Official Title of Study:

A Phase 1, Open-label, Multi-part Study to Evaluate the Safety, Tolerability, Kinetics, Biodistribution, and CNS Signal of the Positron Emission Tomography Ligand 11C-BMS-986196 in Healthy Participants After Intravenous Administration and to Evaluate the Safety, Tolerability, Kinetics, and CNS Signal Repeatability of ^{11}C-BMS-986196 After Repeat Intravenous Administration in Participants With Multiple Sclerosis

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Date: 16-Apr-2021
Revised Date: 30-Jun-2023

CLINICAL PROTOCOL IM038010

A Phase 1, Open-label, Multi-part Study to Evaluate the Safety, Tolerability, Kinetics, Biodistribution and CNS Signal of the Positron Emission Tomography Ligand ^{11}C-BMS-986196 in Healthy Participants after Intravenous Administration and to Evaluate the Safety, Tolerability, Kinetics, and CNS Signal Repeatability of ^{11}C-BMS-986196 after Repeat Intravenous Administration in Participants with Multiple Sclerosis

Brief Title:

Safety, Tolerability, Kinetics, and Biodistribution of the PET Ligand ^{11}C-BMS-986196 after IV Administration in Healthy Participants and the Evaluation of CNS Signal Repeatability after Repeat IV Administration in Participants with Multiple Sclerosis

Protocol Amendment Number 05

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EudraCT/EU Trial Number: 2021-001986-19

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Amendment 05	30-Jun-2023	Revisions to: Add a novel Part C to the protocol, to quantify free Bruton's tyrosine kinase (BTK) in the brain before and approximately 24 hours after oral administration of unlabeled BMS-986196 at doses of 15 mg, 30 mg, and 60 mg.
Protocol Amendment 04	09-May-2022	Revisions to: • Accurately account for the radiation exposure resulting from a cranial computed tomography (CT) scan. • To facilitate operational conduct of the study by: o Allowing for a shorter interval between positron emission tomography (PET) scans. o Allowing a third PET scan in Part B in case 1 PET scan procedure is not successful. o Allowing up to 6 cranial CT scans in Part B (1 before and 1 after each PET scan) to account for potential movement during the PET procedure. o Specifying that fasting requirements are only for Part A participants. o Allowing vital sign assessment in sitting position.
Protocol Amendment 03	21-Feb-2022	Revisions to allow venous blood sampling during cranial positron emission tomography (PET). This would be necessary if emerging data from this ongoing study indicate that a (pseudo) reference region cannot be reliably established, therefore making future studies with ^{11}C-BMS-986196 without arterial input function challenging.
Protocol Amendment 02	02-Nov-2021	1) Revisions to AE-based stopping rules Updated the procedures for study restart after stopping rules have been met.
Protocol Amendment 01	22-Oct-2021	1) Revisions to Exclusion Criteria • Removal of required consultation with the BMS clinical trial physician regarding the eligibility of a participant with any sequelae from a prior SARS-CoV-2 infection. • Removal of participants with malaria falciparum infection. • Removal of any exception granted by the Sponsor medical monitor regarding the use of any prescription drugs within 4 weeks or 5 times the

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Document	Date of Issue	Summary of Change
		elimination half-life (if known), whichever is longer before tracer administration. • Removal of any exception granted by the Sponsor medical monitor regarding the use of any investigational drugs or placebo within 4 weeks or 5 times the elimination half-life (if known), whichever is longer before tracer administration. • Removal of any exception granted by the Sponsor medical monitor with regards to the participant's participation in another clinical trial concurrent with this study. Addition of the investigator assessment on whether or not to enroll the participant meeting this criterion. 2) Revisions to (S)AE-based stopping rules • Specifying stricter criteria for triggering (S)AE-based stopping rules and specifying the procedures for study restart after stopping have been met.
Administrative Letter 01	22-Aug-2021	This administrative letter addresses an inconsistency between different sections in the protocol regarding the site personnel placing arterial lines. Table 3.3.1-1 of the protocol specifies that arterial line placement is performed by experienced staff, whereas Section 3.3 (Benefit/Risk Assessment) and Section 9.1.1.1 (PET Assessment) state that the arterial line placement is performed by an experienced physician. This administrative letter clarifies that arterial line placement will be performed by experienced staff. Experienced staff includes technicians, who are not physicians. This clarification ensures that arterial line placement is performed according to the standard practice at the participating sites.
Original Protocol	16-Apr-2021	Not applicable

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OVERALL RATIONALE FOR PROTOCOL AMENDMENT 05:

The overall rationale for Amendment 05 is to add a novel Part C to the study protocol, in which free Bruton's tyrosine kinase (BTK) in the brain will be quantified in healthy participants before and approximately 24 hours after oral administration of unlabeled BMS-986196 at doses of 15 mg, 30 mg, and 60 mg once daily (QD).

These amendment changes will apply to future participants.

SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Title Page	Clinical Scientist information removed.	Administrative change to align with the current Bristol-Myers Squibb (BMS) protocol model document.
Section 1, Protocol Summary	Text in protocol summary updated to reflect changes from protocol body.	Updated for consistency.
Section 2, Schedule of Activities (Table 2-1)	• Table title updated to include Part C for screening procedures. • Columbia-Suicide Severity Rating Scale (C-SSRS) and QuantiFERON-TB Gold Plus procedures added as a screening for Part C participants only. • Clarification added that Allen's test procedure only required for Part A and Part B. • Clarification added that hematology, chemistry, urinalysis, coagulation, urine drug screen, and urine cotinine test only required for Part A and Part C. [redacted]	To account for the assessments in the newly added Part C.
Section 2, Schedule of Activities (Table 2-4)	New table added for Part C.	To account for the assessments in the newly added Part C.
Section 3, Introduction; Section 3.3 Benefit/Risk Assessment; Section 5.4, Scientific Rationale for Study Design; Section 5.5 Justification for Dose; Section 6.3.2 Caffeine, Alcohol, and Tobacco;	Additional information for Part C added.	To account for the newly added Part C.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.4 Dosage Modification; Section 9.2.5 Pregnancy		
Section 3.1 Study Rationale	Removed "in patients with MS" from first bullet.	Clarification made to facilitate the broader population and not only the specific population.
Section 3.2.7, BMS-986196 Clinical Experience; Section 3.2.8, ^{11}C-BMS-986196 Clinical Experience	New sections added.	To provide newly available clinical information for BMS-986196 and ^{11}C-BMS-986196.
Section 3.3 Benefit/Risk Assessment; Section 9.1.1.1 PET Assessments	Site information updated.	Site information has been updated to include more sites for Part C.
Section 4 Objectives and Endpoints	Additional primary [redacted] objectives and endpoints added for unlabeled BMS-986196.	To account for the newly added Part C.
Section 5, Study Design	Additional information for Part C added: • Study design updated to include Part C. • Total number of participants updated from 16 to 28. • Treatment period and safety follow-up updated with additional information relevant to Part C.	To account for the newly added Part C.
Section 5.2, Number of Participants	Total number of participants updated from 16 to 28. Additional information for the participants to be considered in Part C added.	To account for the study participants in the newly added Part C.
Section 6.1 Inclusion Criteria	New criteria added for Part C participants in 2) and 4).	To account for the inclusion criteria in the newly added Part C.
Section 6.2 Exclusion Criteria	• Two new criteria added for Part C participants in 1). • Added "Part C" in criteria 1) a), 1) g), 1) w), 3) b), 4) b), and 4) c). • Added "Part A and Part B" in criterion 1) t).	To account for the exclusion criteria in the newly added Part C.
Section 7.1 Study Interventions Administered	New information on Part C added in Table 7.1-1.	To account for study interventions in the newly added Part C.
Section 7.2 Method of Study Intervention Assignment	Additional details for assignment of participants in Part C added.	To account for the newly added Part C.

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SUMMARY OF KEY CHANGES FOR PROTOCOL AMENDMENT 05		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 7.5 Preparation/Handing/Storage/ Accountability	Added statement: "Only participants enrolled in the study may receive study intervention, and only authorized staff may supply, prepare, or administer study intervention."	Statement added to align with the current BMS protocol model document.
Section 7.6 Treatment Compliance	Additional Part C information added.	To account for the assessment of compliance in the newly added Part C.
Section 7.7.1 Prohibited and/or Restricted Treatments	Added clarification text "or 5 times the elimination half-life (if known), whichever is longer," to bullet 6).	Added for consistency.
Section 9.1.1.1 PET Assessments	Additional Part C information added under PET assessment.	To account for the assessments in the newly added Part C.
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Part C serious adverse event collection time period added.	To account for the assessments in the newly added Part C.
Section 9.4.1: Physical Examinations	• Added "Part C".	To account for the assessments in the newly added Part C.
Section 9.4.4: Allen's Test (Part A and Part B only)	• Added "Part A and Part B only" to section heading.	To account for the assessments in the newly added Part C.
Section 9.4.6: Clinical Safety Laboratory Assessments	• Added "Part C". • Added TB test for Part C under "Other Analyses".	To account for the assessments in the newly added Part C.
Section 9.4.7 Suicidal Risk Monitoring (Part C only)	New section added.	To specify C-SSRS assessments in the newly added Part C.
[redacted]		
Section 9.8 Biomarkers	Section updated to include Part C sampling schedule.	To specify biomarker assessments in the newly added Part C.
Section 10.3: Analysis Sets; Section 10.4.2: Primary Endpoint(s); [redacted]	Updated to include Part C.	To address statistical considerations for the newly added Part C.
Throughout the protocol	Minor language and formatting changes.	To improve clarity of the protocol.

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1 PROTOCOL SUMMARY

Protocol Title:

A Phase 1, Open-label, Multi-part Study to Evaluate the Safety, Tolerability, Kinetics, Biodistribution, and CNS Signal of the Positron Emission Tomography Ligand ^{11}C-BMS-986196 in Healthy Participants after Intravenous Administration and to Evaluate the Safety, Tolerability, Kinetics, and CNS Signal Repeatability of ^{11}C-BMS-986196 after Repeat Intravenous Administration in Participants with Multiple Sclerosis

Brief Title:

Safety, Tolerability, Kinetics, and Biodistribution of the PET Ligand ^{11}C-BMS-986196 after IV Administration in Healthy Participants and the Evaluation of CNS Signal Repeatability after Repeat IV Administration in Participants with Multiple Sclerosis

Rationale:

^{11}C-BMS-986196 covalently binds and inhibits Bruton's tyrosine kinase (BTK), a kinase expressed in B-cells, monocytes, macrophages, microglia, dendritic cells, natural killer cells, granulocytes, mast cells, basophils, eosinophils, osteoclasts, and platelets. BTK plays a role in intracellular signaling cascades downstream of the B-cell receptor, activating immunoglobulin G immune complex receptors (FCγRIIa and FCγRIIIa), the high affinity immunoglobulin E receptor (FcεRI), and the receptor activator of nuclear factor kappa-B (RANK).

BTK is not expressed in neurons, astrocytes, or oligodendrocytes and is not known to have functions in a healthy central nervous system (CNS) without inflammatory conditions. Based on the cellular expression profile of BTK, the known presence of B-cells, macrophages, and microglia in multiple sclerosis (MS) lesions, and the short half-life of [C-11], ^{11}C-BMS-986196 has the potential to be a Positron Emission Tomography (PET) tracer for the detection of (chronic) microglial inflammation, (acute) lesions with infiltrating macrophages, and B-cell infiltrates in the brain or meninges of patients with MS. Preclinical experiments in experimental autoimmune encephalitis (EAE) mice support that ^{11}C-BMS-986196 has the potential to detect MS.

This is the first study testing ^{11}C-BMS-986196 as a PET ligand in humans. This study is supported by preclinical Good Laboratory Practices (GLP) toxicity and safety studies, including in rats and cynomolgus monkeys, in the context of an Investigational New Drug (IND) submission. There is no formal primary research hypothesis for this study to be statistically tested. The purpose of this study is to assess ^{11}C-BMS-986196, a novel PET tracer for BTK in healthy participants and in participants with MS to facilitate its use for:

- Assessment of CNS [redacted] in future clinical studies
- Dose selection of compounds that target the BTK receptor in the CNS, including dose selection for unlabeled BMS-986196
- Assessing the presence of BTK-expressing cells in participants with inflammatory CNS diseases, including MS

Overall, the data from this study will contribute to general research and the development of a novel means to visualize CNS inflammation, and are expected to facilitate development of therapies for progressive MS.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary**
• To assess safety, tolerability, kinetics, and CNS signal repeatability of the novel tracer ^{11}C-BMS-986196 in healthy participants and in participants with MS • To assess the safety of BMS-986196	• Incidence, severity, seriousness, and type of AEs; clinically significant abnormalities in ECG, VS, laboratory values, physical examination, and C-SSRS • Radiation dosimetry calculated from PET-CT images in healthy participants • Image acquisition window after administration of ^{11}C-BMS-986196 • Test-retest repeatability based on quantitative analysis of CNS PET-MRI images (eg, SUV and/or V_T) in participants with MS
• To quantify the proportion of free BTK in the brain after administration of unlabeled BMS-986196	• % Free brain BTK relative to baseline
Secondary	**Secondary**
• To assess ^{11}C-BMS-986196 signal characterization	• Calculated SUV and V_T in the brain

Abbreviations: AE, adverse event; BTK, Bruton's tyrosine kinase; CNS, central nervous system; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; MS, multiple sclerosis; PET-CT, positron emission tomography - computed tomography; PET-MRI, positron emission tomography - magnetic resonance imaging; SUV, standardized uptake value; VS, vital signs; V_T, volume of distribution.

Overall Design:

This is a Phase 1, open-label study in healthy participants and participants with MS to evaluate a novel, positron-emitting ligand ^{11}C-BMS-986196, for measurement of free BTK. The study will include up to 28 evaluable participants (Part A: up to 8 healthy participants; Part B: up to 8 participants with MS; Part C: up to 12 healthy participants). The study consists of 3 periods: screening, treatment, and safety follow up. See Figure 1.

All participants will undergo PET scanning with ^{11}C-BMS-986196. An initial dose of ^{11}C-BMS-986196 will be administered at doses up to 20 µg with the radioactivity of the dose at approximately 370 MBq (10 mCi). In Part B and Part C, the radioactive dose and participant preparation may be revised based on results of radiation dosimetry obtained in Part A, but administered mass will not exceed 20 µg.

