

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

2) Prior/Concomitant Therapy

a) Prior 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

b) Prior exposure to any other investigational agent within 4 weeks or 5 half-lives (whichever is longer) of study treatment administration

c) Prior 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

3) Physical and Laboratory Test Findings

a) Body weight ≤ 50 kg or ≥ 180 kg

4) Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reaction to monoclonal antibodies or related compounds.

5) Other Exclusion Criteria

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

b) Participants who are compulsorily detained for treatment of either a psychiatric or physical illness

c) Concurrent participation in another interventional clinical trial of an investigational drug

d) Presence of an advanced directive to withhold or withdraw life-sustaining treatment, a do not resuscitate (DNR) order, a no CPR order, or a comfort measures only (CMO) order

e) Participant's family, treating physician, or both are not in favor of aggressive support of the participant

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

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

Not applicable.

6.3.2 Caffeine, Alcohol and Tobacco

Not applicable.

6.3.3 Activity

Not applicable.

6.4 Screen Failures

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

6.4.1 Retesting During Screening or Lead-In Period

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

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

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

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

7. TREATMENT

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

Study treatment includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- Nivolumab

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

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

Table 7.-1: Study treatments for CA209923

Product Description / Class and Dosage Form	Potency	IP/ Non-IMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL) and 40 mg (10 mg/mL)	IP	Open label [a]	Clear to opalescent colorless to pale yellow liquid. May contain particles. 240 mg kit contains: 2 x 100 mg vials (10 mL/vial) and 1 x 40 mg vial (4 mL/vial) or carton containing 5 vials of 100 mg (10 mL/vial)	2 to 8°C. Protect from light and freezing

May be labelled as either 'BMS-936558-01' or 'Nivolumab'.

[a] The term 'Open label' refers to the medication as it is upon receipt at the pharmacy (unblinded pharmacist). Trial design and conduct are double-blind.

7.1 Treatments Administered

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

Table 7.1-1: Selection and Timing of Dose

Study Treatment	Unit dose strength(s)	Dosage formulation Frequency of Administration	Route of Administration
BMS-936558-01 (nivolumab) 480 mg or 960 mg	100 mg (10 mg/mL) and 40 mg (10 mg/mL) sterile solution	Single dose infusion	Intravenous

Participants are randomized to receive double-blind nivolumab at a dose of 480 mg or 960 mg as a 90 minute infusion on Day 1.

Infusions will be prepared by an unblinded pharmacist according to a pharmacy manual, provided separately. The infusion volume for the two treatment groups will be the same, to preserve the blind.

Participants should be carefully monitored for infusion reactions during nivolumab administration. Nivolumab contains only human immunoglobulin protein sequences, therefore it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to CTCAE (Version 4) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor participant until recovery from symptoms.

For Grade 2 symptoms: (moderate reaction requiring infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]):

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the participant with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor participant until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor participant closely. If symptoms recur, then no further nivolumab will be administered.

For Grade 3 or 4 symptoms: (Grade 3: severe reaction: prolonged symptoms [e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion] or recurrence of symptoms following initial improvement; Grade 4: Life-threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the participant as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Participant should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor participant until recovery from the symptoms.

For late-occurring hypersensitivity symptoms: (eg, appearance of a localized or generalized pruritus within 1 week after treatment) symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

7.2 Method of Treatment Assignment

Study using Interactive Response Technology (IRT): All participants will be centrally randomized using 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.

Study treatment will be dispensed at the study visits as listed in Schedule of Activities (Section 2).

Enrolled participants, including those not dosed, will be assigned sequential participant numbers comprised of the site number and a unique participant identifier. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be randomized. Randomization numbers will be assigned prior to dosing.

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.

7.3 Blinding

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. This unblinding is not expected to affect the integrity of the trial. PK endpoints are objective assessments that should not be affected by unblinding.

7.4 Dosage Modification

Not applicable.

7.5 Preparation/Handling/Storage/Accountability

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

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

Study treatment not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g., required diluents, administration sets).