- **Part A (Whole-Body Radiation Dosimetry and Cranial PET Imaging):** Up to 6 evaluable healthy adult participants (at least 2 male and 2 female participants are planned) will complete whole-body positron emission tomography - computed tomography (PET-CT) imaging after a

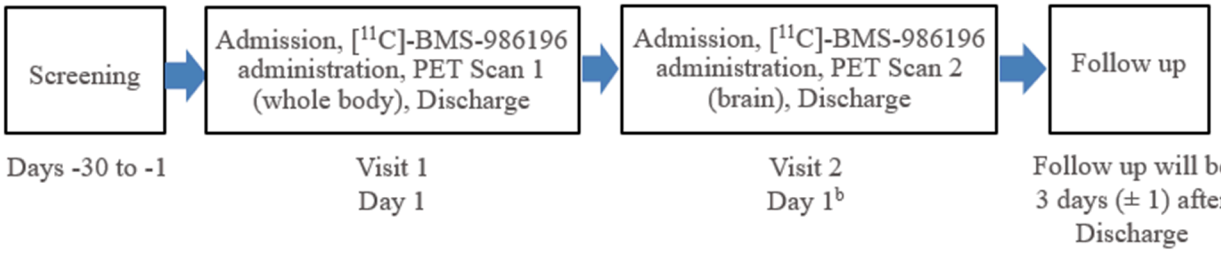
bolus intravenous (IV) administration of ^{11}C-BMS-986196 under fasting conditions, to confirm tracer safety, assess image acquisition window, determine radiation dosimetry of the administered radiotracer, and assess optimal imaging time. The PET scan will last approximately 2 hours. At least 2 hours and at most 6 days after the first tracer administration, participants will receive a second tracer administration and undergo cranial PET imaging using either PET-CT or positron emission tomography - magnetic resonance imaging (PET-MRI), depending on the availability of equipment. If the interval between the first and second PET scan is 4 days or more, the study site staff must contact the participant remotely (eg, by phone) on Day 4 (ie, 3 days after the first PET scan) and record adverse events (AEs) and any concomitant medications. Following an observation period of approximately 1 hour after completion of all PET scanning procedures, participants will be discharged from the PET center and enter the safety follow-up period. Up to 6 healthy participants will complete Part A before initiation of Part B. If emerging data from Part B indicate that venous blood sampling is likely to be required in future studies using ^{11}C-BMS-986196 without arterial blood sampling (eg, because a [pseudo]-reference region cannot be reliably established), 2 additional participants can be enrolled in Part A at the discretion of the Sponsor. These additional 2 participants will only undergo cranial PET imaging using either PET-CT or PET-MRI, depending on the availability of equipment (ie, not whole body PET-CT).

- **Part B (Characterization of ^{11}C-BMS-986196 binding in the human brain):** Up to 8 participants with MS will complete 2 evaluable cranial PET-CT or PET-MRI scans (depending on equipment availability) after a bolus IV administration of ^{11}C-BMS-986196, separated by at least 2 hours and at most 6 days to determine the optimal quantification parameters, including within-participant variability under test and retest conditions. Following an observation period of approximately 1 hour after completion of PET scanning procedures, participants will be discharged from the PET center and enter the safety follow-up period. If the interval between the first and second PET scan is 4 days or more, the study site staff must contact the participant remotely (eg, by phone) on Day 4 (ie, 3 days after the first PET scan) and record AEs and any concomitant medications. Participants who had a MS relapse within 30 days prior to Day 1 must start Scan 2 on Day 1 or Day 2. Up to 8 participants with MS will complete Part B.
- **Part C (Quantification of free BTK availability in the human brain):** Up to 12 evaluable healthy adult participants will complete 2 evaluable cranial PET-CT or PET-MRI scans (depending on equipment availability). The first cranial PET scan will occur on Day 1 after a bolus IV administration of ^{11}C-BMS-986196. After completion of the first evaluable PET scan (on the same day or the day following the PET scan), participants will receive orally administered unlabeled BMS-986196 on-site or at home once daily (QD) for preferably 1 day; and approximately 24 hours after the (last) dose of BMS-986196, participants will undergo the second cranial PET scan after a bolus IV administration of ^{11}C-BMS-986196. If the second PET scan cannot be performed in this time frame, it is permissible to administer a single dose of unlabeled BMS-986196 up to 7 days after the Day 1 PET (eg, in case of scheduling conflicts). In addition, in case of synthesis failure of PET tracer it is permissible to administered multiple doses of unlabeled BMS-986196 in order to have BMS-986196 administered 24 hours prior to the second PET scan, if Sponsor agrees. No more than 7 doses can be administered. Up to 3 dose levels of (unlabeled) BMS-986196 will be tested (15 mg, 30 mg, and 60 mg QD) and approximately 4 participants per dose level will be tested. Initially, participants will be

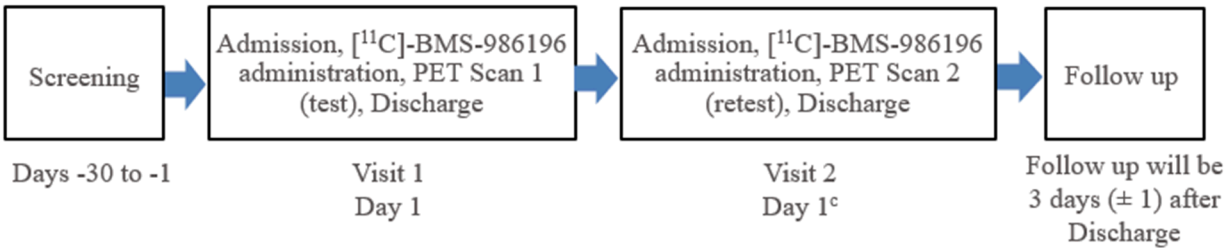
assigned to the 30 mg dose level. After an interim review of PET results from 2 to 4 evaluable participants, the next dose level (15 mg or 60 mg) will be determined. At least 2 evaluable participants should have completed PET imaging at the second dose level before participants are assigned to the last dose level.

Figure 1: Study Design Schema

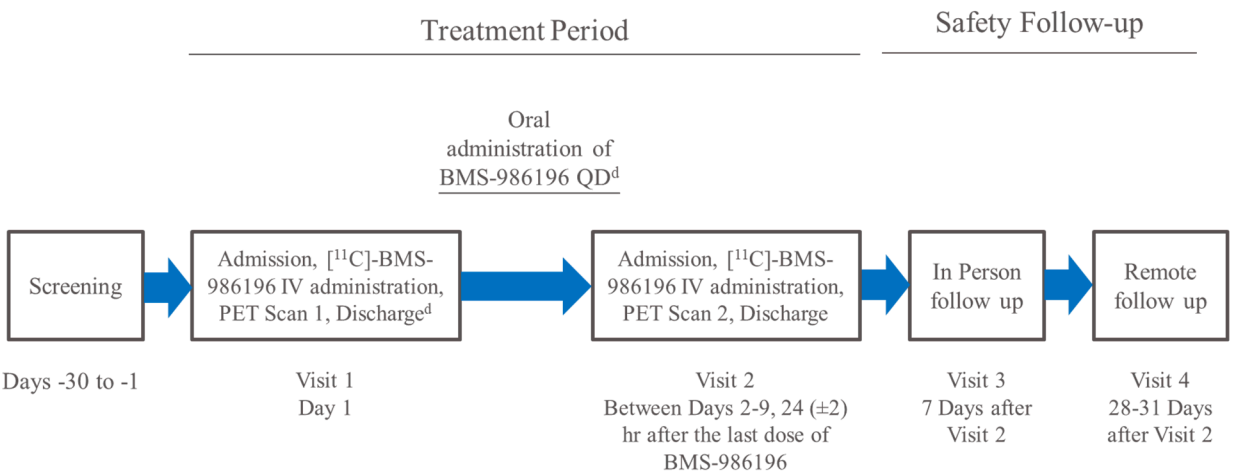
Part A - Safety, Tolerability, and Dosimetry in Healthy Participants[a]



Part B - Repeatability of ^{11}C-BMS-986196 PET in Participants with MS



Part C - Quantification of Free BTK Availability in Healthy Participants



Abbreviations: BTK, Bruton's tyrosine kinase; IV, intravenous; hr, hour; MS, multiple sclerosis; PET, positron emission tomography; QD, once daily.

[a] Prior to initiation of Part B, all Part A participants will undergo Visits 1 and 2. After initiation of Part B, up to 2 participants may be added to Part A and will not undergo Visit 1, only Visit 2. For these participants only, Visit 2 will be regarded as Day 1.

[b] Visit 2 tracer administration must be done at least 2 hours and at most 6 days after Visit 1 tracer administration (ie, Day 2 to Day 7).

[c] Participants who had a MS relapse within 30 days prior to Day 1 must start Scan 2 on Day 1 or Day 2.

[d] After completion of the first evaluable PET scan (on the same day or the day following the PET scan), participants will receive orally administered unlabeled BMS-986196 QD for preferably 1 day; and approximately 24 hours after the (last) dose of BMS-986196, participants will undergo the second cranial PET scan. If the second PET scan cannot be performed in this time frame, it is permissible to administer a single dose of unlabeled BMS-986196 up to 7 days after the Day 1 PET (eg, in case of scheduling conflicts) or to dose unlabeled BMS-986196 QD for up to 7 days (eg, in case of synthesis failure of the PET tracer), if the Sponsor agrees.

Number of Participants:

Up to 28 evaluable participants are planned to be enrolled, up to 8, 8, and 12 in Parts A, B, and C, respectively. In Part A, evaluable participants for dosimetry outcomes are defined as those with adequate PET-CT whole-body scans collected over > 60 minutes. Part A evaluable participants for cranial PET are defined as those with cranial scans of adequate quality to be evaluable. In Part B, participants must have 2 cranial PET-CT/PET-MRI scans of adequate quality to be evaluable. To be evaluable in Part C, participants must have 1 cranial PET-CT/PET-MRI scan of adequate quality before administration of (unlabeled) BMS-986196 and 1 cranial PET-CT/PET-MRI scan of adequate quality after administration of (unlabeled) BMS-986196. Participants with non-evaluable PET images may be substituted with new study participants.

Study Population:

Key Inclusion Criteria:

Women of childbearing potential (WOCBP) and men, 18 to 55 years of age, inclusive. (Parts A and B).

Women **not** of childbearing potential (WNOCBP) and men, 18 to 55 years of age, inclusive (Part C only).

Investigators shall counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of ^{11}C-BMS-986196, present in seminal fluid, to a developing fetus even if the participant has undergone a successful vasectomy or if the partner is pregnant.

- **Type of Participant and Target Disease Characteristics**
  - **For Part A and Part B:**
    - Body mass index (BMI) of 18 to 34 kg/m^2, inclusive, and total body weight ≥ 50 kg (BMI may be rounded, eg, a participant with a BMI of 34.4 would qualify).
    - Documentation of normal Allen's test result at Screening and on PET scanning days in the arm that will be used for arterial line placement.
  - **Part A only:**
    - Healthy male and female participants without clinically significant deviation from normal in medical history, physical examination (PE), electrocardiograms (ECGs), and clinical laboratory determinations.

- **Part B only:**
  - Male or female participant diagnosed with MS according to the 2017 revisions of the McDonald diagnostic criteria.
  - Expanded Disability Status Scale (EDSS) score between 0 to 6.5, inclusive, at Screening.
- **For Part C:**
  - Body mass index (BMI) of 18 to 34 kg/m^2, inclusive, and total body weight ≥ 50 kg (BMI may be rounded, eg, a participant with a BMI of 34.4 would qualify).
  - Healthy male and WNOCBP participants without clinically significant deviation from normal in medical history, physical examination (PE), ECGs, and clinical laboratory determinations.

Key Exclusion Criteria:

- **Medical Conditions**
  - Any significant acute or chronic medical illness (Part A and Part C). Any significant acute or chronic medical illness (other than MS) posing a risk to the participant's safety or negatively affecting the ability to detect CNS PET signal (Part B only).
  - Benign MS defined as a baseline EDSS of 2.0 with MS diagnosis ≥ 10 years prior to Day 1. Spinal MS without clinical or radiological evidence of brain lesions. Any other combination of clinical and radiological data suggestive of an absence of inflammatory brain lesions.
  - MS relapse within 14 days prior to Day 1. Participants with a MS relapse within 30 days prior to Day 1 must agree to have their second PET scan scheduled on Day 1 or Day 2 (Part B only).
  - Any major surgery within 4 weeks of study treatment administration and/or any minor surgery within 2 weeks of tracer administration.
  - A history of pancreatitis.
  - A history of prolonged bleeding or excessive bruising.
  - Known or suspected autoimmune disorder, including but not limited to rheumatoid arthritis, fibromyalgia, systemic lupus erythematosis, polymyalgia rheumatica, giant cell arteritis, Behcet's disease, dermatomyositis, severe asthma, any autoimmune vasculitis, autoimmune hepatitis, or any other active autoimmune disease for which a participant requires medical follow-up or medical treatment. Participants in Part A and Part C must not have a diagnosis of MS.
  - Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the participant's immune status and/or confound tracer dosimetry and signal detection (eg, splenectomy).
  - Presence of any factors that would predispose the participant to develop infection (eg, rectal fissures, poor dentition, open skin lesions, and presence of pre-existing skin conditions that increase risks for injection site complications [eg, Behcet's disease, psoriasis, pustular dermatoses]).

- Known currently active tuberculosis (TB) (Part A and Part B).
- Any serious acute or chronic bacterial or viral infection (eg, pneumonia, septicemia) within 3 months prior to Screening.
- In the case of prior severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, symptoms must have completely resolved and based on investigator assessment, there are no sequelae (eg, shortness of breath, persistent cough, excessive fatigue, loss of smell) that would place the participant at a higher risk of receiving investigational treatment.
- Positive test result for the presence of SARS-CoV-2 virus (eg, polymerase chain reaction [PCR] test) within 14 days of Day 1.
- Any recent infection requiring antibiotic treatment within 4 weeks of Day 1.
- Active herpes infection, including herpes simplex 1 and 2 and herpes zoster.
- Known active malaria.
- History or any evidence of active infection or febrile illness within 7 days of tracer administration (eg, bronchopulmonary, urinary, or gastrointestinal).
- Donation of blood to a blood bank or to another clinical study within 4 weeks of tracer administration (within 2 weeks for plasma only).
- Inability to be venipunctured and/or tolerate venous access.
- Have any contraindication to arterial line insertion, including but not limited to, an abnormal Allen's test result, coagulation profile, allergy to local anesthetics, or other medical history or examination findings that in the opinion of the Investigator would make radial artery cannulation contraindicated (international normalized ratio [INR]/partial thromboplastin time [PTT]) at Screening (Part A and Part B).
- Contraindications against MRI imaging, including non-MRI compatible metal implants, cardiac pacemakers, cochlear implants, ventricular shunt systems; metal particles in the body that pose a risk to the participant, including large tattoos in regions affected by cranial MRI scanning; severe claustrophobia. Contraindications against gadolinium-based contrast agents including known hypersensitivity to gadolinium-based contrast agents (Part B only).
- Recent (within 6 months of study intervention administration) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5), Diagnostic Criteria for Drug and Alcohol Abuse.
- Use of any tobacco- or nicotine-containing products (including but not limited to cigarettes, pipes, cigars, electronic cigarettes, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 3 months prior to the first dose of tracer administration (Part A and Part C).
- Any other sound medical, psychiatric, and/or social reason as determined by the investigator.
- Inability to lie on the scanner for the duration of a PET scan acquisition.
- Current clinical or laboratory evidence of active TB. Participants with a positive QuantiFERON-TB Gold Plus test or 2 successive indeterminate QuantiFERON-TB Gold Plus tests at Screening will be excluded (Part C only).

  - Participants who answer "yes" to items 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) or who answer "yes" to any suicidal behavior item (excluding non-suicidal self-injurious behavior) within 6 months prior to Day 1 or at Day -1 (See Section 9.4.7 for details on suicidal risk monitoring) (Part C only).

- **Reproductive Status**
  - Women who are pregnant
  - Women who are breastfeeding
- **Physical and Laboratory Test Findings**
  - Evidence of organ dysfunction or any clinically significant deviation from normal in PE, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population, in the opinion of the investigator
  - Positive urine screen for drugs of abuse (Part A and Part C)
  - Positive cotinine test (Part A and Part C)
  - Positive blood screen for hepatitis C antibody, hepatitis B core antibody, hepatitis B surface antigen, or human immunodeficiency virus (HIV)-1 and -2 antibody
  - Estimated renal creatinine clearance < 30 ml/min based on the Cockgroft-Gault formula
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)
  - Total bilirubin > 2 x ULN (unless in the context of Gilbert syndrome)

Intervention Groups and Duration:

Study intervention:

Study Intervention for IM038010		
Medication	**Potency**	**IP/Non-IP/AxMP**
^{11}C-BMS-986196	Approximately 370 MBq, equivalent to up to 20 µg	IP
BMS-986196 tablet	15 mg, 30 mg, or 60 mg	IP

AxMP, auxiliary medicinal product; IP, investigational product; MBq, megabecquerel.

Study duration:

The estimated duration from screening through safety follow-up phone call (or in-person study site visit) is up to approximately 6 weeks for Part A, approximately 6 weeks for Part B, and up to 10 weeks for Part C.

- Screening: Within 30 days prior to administration of ^{11}C-BMS-986196

- Treatment Period:
  - Part A: After the first tracer administration (Day 1), participants will receive a second tracer administration at least 2 hours and at most 6 days and undergo cranial PET imaging using either PET-CT or PET-MRI, depending on the availability of equipment
  - Part B: After the first tracer administration (Day 1), participants will receive a second tracer administration at least 2 hours and at most 6 days, and undergo cranial PET imaging using either PET-CT or PET-MRI, depending on the availability of equipment
  - Part C: After the first tracer administration and cranial PET imaging (Day 1), participants will receive unlabeled BMS-986196 for oral administration on-site or at home QD for approximately 1 day (at least 1 and at most 7 days), and will undergo a second cranial PET procedure approximately 24 hours after the last dose of unlabeled BMS-986196. PET imaging will be performed with PET-CT or PET-MRI, depending on the availability of equipment
- Safety Follow-up:
  - Parts A and B: Participants will be contacted remotely by phone 3 days (± 1 day) after completion of all PET scanning procedures. An in-person visit is optional.
  - Part C: Participants will have 1 in-person visit 7 days after Visit 2 after completion of all PET scanning procedures and will be contacted remotely by phone 28 days (+ 3 days) after Visit 2.

Statistical Methods:

Statistical analyses in this study will be detailed in the statistical analysis plan (SAP). There are no formal statistical hypotheses for this Phase 1, open-label study. Descriptive statistics or frequency summary, as appropriate, will be used to analyze most all primary endpoints (ie, incidence, severity, seriousness, and type of adverse events; incidence of clinically significant abnormal findings; radiation dosimetry [Part A only]; test-retest repeatability [Part B only]; proportion of free brain BTK relative to baseline [Part C only]; C-SSRS [Part C only]).

Data Monitoring Committee: No

A Data Monitoring Committee will not be used in the study.

Other Committee: No

Other review committees will not be used in the study.

Brief Summary:

The purpose of this study is to evaluate the safety, tolerability, kinetics, biodistribution, and central nervous system (CNS) signal of the positron emission tomography (PET) ligand ^{11}C-BMS-986196 in healthy participants after intravenous administration and to evaluate the safety, tolerability, kinetics, and CNS signal repeatability of ^{11}C-BMS-986196 after repeat intravenous administration in participants with multiple sclerosis. In Part C, the purpose is to quantify the amount of free BTK in the brain before and after administration of unlabeled BMS-986196. ^{11}C-BMS-986196 is a

novel PET tracer for Bruton's tyrosine kinase (BTK), and this study will facilitate its future use for:

- Assessment of CNS [redacted] in future clinical studies in patients with multiple sclerosis (MS)
- Dose selection of compounds that target the BTK receptor in the CNS, including dose selection for unlabeled BMS-986196
- Assessing the presence of BTK-expressing cells in participants with inflammatory CNS diseases, including MS

Study details include:

Study Duration: For Part A and Part B, up to approximately 6 weeks; for Part C, up to approximately 10 weeks

Study Intervention Duration: For Part A and Part B, up to 6 days; for Part C, up to 9 days

Study Visit Frequency: For Part A and Part B, up to two visits in 1 week and a safety follow-up phone call or study site visit 3 days (± 1 day) after the last visit; for Part C, up to two visits in up to 2 weeks, one safety follow-up study site visit 7 days after the last visit, and one safety follow-up phone call 28 days (+ 3 days) after the last visit.

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2 SCHEDULE OF ACTIVITIES

Study assessments and procedures are presented for screening in Table 2-1 and are presented for imaging assessments and procedures in Table 2-2 (Part A), Table 2-3 (Part B), and Table 2-4 (Part C).

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Table 2-1: Screening Procedural Outline for Parts A, B, and C (IM038010)

Procedure	Screening Visit(s) (Day -30 to Day -1)	Notes
Eligibility Assessments and Related Procedures		
Informed Consent	X	A participant is considered enrolled only when a protocol-specific informed consent is signed. Must be obtained prior to performing any screening procedures.
Inclusion/Exclusion Criteria	X	
Demographics	X	
Medical History	X	Include any toxicities or allergies related to previous treatments. For Part B, all medical history relevant to MS should be obtained.
Safety Assessments		
Height, Weight, and BMI	X	BMI will be calculated.
Complete PE	X	If the Screening PE is performed within 24 hrs prior to tracer administration on Day 1, then a single complete PE is sufficient for both the Screening and Day 1 PE. See Section 9.4.1.
12-Lead ECG	X	ECGs should be recorded after the participant has been supine for at least 5 min. If the Screening ECG is performed within 24 hrs prior to tracer administration on Day 1, then a single ECG is sufficient for both the Screening and Day 1 ECG. See Section 9.4.5.
Vital Signs	X	VS (including body temperature, respiration rate, seated BP, and HR) should be measured after the participant has been resting quietly in a supine position for at least 5 min. See Section 9.4.3.
Allen's Test	X	Parts A and B only. Normal result must be documented in at least 1 arm.
C-SSRS	X	Part C only. Screening/baseline version with lifetime and 6 months review interval.
SAE Assessment	X	All SAEs must be collected from the time of signing the consent until 10 days after the last tracer administration or the final visit, whichever is later.

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Table 2-1: Screening Procedural Outline for Parts A, B, and C (IM038010)

Procedure	Screening Visit(s) (Day -30 to Day -1)	Notes
		All AEs (SAEs and non-serious AEs) associated with SARS-CoV-2 infection must be collected from the date of participant's written consent. See Section 9.2.1.
Prior and Concomitant Medication Use	X	Includes prescription, over-the-counter medications, and herbal supplements. See Section 7.7.1 for Prohibited and/or Restricted Treatments.
Laboratory Tests		
HBsAg, anti-HBc, HCV Ab, HIV Serology	X	Results must be confirmed as negative prior to tracer administration on Day 1.
Hematology, Chemistry, Urinalysis, and Coagulation	X	Parts A and C participants: Participants are required to fast for at least 10 hrs prior to specimen collection. Screening results must be reviewed for eligibility prior to tracer administration on Day 1. See Section 9.4.6 for full list of clinical laboratory safety tests/assessments.
Urine Drug Screen	X	Parts A and C only. Includes amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, and opiates.
Urine or Breath Alcohol Test	X	
Urine Cotinine Test	X	Parts A and C only.
Pregnancy Test (WOCBP only)	X	Urine or serum test. Result must be confirmed as negative prior to tracer administration on Day 1. Acceptable methods of contraception are specified in Appendix 4.
FSH Test	X	Women < 55 years for confirmation of postmenopausal status. Refer to Appendix 4.
QuantiFERON-TB Gold Plus	X	Part C only.
Imaging		
Cranial MRI Scan	X	Part B only. MRI scan should only be performed after all Screening assessments for safety, clinical laboratory tests, and medical history have established eligibility for the study. See Section 9.1.1.2. MRI scan with and without gadolinium contrast agent. If gadolinium contrast agent will be used during PET-MRI, gadolinium-based contrast agent is not required during Screening MRI.

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Table 2-1: Screening Procedural Outline for Parts A, B, and C (IM038010)

Procedure	Screening Visit(s) (Day -30 to Day -1)	Notes
		MRI scan should be performed within 14 days of Day 1.
[redacted]		

Abbreviations: AE, adverse event; anti-HBc, anti-hepatitis B core antibody; BMI, body mass index; BP, blood pressure; C-SSRS, Columbia-suicide severity rating scale; ECG, electrocardiogram; [redacted] FSH, follicle-stimulating hormone; HBsAG, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; HIV, human immunodeficiency virus; HR, heart rate; hrs, hours; MRI, magnetic resonance imaging; MS, multiple sclerosis; min, minutes; PE, physical examination; PET, positron emission tomography; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VS, vital signs; WOCBP, women of childbearing potential.

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Table 2-2: Imaging Procedural Outline for Part A (IM038010)

Procedure	Visit 1 Day 1[a]	Visit 2 (2 hrs to 6 days after Visit 1 tracer administration)[b]	Safety Follow-up 3 days (± 1 day) after most recent PET Scan[c]/Early Termination[d]	Notes
Safety Assessments				
Weight Measurement	X	X		
Partial PE	X	X		PE must be done within 24 hrs of tracer administration. Symptom-based PE only.
12-Lead ECG	X	X		ECGs should be recorded after the participant has been supine for at least 5 min. ECG will be conducted prior to tracer administration and after completion of the PET scan. See Section 9.4.5.
Vital Signs	X	X		VS will be obtained before tracer administration, after PET scan completion, and prior to discharge on Visits 1 and 2. See Section 9.4.3.
Allen's Test		X		Normal result (in the arm that will be used for arterial line placement) must be documented prior to arterial line placement.
Hematology, Chemistry, Urinalysis	X	X		Participants are required to fast for at least 10 hrs prior to specimen collection. Specimens will be collected at least 1.5 hrs after the first tracer administration and at least 1.5 hours after the second tracer administration. See Section 9.4.6 for full list of clinical laboratory safety tests/assessments.
Pregnancy Test (WOCBP only)	X	X		Urine or serum test. Result must be confirmed as negative prior to tracer administration on Day 1.
Review of Emergency Contact Instructions	X	X		Prior to discharge on Visits 1 and 2.

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Table 2-2: Imaging Procedural Outline for Part A (IM038010)

Procedure	Visit 1 Day 1[a]	Visit 2 (2 hrs to 6 days after Visit 1 tracer administration)[b]	Safety Follow-up 3 days (± 1 day) after most recent PET Scan[c]/Early Termination[d]	Notes
Non-serious AE and SAE Assessments	X	X	X	All SAEs must be collected from the time of signing the consent until 10 days after the last tracer administration or the final visit, whichever is later. All AEs (SAEs and non-serious AEs) associated with SARS-CoV-2 infection must be collected from the date of participant's written consent. See Section 9.2.1.
Concomitant Medication Use	X	X	X	
Imaging Assessments and Subsequent Procedures				
Arterial Line Placement		X		Prior to tracer administration.
Venous Line Placement for Venous Blood Sampling (During Visit 2 PET Scan)		X		Prior to tracer administration (on the arm opposite to the tracer administration). Only in up to 2 participants (added to Part A after initiation of Part B) undergoing simultaneous arterial and venous blood sampling.
Whole-body PET-CT Scan	X			Whole-body PET-CT scan is from apex to the upper-thigh level.
Cranial PET-CT Scan or PET-MRI Scan		X		PET-CT or PET-MRI is performed, depending on equipment availability. The cranial PET scan is performed after the whole-body PET-CT scan. If scans are performed on the same day, participants are allowed to have a light meal between the whole-body PET scan and the cranial PET scan.
Check Pressure Dressing, Hand and Finger Circulation		X		After arterial line placement, throughout the PET procedure, following removal of the arterial line, and before discharge

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Table 2-2: Imaging Procedural Outline for Part A (IM038010)

Procedure	Visit 1 Day 1[a]	Visit 2 (2 hrs to 6 days after Visit 1 tracer administration)[b]	Safety Follow-up 3 days (± 1 day) after most recent PET Scan[c]/Early Termination[d]	Notes
Radiotracer Administration				
Overnight and Post-dose Fasting	X	X		The night before tracer administration, participants will fast for at least 8.5 hrs before tracer administration and will remain fasted until at least 1.5 hrs after tracer administration. If 2 tracer administrations are performed on the same day, participants can have a light meal after the first tracer administration.
^{11}C-BMS-986196 Tracer Administration	X[a]	X[a]		Tracer is administered by a slow IV bolus prior to the whole-body PET scan and again prior to the cranial PET scan.

Abbreviations: AE, adverse event; ECG, electrocardiogram; hr, hour; IV, intravenous; min, minute; PE, physical examination; PET, positron emission tomography; PET-CT, positron emission tomography - computed tomography; PET-MRI, positron emission tomography - magnetic resonance imaging; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VS, vital signs; WOCBP, women of childbearing potential.

[a] Prior to initiation of Part B, all Part A participants undergo Visits 1 and 2. After initiation of Part B, up to 2 participants may be added to Part A, and will not undergo Visit 1, only Visit 2. For these participants only, Visit 2 will be regarded as Day 1.

[b] Visit 2 tracer administration must be done at least 2 hours after and at most 6 days after Visit 1 tracer administration. If Visit 2 is performed on Days 5, 6, or 7, the site staff must contact the participant remotely (ie, by phone) on Day 4 and record AEs and concomitant medications. If 2 scans are performed on the same day, hematology and clinical chemistry sample collection, VS measurement, ECG, and review of AEs and concomitant medications are the only safety assessments that must be assessed in duplicate, and the same arterial line may be used for both scans.

[c] If the interval between Visit 1 (PET Scan 1) and Visit 2 (PET Scan 2) is ≥ 4 days, 2 follow up remote contacts (ie, phone calls) must be performed. In this case, each follow up contact will be performed 3 days (± 1 day) after the most recent PET procedure.

[d] For participants who are prematurely discontinued from the study.