Participants should be carefully monitored for infusion reactions during nivolumab administration. Infusion of nivolumab may be interrupted or discontinued depending on how well the participant tolerates the treatment. If an acute infusion reaction is noted, participants should be managed according to Section 7.1.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/mL (10 mg/mL) Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Infusion-related supplies (eg. IV bags, in-line filters, 0.9% NaCl solution) will not be provided by the Sponsor and should be purchased locally if permitted by local regulations.

No incompatibilities have been observed between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

Further guidance and information for final disposition of unused study treatment are provided in Appendix 2.

7.6 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

7.7 Treatment Compliance

Study drug will be administered in the clinical facility. Treatment compliance will be monitored by drug accountability and eCRF.

7.8 Concomitant Therapy

7.8.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to study treatment administration or during the study are described below. Medications administered during the index hospitalization within

1 week prior to study treatment administration must be recorded on the CRF. Any concomitant therapies must be recorded on the CRF.

1) During the study, immunosuppressive agents are prohibited unless utilized to treat a drug related adverse event. **NOTE**: Adrenal replacement steroid doses up to the equivalent of hydrocortisone 300 mg/day for the treatment of septic shock are permitted.

7.8.2 Other Restrictions and Precautions

Not applicable.

7.9 Treatment After the End of the Study

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

8. DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Treatment

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

- Participant's request to stop study treatment. Participants who request to discontinue study treatment will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information.
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical illness

Discontinuation of the study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined Section 9.2.8 or if the investigator believes that it is in best interest of the participant.

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

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. Please call the BMS Medical Monitor/designee within 24 hours of awareness of the pregnancy. See Section 9.2.6 for additional details.

All participants who discontinue study treatment should comply with protocol specified follow-up procedures as outlined in Section 2. The only exception to this requirement is when a participant withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

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

8.1.1 Post Study Treatment Study Follow-up

Participants who discontinue study treatment may continue to be followed.

8.2 Discontinuation from the Study

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

- Participants should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible.
- The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study treatment only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-Up

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

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

8.4 Study Stopping Rules

If, at any time during the study, the perceived risk/benefit changes, the BMS Medical Monitor and BMS Medical Surveillance Team Lead have the authority to determine whether or not the study should stop or be modified. Enrollment will be paused in the event of the following observations, confirmed by review of unblinded safety data:

- Mortality that is unusual for the study population as determined by the BMS team and Investigators
- 2 or more participants experience the same SAE and the event is not expected for the study population, is not expected for nivolumab, and is considered related to study treatment administration
- 1 participant has potential drug-induced liver injury (pDILI) as defined in Section 9.2.8

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (See Section 2).
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the Schedule of Activities.

9.1 Efficacy Assessments

Exploratory efficacy assessments include the following:

- Organ failure will be assessed by collection of SOFA score during index hospitalization

- Organ support will be assessed by duration of mechanical ventilation, vasopressor use, or dialysis use separately during the index hospitalization
- Length of stay in the ICU and in the hospital during the index hospitalization will be assessed

9.1.1 Imaging Assessment for the Study

Not applicable.

9.2 Adverse Events

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

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

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

Contacts for SAE reporting are specified in Appendix 3.

9.2.1 Immune-mediated Adverse Events

Immune-mediated AEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (e.g. infection or tumor progression) have been ruled out. Immune-mediated AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

9.2.2 Time Period and Frequency for Collecting AE and SAE Information

The collection of nonserious AE information should begin at initiation of study treatment at the time points specified in the Schedule of Activities (Section 2) and for a minimum of 90 days following discontinuation of study treatment. Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on the participant's case report form. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the participants.

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the participant's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

All SAEs must be collected that occur during the screening period and within 90 days of discontinuation of dosing.

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

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

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

9.2.3 Method of Detecting AEs and SAEs

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

9.2.4 Follow-up of AEs and SAEs

- Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study treatment and for those present at the end of study treatment as appropriate.
- All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious immune-mediated AEs (as defined in Section 9.2 will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3).

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

9.2.5 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Sponsor or designee will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.6 Pregnancy

If, following initiation of the study treatment, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

In most cases, the study treatment will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor or designee. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.2.7 Laboratory Test Result Abnormalities

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

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

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

9.2.8 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 9.2 and Appendix 3 for reporting details).

Potential drug induced liver injury is defined as:

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

AND

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

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Hepatotoxicity, such as transaminase elevations and hepatitis, has been identified as an important risk for nivolumab. Hepatic AE management recommendations for managing drug-induced liver injury (DILI) cases are provided in the nivolumab (OPDIVO®) label. The experience to date shows that hepatic AEs, including potential DILI cases, were manageable using the established management recommendations and thus do not meaningfully alter the benefit/risk of nivolumab.

9.2.9 Other Safety Considerations

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

9.3 Overdose

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

For this study, any dose of nivolumab greater than 960 mg within a 24-hour time period will be considered an overdose.

9.4 Safety

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

Safety assessments will be based on medical review of physical examination findings, vital sign measurements, ECG, adverse event reports and clinical laboratory tests. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Mortality will be assessed as all-cause mortality rates at 28 and 90 days as well as time to death.

Only data for the procedures and assessments specified in the protocol should be submitted to BMS on a case report form (CRF). Additional procedures and assessments may be performed as part of the standard of care; however data from these assessments should remain in the participant's medical record and should not be provided to BMS, unless specifically requested by BMS.

9.4.1 Physical Examinations

Refer to Schedule of Activities.

9.4.2 Vital signs

Refer to Schedule of Activities.

9.4.3 Electrocardiograms

Refer to Schedule of Activities.

9.4.4 Clinical Safety Laboratory Assessments

Local laboratories will perform the analyses below and will provide reference ranges for these tests. Investigators must document their review of each laboratory safety report. Results of clinical laboratory tests performed at Screening/Baseline must be available prior to dosing.

<table>
<tr><td colspan="2">Hematology</td></tr>
<tr><td colspan="2">Hemoglobin</td></tr>
<tr><td colspan="2">Hematocrit</td></tr>
<tr><td colspan="2">WBC count with differential to calculate absolute lymphocyte count</td></tr>
<tr><td colspan="2">Platelet count</td></tr>
<tr><td colspan="2">CD4+, CD8+ T-cell count and CD4+/CD8+ ratio</td></tr>
<tr><td colspan="2">Serum Chemistry</td></tr>
<tr><td>Sodium
Potassium
Chloride
Bicarbonate
Blood Urea Nitrogen (BUN)
Creatinine
Glucose
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Total bilirubin [reflex to direct Bilirubin if total bilirubin is > ULN]
Alkaline phosphatase
Lactate dehydrogenase (LDH)</td><td>Total Protein
Albumin
Calcium
Phosphorus
Magnesium
Amylase
Lipase</td></tr>
<tr><td colspan="2">Urinalysis</td></tr>
<tr><td colspan="2">Protein</td></tr>
<tr><td colspan="2">Glucose</td></tr>
</table>

Blood
Leukocyte esterase
Specific gravity
pH
Microscopic examination of the sediment if blood, protein or leukocytes esterase are positive on the dipstick
Other Analyses
Pregnancy test for WOCBP only: at screening; within 24 hours prior to the start of study drug (an extension up to 72 hours prior to start of study drug is permissible in situations where results cannot be obtained within the standard 24 hour window); monthly until Study Discharge; whenever pregnancy is suspected.
Follicle stimulating hormone (FSH) for women only: at screening, refer to Appendix 4 for applicability.
Thyroid function testing (TSH with reflex to free T3 and free T4): at baseline; at Day 56, at index hospitalization discharge and at study discharge.

9.4.5 Suicidal Risk Monitoring

Not applicable.

9.4.6 Imaging Safety Assessment

Not applicable.

9.5 Pharmacokinetic

Pharmacokinetics of nivolumab will be derived from serum concentration versus time data. The pharmacokinetic parameters to be assessed from Day 1 to Study Discharge include, but are not limited to:

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

Table 9.5-1 lists the sampling schedule to be followed for the assessment of pharmacokinetics after single doses.