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Table 2-3: Imaging Procedural Outline for Part B (IM038010)

Procedure	Visit 1 Day 1	Visit 2 (2 hrs to 6 days after Visit 1 tracer administration)[a]	Safety Follow-up 3 days (± 1 day) after most recent PET Scan[b]/Early Termination[c]	[redacted]	Notes
Safety Assessments					
Weight Measurement	X				
Partial PE	X	X			On Visits 1 and 2, PE must be done within 24 hrs of tracer administration. Symptom-based PE only.
[redacted]					
12-Lead ECG	X	X			ECGs should be recorded after the participant has been supine for at least 5 min. On days with tracer administration, ECG should be conducted prior to tracer administration and after completion of the PET scan. See Section 9.4.5.
Vital Signs	X	X			VS will be obtained before tracer administration, after PET scan completion, and prior to discharge on Visits 1 and 2. See Section 9.4.3.
Allen's Test	X	X			Normal result (in the arm that will be used for arterial line placement) must be documented prior to arterial line placement.
Hematology, Chemistry, and Urinalysis	X	X			For Visits 1 and 2, specimens will be collected at least 1.5 hours after tracer administration. See Section 9.4.6 for full list of clinical laboratory safety tests/assessments.

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Table 2-3: Imaging Procedural Outline for Part B (IM038010)

Procedure	Visit 1 Day 1	Visit 2 (2 hrs to 6 days after Visit 1 tracer administration)[a]	Safety Follow-up 3 days (± 1 day) after most recent PET Scan[b]/Early Termination[c]	[redacted]	Notes
Pregnancy Test (WOCBP only)	X	X			Urine or serum test. Result must be confirmed as negative prior to tracer administration on Day 1.
Review of Emergency Contact Instructions	X	X			Prior to discharge on Visits 1 and 2.
Non-serious AE and SAE Assessments	X	X	X		All SAEs must be collected from the date of participant's written consent until 10 days after the last tracer administration or the final visit, whichever is later. All AEs (SAEs and non-serious AEs) associated with SARS-CoV-2 infection must be collected from the date of participant's written consent. See Section 9.2.1
Concomitant Medication Use	X	X	X		
Imaging Assessments and Subsequent Procedures					
Arterial Line Placement	X	X			Prior to tracer administration.
Venous Line Placement for Venous Blood Sampling	X				Prior to tracer administration (on the arm opposite to the tracer administration). Only in up to 6 participants if requested by Sponsor, and only during one cranial PET scan, preferably during Visit 1.

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Table 2-3: Imaging Procedural Outline for Part B (IM038010)

Procedure	Visit 1 Day 1	Visit 2 (2 hrs to 6 days after Visit 1 tracer administration)[a]	Safety Follow-up 3 days (± 1 day) after most recent PET Scan[b]/Early Termination[c]	[redacted]	Notes
Cranial PET-MRI Scan or PET-CT Scan	X[d]	X[b,d]			PET-MRI or PET-CT is performed, depending on equipment availability. Same scan type (ie, PET-MRI or PET-CT) should be performed for both Visits 1 and 2.
Check Pressure Dressing, Hand and Finger Circulation	X	X			After arterial line placement, throughout the PET procedure, following removal of the arterial line, and before discharge.
Radiotracer Administration					
^{11}C-BMS-986196 Tracer Administration	X	X[e]			Tracer is administered by a slow IV bolus prior to each PET scan.

Abbreviations: AE, adverse event; ECG, electrocardiogram; [redacted] hr, hour; IV, intravenous; min, minute; [redacted] PE, physical examination; PET, positron emission tomography; PET-CT, positron emission tomography computed tomography; PET-MRI, positron emission tomography magnetic resonance imaging; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VS, vital signs; WOCBP, women of childbearing potential.

[a] Visit 2 tracer administration must be done at least 2 hours after and at most 6 days after Visit 1 tracer administration. If Visit 2 is performed on Days 5, 6, or 7, the site staff must contact the participant remotely (ie, by phone) on Day 4 and record AEs and concomitant medications. Participants who had a [redacted] within 30 days prior to Day 1 must start Scan 2 on Day 1 or Day 2. If 2 scans are performed on the same day, VS measurement, ECG, and review of AEs and concomitant medications are the only safety assessments that must be assessed in duplicate, and the same arterial line may be used for both scans.

[b] If the interval between Visit 1 (PET Scan 1) and Visit 2 (PET Scan 2) is ≥ 4 days, 2 follow up remote contacts (ie, phone calls) must be performed. In this case, each follow up contact will be performed 3 days (± 1 day) after the most recent PET scan.

[c] For participants who are prematurely discontinued from the study.

[d] Dynamic PET image acquisition.

[e] A third administration is permissible if a PET scan has to be repeated (eg, due to failure of a prior scan).

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Table 2-4: Imaging Procedural Outline for Part C (IM038010)

Procedure	Visit 1 Day 1	Visit 2 approximately 24 hrs after the last dose of BMS-986196 (Days 2-9)	Visit 3 7 Days (±2) after Visit 2/ET	Visit 4 (28 - 31 days after Visit 3)	Notes
In-person Visit to Clinical Site	X	X	X		
Phone call/Telemedicine visit				X	In-person visit is optional. Email or text messaging is not sufficient.
Safety Assessments					
Weight Measurement			X		
Partial PE	X	X	X		
12-lead ECG	X	X	X		
Vital Signs	X	X	X		
Hematology, Clinical Chemistry, Urine analysis	X		X		Participants are required to fast for at least 10 hrs prior to specimen collection. Specimens will be collected prior to tracer administration on Visits 1 and 2. See Section 9.4.6 for full list of clinical laboratory safety tests/assessments.
C-SSRS	X	X	X		Since last visit version of C-SSRS.
Review Emergency Contact Information	X	X	X		
AE and SAE assessment	X	X	X	X	All AEs and SAEs must be collected from the time of signing the informed consent form, including those thought to be associated with protocol-specified procedures and until 28 days following discontinuation of dosing.
Concomitant Medication Use	X	X	X	X	
Imaging Assessments and Procedures					
Venous Line Placement for Blood Sampling	X	X			Prior to tracer administration (on the arm opposite to the tracer administration).

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Table 2-4: Imaging Procedural Outline for Part C (IM038010)

Procedure	Visit 1 Day 1	Visit 2 approximately 24 hrs after the last dose of BMS-986196 (Days 2-9)	Visit 3 7 Days (±2) after Visit 2/ET	Visit 4 (28 - 31 days after Visit 3)	Notes
Cranial PET/CT or PET/MRI	X	X			PET-CT or PET-MRI is performed, depending on equipment availability.
^{11}C-BMS-986196 Tracer Administration	X	X			Tracer is administered by a slow IV bolus prior to each PET scan.
[redacted] **PD Assessments** [redacted]					
PD Sample for [redacted]	X	X			At Visit 2, collected prior to radiotracer administration
Administration of Unlabeled BMS-986196					
Dispensing and Oral Administration of Unlabeled BMS-986196[a]	X				Unlabeled BMS-986196 is administered orally with food. Administration starts on Day 1 after completion of the PET procedure or on Day 2. BMS-986196 is preferably administered once; approximately 24 hrs after the (last) dose of BMS-986196, participants will undergo the second cranial PET scan. If the second PET scan cannot be performed in this time frame, it is permissible to administer a single dose of unlabeled BMS-986196 up to 7 days after the Day 1 PET (eg, in case of scheduling conflicts) or to dose unlabeled BMS-986196 QD for up to 7 days (eg, in case of synthesis failure of the PET tracer), if the Sponsor agrees. Administration must be documented and can occur on-site and/or at home according to site preference
Reconciliation of Unlabeled BMS-986196		X			See Section 7.6 for additional information on reconciliation

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Table 2-4: Imaging Procedural Outline for Part C (IM038010)

Procedure	Visit 1 Day 1	Visit 2 approximately 24 hrs after the last dose of BMS-986196 (Days 2-9)	Visit 3 7 Days (±2) after Visit 2/ET	Visit 4 (28 - 31 days after Visit 3)	Notes
					of study intervention, drug accountability, and review of dosing diary.

Abbreviations: AE, adverse event; [redacted] C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ET, end of treatment; hr, hour; PD, pharmacodynamic; PE, physical examination; PET-CT, positron emission tomography - computed tomography; PET-MRI, positron emission tomography - magnetic resonance imaging; [redacted] SAE, serious adverse event; QD, once daily.

[a] BMS-986196 will be supplied by BMS and dispensed by the site before the participant leaves on Day 1. Participants should return the BMS-986196 container and any unused tablets to the facility for drug reconciliation if they take the medication home.

In the event that multiple procedures are required at a single time point, the following is a list of procedures from highest to lowest priority to minimize the effect of procedures on vital signs and electrocardiogram (ECG) evaluations:

Safety (12-lead ECG)

Safety (vital signs measurements)

Safety (clinical labs)

Safety assessment in response to AEs are not impacted by this priority list.

If the scheduled time for a 12-lead ECG coincides with any blood collection (ie, clinical safety labs), the blood draw should be performed as scheduled, with the 12-lead ECG being performed prior to any blood collection (up to 15 minutes earlier). ECGs will also be collected prior to the vital sign measurements.

3 INTRODUCTION

This is the first study characterizing ^{11}C-BMS-986196 as a positron emission tomography (PET) tracer in humans.

^{11}C-BMS-986196 is a radiolabeled version of BMS-986196, a central nervous system (CNS)-penetrant Bruton's tyrosine kinase inhibitor (BTKi) which is being developed for the treatment of multiple sclerosis (MS). ^{11}C-BMS-986196 is intended to facilitate clinical development of unlabeled, therapeutically dosed BMS-986196 by enabling quantification of Bruton's tyrosine kinase (BTK) receptor occupancy in the CNS of patients with MS. Measuring BTK receptor occupancy in the CNS is relevant for dose selection of BTKi, which generally requires > 95% receptor occupancy for efficacy.[1,2,3] While BTK occupancy in white blood cells can be measured ex vivo, no tools exist for in vivo measurement of BTK occupancy in the human

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CNS, which is the tissue affected in MS. The current study is intended to characterize ^{11}C-BMS-986196 as a suitable PET ligand for detection of free BTK in the CNS.

In mice with experimental autoimmune encephalitis (EAE), a preclinical model of MS, BMS-986196 labelled inflammatory lesions (confirmed by ^{11}C-BMS-986196 PET and [^{3}H]BMS-986196 autoradiography) and demonstrated in vivo dose-dependent target engagement in mice pretreated with unlabeled BMS-986196 (see Investigator Brochure [IB] for details). In healthy non-human primates without inflammatory CNS lesions, ^{11}C-BMS-986196 elicits a transient, diffuse signal in the CNS that is believed to reflect diffusion of ^{11}C-BMS-986196 into the CNS without target engagement and is followed by rapid wash-out (see IB for details).

In this study, ^{11}C-BMS-986196 will be dosed at microdoses of up to 20 µg, which is below the general microdose criterion of 100 µg for small molecule PET ligands. At doses of up to 20 µg, ^{11}C-BMS-986196 is not expected to elicit meaningful biological or pharmacological effects. Concurrent with this study, Study IM038008 is testing the safety, tolerability, pharmacokinetics, and target engagement as pharmacodynamics of BMS-986196 in healthy participants. In Study IM038008, the starting dose of unlabeled, orally administered BMS-986196 is 1 mg, which is projected to not have biologically meaningful effects and result in area under the plasma concentration-time curve (AUC) exposure more than 1,000-fold below that at the no-observed-adverse-effect level (NOAEL) from the 1-month toxicology studies. The AUC exposure associated with single intravenous (IV) administration of 20 µg ^{11}C-BMS-986196 is projected to be approximately 7.5-fold below the exposure associated with an oral dose of 1 mg. Orally administered doses ≥ 10 mg are projected to result in peak BTK occupancy > 95% in blood, and therefore, are projected to approach therapeutic levels.

In Part C of this study, non-radioactively labeled (unlabeled) BMS-986196 will be administered at dose levels up to 60 mg once daily (QD) up to 7 days. Hence, in Part C, (unlabeled) BMS-986196 will be administered at therapeutic dose levels and is expected to result in near maximum BTK occupancy. In Study IM038008, the first-in-human study testing unlabeled BMS-986196 at therapeutically relevant doses, administration of BMS-986196 at doses up to 90 mg QD for 14 days was shown to be safe and tolerated.

3.1 Study Rationale

This is the first study testing ^{11}C-BMS-986196 as a PET ligand in humans. This study is supported by preclinical Good Laboratory Practices (GLP) toxicity and safety studies, including in rats and cynomolgus monkeys, in the context of an Investigational New Drug (IND) submission. There is no formal primary research hypothesis for this study to be statistically tested. The purpose of this study is to assess ^{11}C-BMS-986196, a novel PET tracer for BTK in healthy participants and in participants with MS to facilitate its use for:

- Assessment of CNS [redacted] in future clinical studies
- Dose selection of compounds that target the BTK receptor in the CNS, including dose selection for unlabeled BMS-986196
- Assessing the presence of BTK-expressing cells in participants with inflammatory CNS diseases, including MS

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Overall, the data from this study will contribute to general research and the development of a novel means to visualize CNS inflammation, and are expected to facilitate development of therapies for progressive MS.

3.2 Background

A detailed description of the chemistry, pharmacology, preclinical efficacy, and safety of BMS-986196 and its PET ligand ^{11}C-BMS-986196 are provided in the Investigator's Brochure (IB).[4]

3.2.1 ^{11}C-BMS-986196

^{11}C-BMS-986196 covalently binds, and inhibits BTK, a kinase expressed in B-cells, monocytes, macrophages, microglia, dendritic cells, natural killer cells, granulocytes, mast cells, basophils, eosinophils, osteoclasts, and platelets.[5,6,7,8] BTK plays a role in intracellular signaling cascades downstream of the B-cell receptor, activating immunoglobulin G (IgG) immune complex receptors (FCγRIIa and FCγRIIIa), the high affinity immunoglobulin E receptor (FcεRI), and the receptor activator of nuclear factor kappa-B (RANK).[9]

BTK is not expressed in neurons, astrocytes, or oligodendrocytes and is not known to have functions in a healthy CNS without inflammatory conditions. Based on the cellular expression profile of BTK, the known presence of B-cells, macrophages, and microglia in MS lesions, [10] and the short half-life of C-11, ^{11}C-BMS-986196 has the potential to be a PET tracer for the detection of (chronic) microglial inflammation, (acute) lesions with infiltrating macrophages, and B-cell infiltrates in the brain or meninges of patients with MS. Preclinical experiments in EAE mice support that ^{11}C-BMS-986196 has the potential to detect MS lesions (see Section 3.2.5 and IB for details).

BMS-986196 is blood-brain barrier penetrant in rats and cynomolgus monkeys and has high in-vitro selectivity over other kinases (for details see the IB).