Table 9.5-1: Pharmacokinetic and Immunogenicity Sampling Schedule

Study Day of Sample Collection	Event	Time (Relative To Start of Infusion of nivolumab) Hour: Min	Blood Sample for nivolumab	Immunogenicity Sample
1	predose[a]	00:00	X	X
1	EOI[b]	01:30	X	
2[c]		24:00	X	
3		48:00	X	
4		72:00	X	
5		96:00	X	
6		120:00	X	
7		144:00	X	
10		216:00	X	
14		312:00	X	X
21		480:00	X	
28		648:00	X	X
42		984:00	X	
56		1320:00	X	X
70		1656:00	X	
Date of Index Hospitalization Discharge	Index Hospitalization Discharge	N/A	X	X
90	Study Discharge	2136:00	X	X

[a] Predose samples should be collected just before the administration of the first drug (preferably within 30 minutes).

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

[c] Sample collection beginning on Day 2 and beyond to be performed on specified days ±6 hours from nominal time point. Please ensure accurate collection of time/date of sample collection.

PK samples will be analyzed for nivolumab by a validated assay.

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

9.6 Pharmacodynamics

Refer to Section 9.8 Biomarkers.

9.7 Pharmacogenomics

Not applicable.

9.7.1 ADME Sampling

Not applicable.

9.8 Biomarkers

Blood will be drawn at the times indicated in Table 9.8-1. Further details of blood collection and processing will be provided to the site in the procedure manual.

Table 9.8-1: Biomarker Sampling Schedule

Study Day	Time (Event) Hour	Time (Relative To Dosing) Hour: Min	Receptor Occupancy, PD-1 levels	mHLA-DR, caspase-3	Whole blood for DNA[b]	Whole blood for RNA[c]	Exploratory serum/ plasma[d]
1	Predose	00:00	X	X	X	X	X
1	EOI[a]	01:30	X				
2		24:00	X	X			
3		48:00	X	X		X	X
7		144:00	X	X	X	X	X
14		312:00	X	X	X	X	X
28		648:00	X	X	X	X	X
56		1320:00	X	X	X	X	X
Date of Index Hospitalization Discharge	Index Hospitalization Discharge	N/A	X	X	X	X	X
90	Study Discharge	2136:00	X	X	X	X	X

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

[b] DNA will be stored and may be used for genotyping and T-cell receptor diversity.

[c] RNA will be stored and may be used to profile gene expression by RNA sequencing analysis

[d] Exploratory serum/plasma samples will be stored for potential biomarker analysis related to the disease and mechanism of nivolumab

9.8.1 Additional Research Collection

Additional research retention samples are mandatory for all participants, except where prohibited by local laws or regulations.

This protocol will include residual sample storage for additional research (AR).

This collection for additional research is intended to expand the translational R&D capability at Bristol-Myers Squibb, and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. It may also be used to support health authority requests for analysis, and advancement of pharmacodiagnostic development to better target drugs to the right patients. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

All requests for access to samples or data for additional research will be vetted through a diverse committee of the study sponsor's senior leaders in Research and Development to ensure the research supports appropriate and well-defined scientific research activities.

- Residual cells from RO analysis will be saved on ZellKraftWerk Chip for potential analysis on immune cells, including but not limited to immuno-phenotyping.
- Residual samples for PK, immunogenicity, exploratory serum/plasma, whole blood DNA and RNA will be stored for potential exploratory biomarker analysis including proteins, metabolites, DNA and RNA using technologies including but not limited to Next-gen sequencing and RNA sequencing.

Samples will be securely stored by the BMS Biorepository in Hopewell, NJ or at a BMS approved third party storage management facility.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key is securely held by the Investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual

Additional research samples will be retained for 15 years or the maximum allowed by applicable law. No additional sampling is required for residual collections.

Further details of sample collection and processing will be provided to the site in the procedure manual.

Sample Type	Time points for which residual samples will be retained
PK	all
Immunogenicity	All
Exploratory serum and plasma	All
Whole blood DNA	All
Whole blood RNA	all
Whole blood cells	Residual cells from RO analysis will be saved on ZellKraftWerk chip

9.8.2 Immunogenicity Assessments

Serum samples collected at time points identified in Table 9.5-1 will be analyzed for anti-nivolumab antibodies by a validated immunogenicity assay. Additional characterization (i.e. neutralizing antibodies) for any detected anti-drug antibodies (ADA) response to nivolumab may also be performed using a validated functional cell based assay. Selected serum samples may be analyzed by an exploratory method that measures anti-nivolumab antibodies for technology exploration purposes; exploratory data will not be reported.

In addition, serum samples designated for PK assessments may also be used for immunogenicity analysis if required (e.g., insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

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

9.8.3 RNA Transcriptome Research

RNA Transcriptome Research may be conducted using residual samples.

9.8.4 RNA Expression Research of a Subset of RNA Species

RNA Expression Research may be conducted using residual samples.

9.8.5 Proteome Research

Proteome Research may be conducted using residual samples.

9.8.6 Metabolomic Research

Metabolomic Research may be conducted using residual samples.

9.8.7 Other Assessments

Organ failure will be assessed by collection of SOFA score during index hospitalization. Organ support will be assessed by duration of mechanical ventilation, vasopressor use, or dialysis use separately during the index hospitalization.

Length of stay in the ICU and in the hospital during the index hospitalization will be assessed.

9.8.8 Receptor Occupancy

Fresh whole blood will be used to determine PD-1 receptor occupancy on CD3+, CD4+, CD8+ T cells by nivolumab at pre-treatment and selected time points post/on treatment using a flow cytometry based assay.

9.8.9 mHLA-DR

Expression of HLA-DR on monocytes will be measured by flow cytometry before and after treatment to determine if recovery of mHLA-DR is observed following treatment. mHLA-DR expression values from study participants may be compared to expression values from normal healthy volunteers to determine threshold values to identify sepsis participants.

9.9 Health Economics OR Medical Resource Utilization and Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

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 single doses of nivolumab in participants with severe sepsis or septic shock in order to inform feasibility of further study 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. 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.

10.2 Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Enrolled Participants	All participants who signed an informed consent
All Randomized Participants	All participants who are randomized to a treatment
All Treated Participants	All participants who have received at least one dose of study treatment
Pharmacodynamic	All participants that receive any study medication and have PD

Population	Description
(PD) Population	biomarker data available at baseline and at least one other time point
Pharmacokinetic (PK) Population	All participants who receive any study treatment and have any available concentration-time data. Additionally, the evaluable PK Population is defined as participants who have adequate PK profiles. All available derived pharmacokinetic parameters will be included in the PK data set and reported, but only participants with adequate pharmacokinetic profiles will be included in the summary statistics and statistical analysis

10.3 Statistical Analyses

10.3.1 Safety Analyses

All recorded adverse events will be listed and tabulated by system organ class, preferred term, treatment and overall. Death will be listed and summarized. Any significant physical examination findings will be listed. ECG, vital signs and clinical laboratory test results and corresponding change from baseline values will be listed and summarized by treatment. Values for ECG, vital signs and clinical laboratory test results outside the pre-specified criteria will also be listed and summarized. ECG readings will be evaluated by the Investigator and abnormalities, if present, will be listed. Immune-related AEs will be listed and tabulated by system organ class, preferred term, treatment, overall and time points.

10.3.2 Pharmacokinetic Analyses

Pharmacokinetics parameters as defined in Section 9.5 will be derived using serum concentration versus time, as data allow.

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

Serum concentration and PK parameter data will be summarized by treatment. Scatter plots of Cmax, Cmin and Cavg versus dose will be provided.

[redacted]

[redacted]

10.3.4 Secondary Biomarker Analyses

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.

10.3.5 Exploratory Biomarker Analyses

Caspase-3 and surface expression of PD-1 may be tabulated by treatment and time, and the corresponding changes from baseline may be calculated and summarized. Profile plots may be provided. Other exploratory biomarkers may be analyzed and data may be reported separate from the main CSR.

10.3.6 Other Analyses

Immunogenicity analyses:

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.

10.3.7 Interim Analyses

Not applicable.