3.2.2 Multiple Sclerosis

MS is a chronic inflammatory disease; its pathology is characterized by lesions with acute bulk invasion of peripheral white blood cells to plaques and by chronic compartmentalized inflammatory lesions containing microglia and macrophages that are typically at some distance to perivascular or meningeal lymphocyte infiltrates.[10] Within the continuum of relapsing and progressive MS, acute lesions are the predominant pathology in relapsing remitting MS, whereas chronic compartmentalized lesions are predominant in progressive MS. Approved treatments for MS, including anti-cluster of differentiation 20 (CD20) monoclonal antibodies, predominantly address the pathology associated with acute lesions. Importantly, none of the approved disease-modifying therapies for MS have the potential for exerting robust anti-inflammatory effects directly in the CNS or the meninges. Accordingly, the efficacy of approved disease-modifying therapies in MS has predominantly been demonstrated in relapsing forms of MS and is either absent or comparatively weaker in nonrelapsing progressive forms of MS.[11]

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Therefore, an unmet need exists for MS therapies that can exert robust anti-inflammatory effects in the CNS and have robust efficacy in nonrelapsing progressive forms of MS.

3.2.3 BMS-986196 Nonclinical Pharmacology

BMS-986196 administered as an oral (PO) dose to mice potently inactivated BTK in peripheral blood, spleens, and brains of mice with EAE. The inactivation was durable, with recovery of available active sites due to new protein synthesis measured at a rate of approximately 15% per day after the drug was cleared. BMS-986196 provided robust inhibition of disease in the FcγR-dependent, B cell independent collagen antibody-induced arthritis. In the EAE model, BMS-986196 provided efficacy against both clinically-evident disease and histological damage in the brain. BMS-986196 also blocked antigen-dependent germinal center B cell production, a model of the ectopic follicles and CNS draining cervical lymph nodes, critical in driving MS immunopathology.

3.2.4 BMS-986196 Nonclinical Pharmacokinetics

In vitro data indicated that hepatic uptake of BMS-986196 involved both passive diffusion and active transport, but organic anion transporting polypeptides (OATPs) and sodium taurocholate co-transporting polypeptide (NTCP) do not play a role in the uptake.

In vitro, BMS-986196 was extensively metabolized in liver microsomes and hepatocytes across species. Major metabolic pathways in human hepatocytes included oxidation of different moieties

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and hydrolysis of the vinyl amide moiety. Glutathione (GSH)-adduct formation was low in human and monkey hepatocytes, but substantially higher in rodent and dog hepatocytes. No unique metabolite was observed in human in vitro systems. In plasma samples of mice and rats administered with BMS-986196, the parent compound was the predominant drug-related component. Consistent with the results from in vitro data, the metabolic profiles of BMS-986196 in mouse and rat plasma samples revealed the presence of several low level oxidative metabolites, downstream products of GSH-conjugates, and a hydrolysis product. Renal clearance of BMS-986196 was minimal in animals (< 0.1% of the overall clearance).

In vitro, there were few cysteine adducts detected in microsomal incubations fortified with cysteine, suggesting low intrinsic chemical reactivity of BMS-986196 to thiol. There was minimal to no covalent binding to off-target cysteinyl residues in BTK, human hemoglobin, or human serum albumin. Based on the in vitro protein covalent binding in hepatocytes and serum, the estimated daily covalent binding burden (DCBB) of BMS-986196 in humans is 0.95 mg/day at the projected efficacious dose of 66 mg once daily (QD), which is much lower than the literature suggested- upper limit of DCBB (10 mg/day)[12] for clinically safe drugs that are designed as covalent enzyme inhibitors.

[redacted]

3.2.5 Preclinical BMS-986196 PET Tracer Studies

[^{3}H]BMS-986196 distribution in EAE mouse brain was examined by autoradiography at 1 hour and 24 hours after a single IV administration of 0.15 mg/kg or 1.5 mg/kg. [^{3}H]BMS-986196 binding was observed to align with the presence of disease in the sample, with over 3-fold increased radiotracer retention in lesion areas of EAE mice (1.43 nCi/mg) compared to brains of naïve animals (0.41 nCi/mg). In PET studies, ^{11}C-BMS-986196 labelled suspected inflammatory lesions and demonstrated in vivo dose-dependent target engagement in EAE mice pretreated with oral doses of unlabeled BMS-986196 at 0.5 mg/kg or 5 mg/kg. In healthy non-human primates without inflammatory CNS lesions, ^{11}C-BMS-986196 elicits a transient, diffuse signal in the CNS that is believed to reflect diffusion of ^{11}C-BMS-986196 into the CNS without target engagement and is followed by rapid wash-out (see IB for details). Radiation dosimetry of ^{11}C-BMS-986196 was performed in healthy cynomolgus monkeys (2 male and 2 female) to estimate the absorbed radiation dose to human participants. Whole-body BMS-986196 distribution was assessed by serial imaging up to approximately 2 hours following radiotracer administration, covering

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approximately 6 radioactive half-lives of the C-11 isotope. Individual organs with visual tracer signal (eg, brain, heart, lung, liver, spleen, kidney, muscle, bladder, etc.) were identified from the resulting scans. These identified organs were used as source organs for further dosimetry analysis. For additional details, see the IB.

3.2.6 BMS-986196 Nonclinical Toxicology

A battery of nonclinical studies, including single- and/or repeat-dose oral toxicity studies (≤ 1-month) in rats, monkeys, and dogs; in vitro and in vivo genetic toxicology studies; in vitro and in vivo safety pharmacology assessments; and in vitro phototoxicity study have been completed to assess the toxicologic profile of BMS-986196. Rats and monkeys were selected as the species for toxicity evaluation because BMS-986196 is pharmacologically active in both species. Additionally, monkey was selected as the non-rodent species based on the ability to achieve acceptable exposure and tolerability between rats and monkeys. Since there were no sex differences in BMS-986196 exposures in either rats or monkeys, all exposures below are presented as sex-combined mean values. Safety multiples below are calculated relative to either the projected maximum observed plasma concentrations (Cmax) or exposures (AUC) of BMS-986196 at the proposed starting (1 mg) and ending (60 mg) doses in the single ascending dose (SAD)/multiple ascending dose (MAD) clinical study.

BMS-986196 was not phototoxic, mutagenic, or clastogenic in vitro. While it was genotoxic via an aneugenic (indirect) mechanism in vitro and in vivo as part of the 2-week exploratory toxicology study in rats at 300 mg/kg (Day 1 female mean area under the plasma concentration-time curve from time zero to 24 hours postdose [AUC(0-24h)] ≤ 17.177 µg•h/mL), it was not genotoxic when administered to female rats at daily doses up to 200 mg/kg/day (Day 1 mean AUC[0-24h] ≤ 25.2 µg•h/mL; AUC multiple of > 40,000-fold over the projected associated with a 20 µg IV dose proposed in this study) for 4 days in the definitive in vivo micronucleus study with comet evaluation. Based on the overall weight of evidence, BMS-986196 is considered non-genotoxic.

In vitro screening against a panel of receptors, ion channels, transporters, and enzymes demonstrated that BMS-986196 did not significantly alter ligand binding or functional activity and was considered to have a low potential to produce effects related to secondary pharmacology. BMS-986196 did demonstrate weak to moderate inhibitory effects on cardiac human ether-a-go-go-related gene (hERG)/rapid delayed rectifier potassium channel current (IKr) potassium, cardiac SCN5A sodium channel, and L-type calcium channel currents. The cardiac hERG/IKr potassium channel IC50 was 9.1 µM (3.56 µg/mL). BMS-986196 at 1 and 4 Hz stimulation frequency inhibited cardiac sodium currents by 23.7 ± 2.1% and 29.4 ± 2.4%, respectively, at 10 µM (3.91 µg/mL). BMS-986196 inhibited cardiac calcium currents by 46.3 ± 0.7% at 10 µM (3.91 µg/mL). There were no BMS-986196-related adverse cardiovascular changes in exploratory or definitive single-dose monkey telemetry studies at doses up to 100 mg/kg (sex-combined mean plasma concentrations of ≤ 569 ng/mL 6 hours after dose; Cmax multiple of > 1,500-fold over the projected associated with a 20 µg IV dose proposed in this study). In addition, there were no BMS-986196-related effects on the CNS in the neurologic safety pharmacology study in male Sprague-Dawley rats at doses up to 200 mg/kg (mean AUC[0-24h]

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≤ 23.9 µg•h/mL; AUC multiple of > 40,000-fold over the projected associated with a 20 µg IV dose proposed in this study). Overall, BMS-986196 was considered to have low potential for cardiovascular, neurologic, and other off-target pharmacology, at clinically relevant doses and exposures.

In the pivotal, repeat-dose 1-month toxicity study in rats with 2-week recovery, daily oral doses of 20, 75, or 200 mg/kg/day of BMS-986196 were clinically well tolerated at all doses. Pharmacologic activity of BMS-986196 was noted at all doses, including BTK inactivation and suppression of T cell-dependent antibody response to a keyhole limpet hemocyanin (KLH) peptide antigen. The primary target organ of toxicity was the pancreas at all doses (adverse findings of islet/peri-islet congestion/hemorrhage, pigment, inflammation/fibrosis; interstitial hemorrhage, pigment, and inflammation; and peri-islet/lobular acinar cell atrophy). By the end of the 2-week postdose recovery period, partial recovery of the pancreatic findings was observed. However, based on the literature evidence, internal data with BMS-986196, and other BTK inhibitors, the pancreatic findings are considered rat-specific and unlikely to be relevant to humans.[13] Therefore, the NOAEL is considered to be 200 mg/kg/day (mean sex-combined AUC[0-24h] 46.1 µg•h/mL; AUC multiple of > 70,000-fold over the projected associated with a 20 µg IV dose proposed in this study) when excluding the pancreatic findings.

In the pivotal, repeat-dose 1-month toxicity study in cynomolgus monkeys with 2-week recovery, daily oral doses of 10, 30, and 60 mg/kg/day of BMS-986196 were clinically well tolerated at all doses. Decreases in B cells, suppression of IgG antibody response, and BTK inactivation at all doses were considered related to the pharmacologic activity of BMS-986196. Based on the minimal clinical effects and the absence of adverse findings at any dose tested, the NOAEL was considered to be 60 mg/kg/day (mean sex-combined AUC[0-24h] 6.26 µg•h/mL; AUC multiple of > 10,000-fold over the projected associated with a 20 µg IV dose proposed in this study).

The totality of the nonclinical toxicity assessments demonstrate that BMS-986196 has a favorable nonclinical safety profile with NOAELs in rodents (excluding pancreatic findings) and nonrodents providing acceptable exposure margins relative to the planned clinical doses. Exposure multiples at the highest dose tested in the pivotal rat and monkey studies are > 10,000-fold over the projected associated with a 20 µg IV dose proposed in this study. Additional details for the toxicology profile and the full range of exposure margins are provided in Section 4.3 and Section 7.2 of the IB.[4]

Overall, the nonclinical studies established a dose-related pharmacologic, PK, and toxicologic profile for BMS-986196 and its PET ligand that support its early clinical development.

3.2.7 BMS-986196 Clinical Experience

BMS-986196 was evaluated in the first-in-human clinical study IM038008.

IM038008 is a randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study evaluating the safety, tolerability, PK, and target engagement as pharmacodynamics of BMS-986196 in healthy participants. In addition, it includes an open-label assessment of both food and formulation effects on the relative bioavailability of BMS-986196.

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In the SAD, BMS-986196 was administered as single dose ranging from 1 mg to 90 mg. In the MAD, BMS-986196 was administered at dose levels ranging from 20 mg QD to 90 mg QD for 14 days. To evaluate food and formulation effects, 25 mg BMS-986196 was administered in a 4-way crossover design as solution or suspension, and each formulation was administered in the fasted state and after a meal.

BMS-986196 was safe and tolerated at all doses. No SAEs or severe AEs were reported, and no participants discontinued study drug due to AEs.

Following single and multiple oral doses of solution formulation in the fasted state, BMS-986196 was absorbed with a median time of maximum observed concentration (Tmax) of ~1 hour. The terminal elimination half-life (T-HALF) ranged from approximately 1 to 5 hours. Cmax and AUC of BMS-986196 increased in a slightly greater than dose-proportional manner over a dose range of 1 mg to 90 mg.

After 14 doses of BMS-986196 60 mg QD, the observed geometric mean Cmax and AUC(TAU) were approximately 81.4 ng/mL and 227 ng•hr/mL, respectively. At the 90 mg QD dose (Day 14), the observed geometric mean Cmax and AUC(TAU) were approximately 178 ng/mL and 431 ng•hr/mL, respectively. Little to no accumulation was observed after repeat dosing. Apparent mean total body clearance (CLT/F) was approximately 265 L/hr; mean volume of distribution at terminal phase (Vz/F) was approximately 1600 L, and T-HALF ranged from approximately 3 to 5 hours.

When BMS-986196 25 mg was administered as suspension formulation in the fasted state, the geometric mean Cmax and AUC(0-T) were reduced by approximately 84% and 22%, respectively, relative to solution formulation administered in the fasted state.

In comparison to solution in fasted state, the suspension fed Cmax decreased ~64% (43.7 ng/mL vs. 15.8 ng/mL) while AUC(INF) increased 25% (81.5 ng*hr/mL vs. 102 ng*hr/mL).

In Part C of this study, BMS-986196 will be administered in tablet form with food, and the [redacted] profile is expected to be between the solution and suspension formulations.

At doses used in this study (15 mg, 30 mg, and 60 mg), near maximal [redacted] is expected over the treatment period, and [redacted] will be approximately 50% at 7 days after the last dose.

3.2.8 ^{11}C-BMS-986196 Clinical Experience

Clinical experience with ^{11}C-BMS-986196 is based on this current ongoing study, IM038010. As of 21-Mar-2023, the time of Protocol Amendment 05 preparation, no serious or severe AEs were reported in the ongoing study and no participants discontinued due to an AE. Preliminary data indicated that ^{11}C-BMS-986196 binding in the human brain was fairly homogeneous, with no evidence of notable differences between healthy participants and participants with MS. Based on preliminary data, modeling and quantification of [redacted] when using venous blood appears feasible.

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3.3 Benefit/Risk Assessment

BMS-986196 is currently under evaluation in a first-in-human study; limited, if any, human experience is available to date. The ^{11}C-BMS-986196 PET ligand has not been administered in humans prior to this study; therefore, the overall safety profile for ^{11}C-BMS-986196 is based on data from a full battery of the nonclinical toxicology, pharmacology, and PK BMS-986196 studies and nonclinical ^{11}C-BMS-986196 dosimetry.

Risks Associated with Radiation and PET Procedure:

The planned radioactivity administered with a single administration (ie, IV infusion) of ^{11}C-BMS-986196 is approximately 370 MBq (10 mCi), and is projected to result in a radiation effective dose maximum of 1.37 mSv for an average human participant, estimated from nonhuman primate radiation dosimetry studies. The estimated dose from a low-dose apex to upper -thigh (in this document referred to as whole-body scan) computed tomography (CT; for co-registration with PET and attenuation correction) is approximately 2.3 mSv (0.23 rem). Thus, in Part A, total radiation exposure from one ^{11}C-BMS-986196 PET scan and a single whole-body attenuation CT scan is expected to be approximately 3.67 mSv (0.367 rem).