12. APPENDICES

APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
CLT	total body clearance
cm	centimeter

Term	Definition
Cavg	Average observed concentration
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	minimum observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CV	coefficient of variation
CYP	cytochrome p-450
dL	deciliter
DMC	Data monitoring committee
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy

Term	Definition
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
L	liter
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
mg	milligram
Mg^{++}	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR	medical research
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na^+	sodium
N/A	not applicable
ng	nanogram

Term	Definition
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PK	pharmacokinetics
QC	quality control
QD, qd	quaque die, once daily
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF, T1/2	Half life
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
Vd	volume of distribution
WBC	white blood cell
WOCBP	women of childbearing potential
x g	times gravity

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

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

REGULATORY AND ETHICAL CONSIDERATIONS

GOOD CLINICAL PRACTICE

This study will be conducted in accordance with:

- Good Clinical Practice (GCP),
- as defined by the International Council on Harmonisation (ICH)
- in accordance with the ethical principles underlying European Union Directive 2001/20/EC
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- applicable local requirements.

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

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

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

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

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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

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

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and if applicable, also by local health authority) except where necessary to eliminate an immediate hazard(s) to study subjects.

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

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

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

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

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

FINANCIAL DISCLOSURE

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

INFORMED CONSENT PROCESS

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

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

Sponsor or designee will provide the investigator with an appropriate (i.e., Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.
- Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
- Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a participant's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the participant.

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

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

The consent form must also include a statement that BMS and regulatory authorities have direct access to participant records.

Subjects unable to give their written consent (e.g., stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The participant must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this participant become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a participant who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

SOURCE DOCUMENTS

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

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

STUDY TREATMENT RECORDS

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

If	Then
Supplied by BMS (or its vendors):	Records or logs must comply with applicable regulations and guidelines and should include: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • nonstudy disposition (e.g., lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.
Sourced by site, and not supplied by BMS or its vendors (examples include IP sourced from the sites stock or commercial supply, or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study drug integrity in accordance with requirements applicable under law and the SOPs/standards of the sourcing pharmacy. These records should include: • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

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

CASE REPORT FORMS

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

For sites using the Sponsor or designee electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by Sponsor or designee.

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

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

The completed CRF, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form. Subinvestigators in Japan may not be delegated the CRF approval task for electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

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

MONITORING

Sponsor or designee representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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

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

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

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

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

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

It is the investigator's or designee's responsibility to arrange for disposal, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

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

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

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

CLINICAL STUDY REPORT AND PUBLICATIONS

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Participant recruitment (e.g., among the top quartile of enrollers)
- Other criteria (as determined by the study team)

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

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

ADVERSE EVENTS

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

SERIOUS ADVERSE EVENTS

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below) NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: o a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event) o elective surgery, planned prior to signing consent o admissions as per protocol for a planned medical/surgical procedure o routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) o medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases o admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason) o admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 8.1.1 for the definition of potential DILI.)

Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study treatment is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 9.2.5 for reporting pregnancies).

In this study, the following events are study endpoints, per 21CFR 312.32 (c)(5), they are excluded from being reported as an SAE UNLESS the events are related to study drug.

- Death
- Hospitalization prolongation
- ICU admission
- Ventilator use
- Vasopressor use
- Dialysis use

These events will be recorded on other CRF pages instead of the SAE pages.

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

EVALUATING AES AND SAES

Assessment of Causality
The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following: Related: There is a reasonable causal relationship between study drug administration and the AE. Not related: There is not a reasonable causal relationship between study drug administration and the AE. The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Follow-up of AEs and SAEs
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial

SAE report.

All SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

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

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

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

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

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels.

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 4 months after the end of study treatment, plus 30 days (a total of 5 months).

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

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

NOTES:

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

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

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

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

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

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

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until the end of relevant systemic exposure defined as 7 months after the end of treatment in the male participant.
- Female partners of males participating in the study should consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 5 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 5 months after the end of treatment.

- Refrain from donating sperm for the duration of the study treatment and for 7 months after the end of treatment.

COLLECTION OF PREGNANCY INFORMATION

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