In Part A, the cranial PET is performed either as positron emission tomography - computed tomography (PET-CT) or positron emission tomography - magnetic resonance imaging (PET-MRI), depending on availability of equipment. For each cranial PET scan, up to 2 CT scans (1 predose and 1 postdose) are allowed to account for potential movement during the scan. The tracer administration for cranial PET in Part A adds 1.37 mSv effective dose from the tracer and approximately 0.6 mSv if 2 cranial CT scans are performed. Hence, the maximal effective dose in Part A is approximately 5.64 mSv (0.564 rem). If the cranial PET is performed via PET-MRI, the total effective dose in Part A is approximately 5.04 mSv (0.504 rem). In Part B and Part C, either PET-CT scans or PET-MRI scans of the head will be performed, depending on availability of equipment. The estimated dose from a low-dose attenuation CT scan of the head is approximately 0.3 mSv. For each cranial PET scan, up to 6 total CT scans (2 required CT scans [1 predose and 1 postdose] + additional if a repeat scan is necessary at either timepoint) are allowed to account for potential movement during the scan. The total effective dose from 2 administrations of ^{11}C-BMS-986196 with 2 CT scans of the head is expected to be approximately 3.34 mSv (0.334 rem) for participants undergoing PET-CT and approximately 2.74 mSv (0.274 rem) for participants undergoing PET-MRI. However, because participants with MS, more so than healthy participants, may be prone to movement artifacts (eg, due to spasticity) or scan interruptions due to urinary bladder symptoms, in Part B, up to 3 PET tracer administrations and up to 6 cranial CT scans (1 before and 1 after each PET scan) are permissible, for a total cumulative dose of approximately 5.91 mSv (0.591 rem). The same rules also apply to Part C participants for repeat scans.

The Radiation Safety Committees (RSC) at each site will review the use of radiation in this research study, and no participants will be enrolled until RSC approval is obtained. This research study involves exposure to radiation from ^{11}C-BMS-986196 PET-CT scanning. This radiation exposure is not necessary for medical care and is for research purposes only.

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In Parts A, B, and C, the expected radiation effective dose does not exceed 6 mSv (0.6 rem). This is below the relevant 10 mSv (1 rem) limit in the UK, based on the standard established by the International Commission on Radiological Protection (ICRP) in Publication 62 of the annals of the ICRP 22 (3) in 1992. The effective dose is also below the United States (US)-applicable annual effective dose limit of 5 rem (50 mSv) below which radiation exposure can be considered generally safe according to the Code of Federal Regulations (CFR), Title 21, Part 361.1(b)(3)(i). At such low radiation exposures, scientists disagree about the amount of health risk, and there may be very little risk, if any.

All PET scans will be done in the presence of medical supervision and nursing staff in an institution specifically designed to support imaging studies. In the event of serious medical complications, the PET scan facilities have immediate access to or consultation with specialized medical units. Preparation of radiopharmaceuticals and execution of PET scans will be performed by radiochemists, physicians, and technologists at the clinical sites. These professionals are qualified by training and experience in the safe use and handling of radionuclides. Where required, participants will be asked about their previous radiation exposure, and those who have had research exposure within the past year will be excluded if their cumulative annual exposure (including the present study) exceeds applicable limits.

Risk associated with ^{11}C-BMS-986196-derived BTK inhibition

Pharmacologically, ^{11}C-BMS-986196 belongs to the class of BTK inhibitors. In this study, the IV administered dose of ^{11}C-BMS-986196 is up to 20 µg, which is projected to cause approximately up to 2.7% [redacted] in blood with single IV administration and 5.4% with repeat administration during a 24-hour interval and up to approximately 8.1% [redacted] with 3 administrations. For therapeutic efficacy, BTKi generally must be chronically dosed to [redacted] of approximately 95%.[1] Female carriers of BTK null mutations are asymptomatic. A single oral dose of 10 mg BMS-986196 is projected to cause peak [redacted] of 95% in blood, ie, approach therapeutic efficacy. The AUC associated with a single dose IV dose of 20 µg is projected to be approximately 75-fold lower than the AUC associated with a single, orally administered dose of 10 mg. The pharmacological half-life of ^{11}C-BMS-986196 in humans is projected to be approximately 6 hours. Therefore, at the doses and frequency administered in this study, ^{11}C-BMS-986196 is not considered to have pharmacologically or biologically relevant activity.

Risk associated with unlabeled BMS-986196-derived BTK inhibition

In Part C, unlabeled BMS-986196 is administered orally at doses up to 60 mg for up to 7 days in healthy participants. The dose levels tested in Part C are considered therapeutically relevant. In preclinical rat studies, BMS-986196 causes pancreatic injury in rats. However, based on the literature evidence, internal data with BMS-986196, and other BTK inhibitors, the pancreatic findings are considered rat-specific and unlikely to be relevant to humans.[13] Other BTKi have been approved for the treatment of multiple myeloma and other hematological malignancies. At the approved doses, these BTKi typically result in chronic [redacted] > 95% (eg, acalabrutinib US prescribing information[14]). Approved BTKi are associated with increased risk for infections,

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bleeding, arrhythmias, cytopenia, tumor lysis syndrome, secondary malignancies, and embryofetal toxicity (eg, acalabrutinib[14] and ibrutinib[15] US prescribing information). Additional risks associated with therapeutically relevant doses of BMS-986196 are listed in Table 3.3.1-1.

Risks Associated with Use of an Arterial Catheter (Part A and Part B): Participants will have a radial arterial catheter inserted on the day(s) of PET scan to facilitate arterial blood draws (150 mL blood volume) during the cranial PET scanning sessions. Risks associated with placing a radial arterial catheter include mild-to-moderate pain, bruising at the puncture site, bleeding, hematoma, inflammation, infection, arterial occlusion, ischemic damage to the hand, and development of a pseudoaneurysm. Severe complications may require additional treatment. Major complications occur in less than 1% of procedures and permanent ischemic damage or pseudoaneurysm each occur in 0.09% of procedures, according to a meta-review.[16] Risk minimization measures in this protocol include:

1) Laboratory testing for blood coagulation at Screening prior to arterial line placement. Results must be within normal limits.
2) Normal results of the Allen's test must be documented at Screening and on PET scanning days prior to arterial line placement
3) The procedure will be performed by experienced staff
4) Applying skin disinfectant prior to skin puncture
5) Manual compression of the puncture site for ≥ 15 minutes after removal of the arterial catheter
6) Application of a pressure dressing (eg, Coban™)
7) Examination of hand and finger blood supply after arterial cannulation, throughout the PET procedure, following catheter removal, and before discharge
8) Providing participants with a 24-hour emergency physician telephone number to call if they encounter pain, discoloration, numbness, tingling, coolness, hematoma, inflammation, or any other unusual symptoms in the wrist or hand, or fever, chills, or drainage from the vascular puncture sites
9) Excluding fish oil, aspirin, platelet aggregation inhibitors (including nonsteroidal anti-inflammatory drugs with such activity) and anticoagulants for at least 10 days prior to arterial line insertion and at least 7 days following arterial line removal
10) Excluding participants who have donated blood within 4 weeks prior to radial artery puncture

Risk Associated with MRI

In Part A and Part C, participants may undergo cranial PET-MRI, depending on availability of equipment. In Part B, participants will undergo a cranial MRI scan during the screening period, and participants may undergo MRI scans as part of the PET-MRI scans. Participants must have completed all other Screening assessments first and remain eligible for the study before undergoing a Screening MRI scan. MRI scans are generally considered safe procedures and severe complications are very rare. Risks include heat sensations, anxiety in claustrophobic individuals, hearing damage if adequate ear protection is not worn, heating or moving of magnetic devices/particles in the body, magnetic objects in the scanner becoming projectiles, electric

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devices being damaged in/near the scanner, and allergic reactions to gadolinium-based contrast agents. While gadolinium-based contrast agents are retained in the body long term, no AEs have been associated with retention of gadolinium-based contrast agents, to date. Risk mitigation measures include:

1) Screening for and exclusion of participants with contra-indications to MRI, including, but not limited to individuals with severe claustrophobia, metal implants, pacemakers, electronic devices, or any other implants deemed unsafe
2) Exclusion of individuals with known hypersensitivity to gadolinium-based contrast agents
3) Exclusion of individuals with an estimated creatinine clearance of < 30 mL/min at Screening based on the Cockgroft-Gault formula
4) Removal of magnetic and electric devices prior to entering the scanner
5) Wearing of adequate ear protection during the procedure
6) Sites should use gadolinium-based contrast agents resulting in lowest retention in the body (gadoterate meglumine, gadobutrol, gadoteridol)

Should incidental findings be observed, the investigator will discuss them with the participant and determine if follow up is warranted.

Risk associated with severe acute respiratory syndrome coronavirus 2 infection

As long as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues, interactions with site staff as required per the protocol potentially increase the risk for SARS-CoV-2 infection relative to more socially distanced behavior. To reduce the risk of SARS-CoV-2 infection, general risk mitigation against coronavirus disease 2019 (COVID-19) will be implemented in accordance with the site monitoring and prevention control procedures, and relevant governmental and Institutional Review Board (IRB)-associated requirements. Such measures aim to minimize the prevalence and transmission of SARS-CoV-2 amongst site staff and study participants, and may include distancing, sanitization, testing, and the use of personal protective equipment. The risk mitigation measures are part of the site's generic informed consent form (ICF), when and where applicable, will be amended based on emerging guidance. The ICF and any other documentation regarding these general measures are independent of this protocol and will be entered into this study's trial master file (TMF) if used for participants in this study.

In Parts A and B, serum samples will be collected for [redacted]. These [redacted] titers will not be automatically determined in participants at Screening and the results will not be used to determine study eligibility, but information may be helpful for potential evaluation of [redacted] if warranted, eg, if participants develop symptoms compatible with a diagnosis of [redacted]. Participants with known active [redacted] are excluded from the study.

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3.3.1 Risk Assessment

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Nonclinical Risk BMS-986196-induced pancreatic toxicity	Pancreatic toxicity of BTK inhibitors is considered rat-specific, (IB Section 7.1.1 and Erickson, et al, 2017[13]).	Dose and frequency of administration in Parts A and B is not considered to result in pharmacologically or biologically relevant activity. Testing amylase, lipase, glucose in laboratory panel. Excluding participants with history of pancreatitis (Parts A, B, and C).
Nonclinical Risk BMS-986196-induced immune suppression	No evidence of infection in non-clinical studies, but BTKi MoA is consistent with immune suppression. (IB Section 7.1.2).	Dose and frequency of administration in Parts A and B is not considered to result in immune suppression or to have pharmacologically or biologically relevant activity. Exclusion of participants with recent or recurrent infections (Parts A, B, andC).
Nonclinical Risk ^{11}C-BMS-986196-induced liver injury	In GLP 1-month toxicology study, no liver injury in monkeys and rats. Combined preclinical in vivo and in vitro assessment suggest low risk for liver injury (IB Section 7.1.3).	Dose and frequency of administration in this study is not considered to result in pharmacologically or biologically relevant activity in Part A and B. Exclusion of participants with active hepatitis, ALT or AST > 1.5-fold ULN, total bilirubin > 2-fold ULN (unless in the context of Gilbert Syndrome) (Parts A, B, and C).
Risk associated with BMS-986196 CNS penetrance/suicidal ideation and behavior (Part C)	IB Section 7.1.1.4	Exclusion of participants who answer "yes" to item 4 or 5 or who answer “yes”to any suicidal behavior item of the C-SSRS (excluding non-suicidal self-injurious behavior) at screening or Day -1. Suicidality will be assessed by the C-SSRS during the study in Part C. Physical examination, including neurological examination, will be performed at screening and during the study.
Nonclinical Risk associated with BMS-986196 for developmental toxicity (Part C)	IB Section 7.1.1.2	Exclusion of WOCBP from Part C, contraception requirements for male participants.

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Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Clinical risks associated with therapeutic doses of approved BTKi, including infection, bleeding, arrhythmia, cytopenia, tumor lysis syndrome, secondary malignancy, embryofetal toxicity	Acalabrutinib and Ibrutinib US prescribing information	At the dose and frequency of administration used in the study population, the pharmacological risks associated with BMS-986196 and BTK inhibition are not considered relevant.
^{11}C-BMS-986196-associated radiation exposure	CFR, Title 21, Part 361.1(b)(3)(i) Publication 62 of the annals of the ICRP 22 (3), 1992	Risk mitigation by limiting estimated effective dose to < 6 mSv (0.6 rem), below the relevant 10 mSv (1 rem) limit in the UK, based on ICRP standard and below the US-applicable annual effective dose limit of 5 rem (50 mSv), below which radiation exposure can be considered generally safe according to the CFR.
Study Procedures		
Arterial line placement	Major complications associated with arterial line placement occur in less than 1% of procedures; permanent ischemic damage and pseudoaneurysm occur in 0.09% of procedures[16]	Allen's test performed before arterial line placement. Blood coagulation tested at Screening. Arterial line placement performed by experienced staff. Examination of hand/finger circulation after arterial line placement and before discharge. Examination of pressure dressing prior to discharge. Provision of 24 hr emergency phone number. Exclusion of fish oil, aspirin, platelet aggregation inhibitors (including nonsteroidal anti-inflammatory drugs with such activity) and anticoagulants for at least 10 days prior to arterial line insertion and at least 7 days following arterial line removal. (Parts A and B)
MRI and administration of gadolinium-based contrast agent	Body heat sensation, noise, claustrophobia. Magnetic particles inside the MRI may become projectiles. Electric devices inside the MRI may be damaged. Magnetic implants or particles inside the body may move and/or generate heat. Allergic reactions to gadolinium-based contrast agents.[17]	Exclusion of individuals with estimated creatinine clearance < 30 mL/min. Providing adequate ear protection, excluding participants with contraindications to MRI (including non-MRI compatible metal implants/particles, pacemakers, cochlear implants, ventricular shunts, large tattoos in the area affected by the MRI, severe claustrophobia), removing magnetic

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Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		objects prior to entering the MRI scanner, excluding participants with known allergy to gadolinium-based contrast agent.
Other (if applicable)		
SARS-CoV-2 infection risk	During SARS-CoV-2 pandemic, study visits and procedures may increase the risk for infection relative to more socially distanced behavior.	Site-mandated measures for minimization of SARS-CoV-2 transmission. Exclusion of participants with known active SARS-CoV-2 infection.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CFR, Code of Federal Regulations; CNS, central nervous system; C-SSRS, Columbia-Suicide Severity Rating Scale; GLP, Good Laboratory Practices; hr, hour; IB, Investigator's Brochure; ICRP, International Commission on Radiological Protection; MoA, mechanism of action; MRI, magnet resonance imaging; mSv, millisievert; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UK, United Kingdom; ULN, upper limit of normal; US, United States.

3.3.2 Benefit Assessment

Administration of ^{11}C-BMS-986196 does not confer any therapeutic benefit to study participants. Participating in this study contributes to research and to the development of a compound that can visualize inflammation in the CNS in a novel way and that can help develop therapies for progressive MS. Participants will undergo medical evaluations including a physical examination, ECGs, and clinical laboratory safety tests, and a cranial PET scan. [redacted]

3.3.3 Overall Benefit/Risk Conclusion

The protocol was designed to mitigate the risk associated with the study-defined assessments and procedures. The Sponsor will evaluate the risk/benefit profile of the study on an ongoing basis. This evaluation will be based on all available data – with particular attention to: AEs or other safety trends in this study of ^{11}C-BMS-986196 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury.

If such evaluation suggests that the risk/benefit profile of the study has become unfavorable to participants, the Sponsor will pause enrollment and/or tracer administration until further evaluation of data, and interaction with the appropriate Health Authority(ies) can take place on potential actions. Such actions may include (but are not limited to) study continuation, substantial amendment, or termination of the study.

3.3.4 COVID-19-related Risk Mitigation Measures

Serum samples will be collected for [redacted] testing in Parts A and B (see Section 9.8 for biomarker collections). These antibody titers will not be automatically determined in

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participants at Screening, but information may be helpful for potential evaluation of [redacted] if warranted.

General risk mitigation against COVID-19 will be implemented in accordance with the clinical research unit (CRU's) monitoring and prevention control procedures and relevant governmental and Institutional Review Board (IRB)-associated requirements. Such measures aim to minimize the prevalence and transmission of SARS-CoV-2 amongst site staff and participants and may include distancing, sanitization, testing, and the use of personal protective equipment. The risk mitigation measures are part of the CRU's generic informed consent and, when and where applicable, will be amended based on emerging guidance. The ICF and any other documentation regarding these general measures are independent of this protocol and will be entered into this study's trial master file (TMF) if used for participants in this study.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	**Primary**
• To assess safety, tolerability, kinetics, and CNS signal repeatability of the novel tracer ^{11}C-BMS-986196 in healthy participants and in participants with MS	• Incidence, severity, seriousness, and type of AEs; clinically significant abnormalities in ECG, VS, laboratory values, physical examination, and C-SSRS
• To assess the safety of BMS-986196	• Radiation dosimetry calculated from PET-CT images in healthy participants
	• Image acquisition window after administration of ^{11}C-BMS-986196
	• Test-retest repeatability based on quantitative analysis of CNS PET-MRI images (eg, SUV and/or V_T) in participants with MS
• To quantify the proportion of free BTK in the brain after administration of unlabeled BMS-986196	• % Free brain BTK relative to baseline
Secondary	**Secondary**
To assess ^{11}C-BMS-986196 signal characterization	Calculated SUV and V_T in the brain
[redacted]	

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Table 4-1: Objectives and Endpoints

Objectives	Endpoints
[redacted]	

Abbreviations: AE, adverse event; BTK, Bruton's tyrosine kinase; CNS, central nervous system; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; [redacted] MS, multiple sclerosis; PET, positron emission tomography; PET-CT, positron emission tomography - computed tomography; PET-MRI, positron emission tomography - magnetic resonance imaging; [redacted] SUV, standardized uptake value; VS, vital signs; V_T, volume of distribution.

5 STUDY DESIGN

5.1 Overall Design

This is a Phase 1, open-label study in healthy participants and participants with MS to evaluate a novel, positron-emitting ligand ^{11}C-BMS-986196, for measurement of free BTK. The study will include up to 28 evaluable participants (Part A: up to 8 healthy participants; Part B: up to 8 participants with MS; Part C: up to 12 healthy participants).

All participants will undergo PET scanning with ^{11}C-BMS-986196. An initial dose of ^{11}C-BMS-986196 will be administered at doses up to 20 µg with the radioactivity of the dose at approximately 370 MBq (10 mCi). In Part B and Part C, the radioactive dose and participant preparation may be revised based on results of radiation dosimetry obtained in Part A but administered mass will not exceed 20 µg.

The study consists of 3 periods: screening, treatment, and safety follow-up. The estimated duration from screening through safety follow-up phone call (or in-person study site visit) is up to approximately 6 weeks for Part A, approximately 6 weeks for Part B, and approximately 10 weeks for Part C.

Screening Period

Before any study procedures or assessments are performed, study participants must sign and date the informed consent form, after which participants undergo screening assessments within 30 days prior to administration of ^{11}C-BMS-986196. Participants in Part B must undergo a screening cranial MRI scan. Eligible participants will be enrolled to the treatment period.

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Treatment Period

Part A (Whole-Body Radiation Dosimetry and Cranial PET Imaging): Up to 6 evaluable healthy adult participants (at least 2 male and 2 female participants are planned) will complete whole-body PET-CT imaging after a bolus IV administration of ^{11}C-BMS-986196 under fasting conditions, to confirm tracer safety, assess image acquisition window, determine radiation dosimetry of the administered radiotracer, and assess optimal imaging time. The PET scan will last approximately 2 hours. At least 2 hours and at most 6 days after the first tracer administration, participants will receive a second tracer administration and undergo cranial PET imaging using either PET-CT or PET-MRI, depending on the availability of equipment. If the interval between the first and second PET scan is 4 days or more, the study site staff must contact the participant remotely (eg, by phone) on Day 4 (ie, 3 days after the first PET scan) and record adverse events (AEs) and any concomitant medications. Following an observation period of approximately 1 hour after completion of all PET scanning procedures, participants will be discharged from the PET center and enter the safety follow-up period. Up to 6 healthy participants will complete Part A before initiation of Part B.

If emerging data from Part B indicate that venous blood sampling is likely to be required in future studies using ^{11}C-BMS-986196 without arterial blood sampling (eg, because a [pseudo]-reference region cannot be reliably established), 2 additional participants can be enrolled in Part A at the discretion of the Sponsor. These additional 2 participants will only undergo cranial PET imaging using either PET-CT or PET-MRI, depending on the availability of equipment (ie, not whole body PET-CT).

Part B (Characterization of ^{11}C-BMS-986196 binding in the human brain): Up to 8 participants with MS will complete 2 evaluable cranial PET-CT or PET-MRI scans (depending on equipment availability) after a bolus IV administration of ^{11}C-BMS-986196, separated by at least 2 hours and at most 6 days to determine the optimal quantification parameters, including within-participant variability under test and retest conditions. Following an observation period of approximately 1 hour after completion of PET scanning procedures, participants will be discharged from the PET center and enter the safety follow-up period. If the interval between the first and second PET scan is 4 days or more, the study site staff must contact the participant remotely (eg, by phone) on Day 4 (ie, 3 days after the first PET scan) and record AEs and any concomitant medications. Participants who had a MS relapse within 30 days prior to Day 1 must start Scan 2 on Day 1 or Day 2. Up to 8 participants with MS will complete Part B.

Part C (Quantification of free BTK availability in the human brain): Up to 12 evaluable healthy adult participants will complete 2 evaluable cranial PET-CT or PET-MRI scans (depending on equipment availability). The first cranial PET scan will occur on Day 1 after a bolus IV administration of ^{11}C-BMS-986196. After completion of the first evaluable PET scan (on the same day or the day following the PET scan), participants will receive orally administered unlabeled BMS-986196 on-site or at home once daily (QD) for preferably 1 day; approximately 24 hours after the (last) dose of BMS-986196, participants will undergo the second cranial PET scan after a bolus IV administration of ^{11}C-BMS-986196. If the second PET scan cannot be performed in this time frame, it is permissible to administer a single dose of unlabeled BMS-

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986196 up to 7 days after the Day 1 PET (eg, in case of scheduling conflicts). In addition, in case of synthesis failure of PET tracer it is permissible to administered multiple doses of unlabeled BMS-986196 in order to have BMS-986196 administered 24 hours prior to the second PET scan, if Sponsor agrees. No more than 7 doses can be administered. Up to 3 dose levels of (unlabeled) BMS-986196 will be tested (15 mg, 30 mg, and 60 mg QD) and approximately 4 participants per dose level will be tested. Initially, participants will be assigned to the 30 mg dose level. After an interim review of PET results from 2 to 4 evaluable participants, the next dose level (15 mg or 60 mg) will be determined. At least 2 evaluable participants should have completed PET imaging at the second dose level before participants are assigned to the last dose level.

Safety Follow-up Period

For Part A and Part B, participants will be contacted remotely by phone (or web-call; email or text contact without verbal contact is not sufficient) 3 days (± 1 day) after completion of all PET scanning procedures and will be asked about AEs and concomitant medications. An in-person visit is optional. For Part C, participants will attend one in-person follow-up visit (Visit 3) 7 days after completion of all PET scanning procedures on Visit 2. During Visit 3, participants will undergo clinical assessments, have blood collected for laboratory tests, and will be asked about AEs and concomitant medications. For Visit 4, participants will be contacted remotely by phone (or web-call; email or text contact without verbal contact is not sufficient) 28 days (+ 3 days) after completion of Visit 2 and will be asked about AEs and concomitant medications. At the discretion of the investigator, Visit 4 can be conducted in-person.

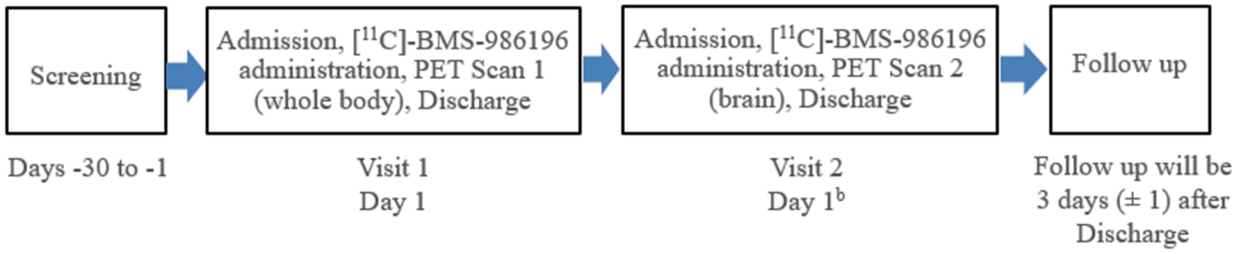
Upon completion of Visit 4 participants will have completed the study.

Safety will be assessed throughout the study by the recording of any AEs experienced during study participation.

The study design schematic is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schema

Part A - Safety, Tolerability, and Dosimetry in Healthy Participants[a]



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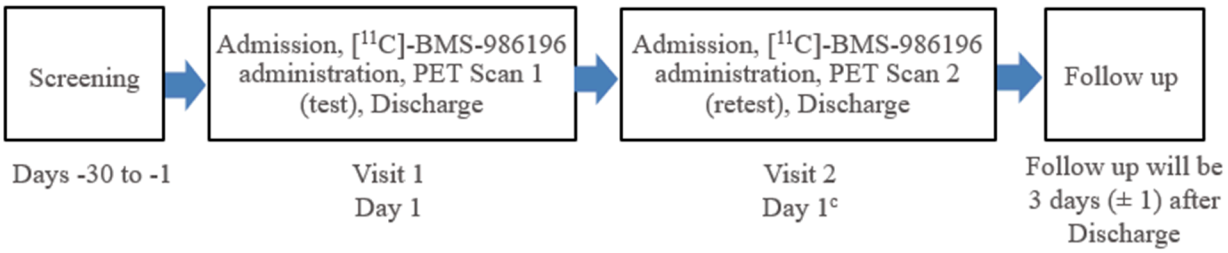
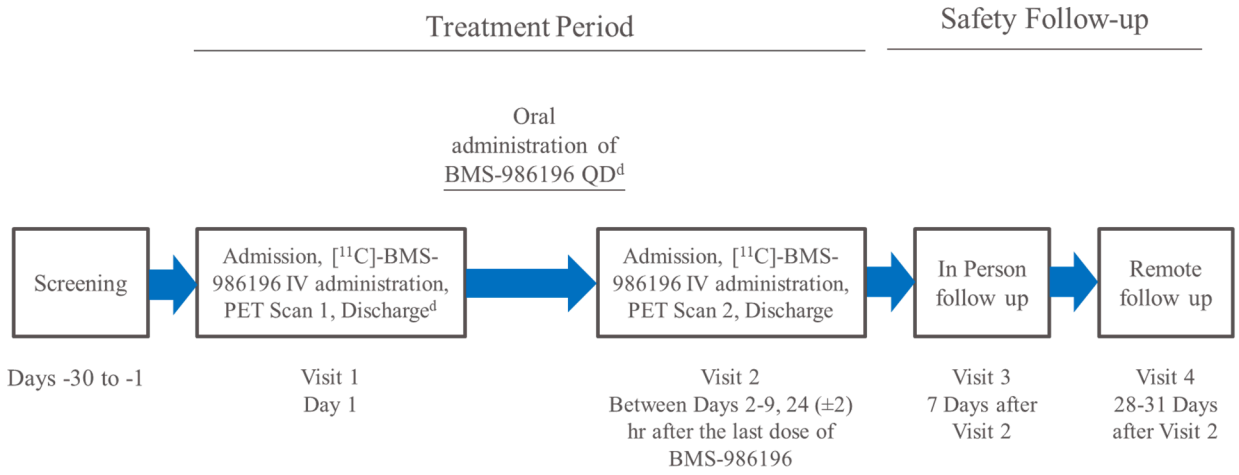
Part B - Repeatability of ^{11}C-BMS-986196 PET in Participants with MS



Part C - Quantification of Free BTK Availability in Healthy Participants



Abbreviations: BTK, Bruton's tyrosine kinase; IV, intravenous; MS, multiple sclerosis; PET, positron emission tomography; QD, once daily.

[a] Prior to initiation of Part B, all Part A participants will undergo Visits 1 and 2. After initiation of Part B, up to 2 participants may be added to Part A and will not undergo Visit 1, only Visit 2. For these participants only, Visit 2 will be regarded as Day 1.

[b] Visit 2 tracer administration must be done at least 2 hours and at most 6 days after Visit 1 tracer administration (ie, Day 2 to Day 7).

[c] Participants who had a MS relapse within 30 days prior to Day 1 must start Scan 2 on Day 1 or Day 2.

[d] After completion of the first evaluable PET scan (on the same day or the day following the PET scan), participants will receive orally administered unlabeled BMS-986196 QD for preferably 1 day; and approximately 24 hours after the (last) dose of BMS-986196, participants will undergo the second cranial PET scan. If the second PET scan cannot be performed in this time frame, it is permissible to administer a single dose of unlabeled BMS-986196 up to 7 days after the Day 1 PET (eg, in case of scheduling conflicts) or to dose unlabeled BMS-986196 once per day for up to 7 days (eg, in case of synthesis failure of the PET tracer) if the Sponsor agrees.

Physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory evaluations will be performed at selected times throughout the study. Participants will be closely monitored for AEs throughout the study.

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In Part A, the maximum volume of blood drawn from a participant is approximately 340 mL (40 mL clinical safety labs + up to 150 mL during the PET scan procedure for participants undergoing Visits 1 and 2 or up to 250 mL for participants only undergoing Visit 2).

In Part B, up to 445 mL of blood will be drawn from participants undergoing 2 PET scans and undergoing simultaneous arterial and venous sampling during 1 scan; approximately 345 mL will be drawn in participants undergoing only arterial sampling. The maximum volume of blood drawn in a period of 24 hours is approximately 420 mL.

In Part C, up to approximately 360 mL of blood will be drawn from participants (up to 150 mL during each of 2 PET scan procedures + 40 mL clinical safety labs + 6 mL QuantiFERON-TB + 10 mL for [redacted] biomarker testing).

Participants who undergo repeat PET scans will not exceed a cumulative blood draw volume of approximately 500 mL.

5.1.1 Data Monitoring Committee and Other Committees

A Data Monitoring Committee will not be used in the study.

5.2 Number of Participants

Up to 28 evaluable participants are planned to be enrolled. In Part A, evaluable participants for dosimetry outcomes are defined as those with adequate PET-CT whole-body scans collected over > 60 minutes. Part A evaluable participants for cranial PET scans are defined as those with cranial scans of adequate quality to be evaluable. In Part B, participants must have 2 cranial PET-CT/PET-MRI scans of adequate quality to be evaluable. To be evaluable in Part C, participants must have 2 cranial PET-CT/PET-MRI scans of adequate quality, one before and one after administration of (unlabeled) BMS-986196. Participants with non-evaluable PET images may be replaced, ie, the total number of enrolled participants may exceed 28 if participants have to be replaced.

5.3 End of Study Definition

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

End of trial is defined as the last participant last visit or scheduled procedure.

Study completion is defined as the final date on which data for the primary endpoint were or are expected to be collected, if this is not the same.

A participant is considered to have completed the study if he/she has completed the last assessment/procedure shown in the Schedule of Activities.

5.4 Scientific Rationale for Study Design

This study is designed to assess the safety, tolerability, repeatability, and feasibility of ^{11}C-BMS-986196 as a PET imaging tracer in healthy participants and participants with MS.

Part A is conducted in healthy adult volunteers. A healthy adult volunteer population facilitates the interpretation of AEs and the characterization of the ^{11}C-BMS-986196 safety profile including ^{11}C-BMS-986196 dosimetry in this first study testing the PET tracer in humans. Part A is planned

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to include up to 8 total participants. Up to 6 participants will undergo whole-body PET-CT, including at least 2 male and at least 2 female participants to enable radiation dosimetry calculation in organ tissue, including in reproductive organs. The [redacted] in Part A will allow determination of the [redacted] of healthy individuals and comparison with brain signal in patients with MS. Part B is conducted in patients with MS, because characterization of BTK expression in inflammatory CNS lesions containing microglia, macrophages, and/or B-cells is a key objective for the development and use of ^{11}C-BMS-986196. Adult patients with MS are the expected population in which ^{11}C-BMS-986196 will be utilized- in future studies. Part C has been added to the study via Protocol Amendment 05, after preliminary results of the current study indicated that ^{11}C-BMS-986196 resulted similar brain PET images in Part A (healthy participants) and Part B (participants with MS) and results from the first-in-human study (IM038008) demonstrated that BMS-986196 was safe and well tolerated at dose levels up to 90 mg QD for 14 days. In Part C, PET imaging allows characterization of brain [redacted] after treatment with unlabeled BMS-986196 at therapeutically relevant doses. For this purpose, an uncontrolled open-label design is adequate and typical. Open-label design without a control group is considered adequate for the purpose of this study, because a blinded study design with a control group is not expected to improve dosimetry or CNS signal detection. Based on the short treatment duration and microdose administered, safety evaluation in an open-label fashion without a control group is considered acceptable in Parts A and B. Based on the results of the first-in-human study (IM038008), safety evaluation is also considered acceptable in Part C. An open-label, uncontrolled study design is common for studies characterizing PET tracers and studies evaluating [redacted] by PET.[18]

5.5 Justification for Dose

A single dose of ^{11}C-BMS-986196 is administered at up to 20 µg in this study. Participants will receive up to 2 doses of ^{11}C-BMS-986196 in Part A and up to 3 doses of ^{11}C-BMS-986196 in Parts B and C. A third administration in Parts B and C is permissible if a PET scan has to be repeated (eg, due to failure of a prior scan). This is consistent with general practice in similar PET studies, in which small molecule tracers are generally administered at doses < 100 µg. The exposure associated with 2 administrations in a 24-hour period is projected to result in up to approximately 5.4% [redacted], and 3 administrations are projected to result in up to approximately 8.1% [redacted]. At the dose and frequency administered in the study population, ^{11}C-BMS-986196 exposure is not considered pharmacologically or biologically relevant (see Section 3.3, Benefit/Risk Assessment for additional details). In Part C, unlabeled BMS-986196 is expected to result in near maximal [redacted].

The administered radioactive dose was selected on the basis of nonclinical radiation dosimetry studies. The radioactivity of a single administration of ^{11}C-BMS-986196 is equivalent to approximately 370 MBq (10 mCi) and in terms of radiation exposure results in an effective dose of approximately 1.37 mSv (0.137 rem). In Part A, a single whole-body CT scan (ie, scan from apex to upper-thigh level) results in an effective dose of approximately 2.3 mSv (0.23 rem). Based on feedback provided by the participating clinical sites, the cranial CT scan sequences used in this study result in an effective dose of approximately 0.3 mSv (0.03 rem). The effective dose derived

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from ^{11}C-BMS-986196 administration and CT scans in Parts A, B, and C and total combined dose is shown in Table 5.5-1. Of note, the total dose depends on whether PET-CT or PET-MRI is used.

Table 5.5-1: Radiation Exposure from PET Tracer Administration and CT Scans

Study Part	Number of ^{11}C-BMS-986196 Administrations (Effective Dose)	Number of CT Scans (Effective Dose)	Total Effective Dose from Tracer Administration and CT Scan	Notes
A	2 (2.74 mSv)	3 (2.3 mSv + 0.6 mSv)	5.64 mSv	Whole-body PET-CT scan + 2 cranial PET-CT scans
A	2 (2.74 mSv)	1 (2.3 mSv)	5.04 mSv	Whole-body PET-CT scan + cranial PET-MRI scan
A	2 (2.74 mSv)	4 (1.2 mSv)	3.94 mSv	Part A participants who only undergo Visit 2 and need a repeat PET scan with pre- and post-CT scans for each PET scan
B+C	2 (2.74 mSv)	0 (0 mSv)	2.74 mSv	Cranial PET-MRI scan if no additional scan is required
B+C	3 (4.11 mSv)	0 (0 mSv)	4.11 mSv	Cranial PET-MRI scan if a third scan is necessary
B+C	2 (2.74 mSv)	2 (0.6 mSv)	3.34 mSv	Cranial PET-CT scan if no additional scans are required
B+C	3 (4.11 mSv)	6 (1.8 mSv)	5.91 mSv	Cranial PET-CT scan if a third PET scan is necessary with pre- and post-PET cranial CT scans for each PET scan

Abbreviations: CT, computed tomography; MRI, magnet resonance imaging; mSv, millisievert; PET-CT, positron emission tomography - computed tomography; PET-MRI, positron emission tomography - magnetic resonance imaging.

The maximum effective dose in Part A is 5.64 mSv (0.564 rem), and the maximum effective dose in Parts B and C (in participants undergoing 2 cranial PET-CT scans) is 5.91 mSv (0.591 rem), which is below the relevant limit of 10 mSv (1 rem) in the UK, based on ICRP standard (Publication 62 of the annals of the ICRP 22 (3), 1992). It is also below 50 mSv (5 rem), the annual effective dose limit below which radiation exposure can be considered generally safe according to the CFR, Title 21, Part 361.1(b)(3)(i). At such low radiation exposures, scientists disagree about the amount of health risk, and there may be very little risk, if any.

All of the exposures required by the study are additional to routine clinical care. The maximum total protocol dose in participants is 5.91 mSv. This is equivalent to 2.5 years of average natural background radiation in the UK.

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Ionizing radiation can cause cancer which manifests itself after many years or decades. The risk of developing cancer as a consequence of taking part in this study is estimated as 0.03%. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

6 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1) Signed Written Informed Consent

Participants must have signed and dated an IRB/Independent Ethics Committee (IEC)-approved written ICF in accordance with regulatory, local, and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.

2) Type of Participant and Target Disease Characteristics

For Part A and Part B:

- Body mass index (BMI) of 18 to 34 kg/m2, inclusive, and total body weight ≥ 50 kg (BMI may be rounded, eg, a participant with a BMI of 34.4 would qualify).
- Documentation of normal Allen's test result at Screening and on PET scanning days in the arm that will be used for arterial line placement.

a) Part A only:

- Healthy male and female participants without clinically significant deviation from normal in medical history, physical examination (PE), ECGs, and clinical laboratory determinations

b) Part B only:

- Male or female participant diagnosed with MS according to the 2017 revisions of the McDonald diagnostic criteria[19]
- EDSS score between 0 to 6.5, inclusive, at Screening

c) For Part C:

- Body mass index (BMI) of 18 to 34 kg/m^2, inclusive, and total body weight ≥ 50 kg (BMI may be rounded, eg, a participant with a BMI of 34.4 would qualify).
- Healthy male and WNOCBP participants without clinically significant deviation from normal in medical history, physical examination (PE), ECGs, and clinical laboratory determinations

3) Age of Participant

Participant must be 18 to 55 years of age, inclusive, at the time of signing the informed consent.

4) Reproductive Status

Investigators shall counsel women of childbearing potential (WOCBP) and male participants who are sexually active with WOCBP on the importance of pregnancy prevention, the implications of

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an unexpected pregnancy, and the potential of fetal toxicity occurring due to transmission of ^{11}C-BMS-986196 present in seminal fluid to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of tracer administration.

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

Women who are not of childbearing potential are exempt from contraceptive requirements.

a) Female Participants:

i) Female participants must have documented proof that they are not of childbearing potential.

ii) WOCBP must have a negative highly sensitive urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at Screening and within 24 hours prior to tracer administration.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 2, Schedule of Activities.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

iii) WOCBP must agree to follow instructions for method(s) of contraception defined in Appendix 4 and as described below and included in the ICF.

(1) WOCBP are permitted to use hormonal contraception methods (as described in Appendix 4).

iv) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 30 hours and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same time period

v) **In Part C only**, WOCBP are not eligible.

b) Male Participants:

- Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as defined in Appendix 4 and as described below.

i) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

ii) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the

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participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding. Males should continue to use a condom during the study intervention period and for at least 30 hours after the last dose of tracer administration in Parts A and B and at least 10 days after the last dose of unlabeled study drug administration in Part C.

iii) Female partners of males participating in the study should be advised to use highly effective methods of contraception during the study intervention period and for at least 30 hours after the last dose of tracer administration in Parts A and B and at least 10 days after the last dose of unlabeled study drug administration in Part C in the male participant.

iv) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participants have undergone a successful vasectomy, during the study intervention period and for at least 30 hours after the last dose of tracer administration in Parts A and B and at least 10 days after the last dose of unlabeled study drug administration in Part C.

v) Male participants must refrain from donating sperm during the study intervention period and for at least 30 hours after the last dose of tracer administration in Parts A and B and at least 10 days after the last dose of unlabeled study drug administration in Part C.

vi) Breastfeeding partners should be advised to consult their health care providers about using appropriate highly effective contraception during the time the participant is required to use condoms.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1) Medical Conditions

a) Any significant acute or chronic medical illness (Part A and Part C). Any significant acute or chronic medical illness (other than MS) posing a risk to the participant's safety or negatively affecting the ability to detect CNS PET signal (Part B only).

b) Benign MS defined as a baseline EDSS of 2.0 with MS diagnosis ≥ 10 years prior to Day 1. Spinal MS without clinical or radiological evidence of brain lesions. Any other combination of clinical and radiological data suggestive of an absence of inflammatory brain lesions.

c) MS relapse within 14 days prior to Day 1. Participants with a MS relapse within 30 days prior to Day 1 must agree to have their second PET scan scheduled on Day 1 or Day 2 (Part B only).

d) Any major surgery within 4 weeks of study treatment administration and/or any minor surgery within 2 weeks of tracer administration

e) A history of pancreatitis

f) A history of prolonged bleeding or excessive bruising

g) Known or suspected autoimmune disorder, including but not limited to rheumatoid arthritis, fibromyalgia, systemic lupus erythematosis, polymyalgia rheumatica, giant cell

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arteritis, Behcet's disease, dermatomyositis, severe asthma, any autoimmune vasculitis, autoimmune hepatitis, or any other active autoimmune disease for which a participant requires medical follow-up or medical treatment. Participants in Part A and Part C must not have a diagnosis of MS.

h) Any history of known or suspected congenital or acquired immunodeficiency state or condition that would compromise the participant's immune status and/or confound tracer dosimetry and signal detection (eg, splenectomy).

i) Presence of any factors that would predispose the participant to develop infection (eg, rectal fissures, poor dentition, open skin lesions, and presence of pre-existing skin conditions that increase risks for injection site complications [eg, Behcet's disease, psoriasis, pustular dermatoses])

j) Known currently active tuberculosis (TB) (Part A and Part B).

k) Any serious acute or chronic bacterial or viral infection (eg, pneumonia, septicemia) within 3 months prior to Screening

l) In the case of prior SARS-CoV-2 infection, symptoms must have completely resolved and, based on investigator assessment, there are no sequelae (eg, shortness of breath, persistent cough, excessive fatigue, loss of smell) that would place the participant at a higher risk of receiving investigational treatment

m) Positive test result for the presence of SARS-CoV-2 virus (eg, polymerase chain reaction [PCR] test) within 14 days of Day 1

n) Any recent infection requiring antibiotic treatment within 4 weeks of Day 1

o) Active herpes infection, including herpes simplex 1 and 2 and herpes zoster

p) Known active malaria

q) History or any evidence of active infection or febrile illness within 7 days of tracer administration (eg, bronchopulmonary, urinary, or gastrointestinal)

r) Donation of blood to a blood bank or to another clinical study within 4 weeks of tracer administration (within 2 weeks for plasma only)

s) Inability to be venipunctured and/or tolerate venous access

t) Have any contraindication to arterial line insertion, including but not limited to, an abnormal Allen's test result, coagulation profile, allergy to local anesthetics, or other medical history or examination findings that in the opinion of the Investigator would make radial artery cannulation contraindicated (international normalized ratio [INR]/partial thromboplastin time [PTT]) at Screening (Part A and Part B)

u) Contraindications against MRI imaging, including non-MRI compatible metal implants, cardiac pacemakers, cochlear implants, ventricular shunt systems; metal particles in the body that pose a risk to the participant, including large tattoos in regions affected by cranial MRI scanning and severe claustrophobia. Contraindications against gadolinium-based contrast agents including known hypersensitivity to gadolinium-based contrast agents (Part B only).

v) Recent (within 6 months of study intervention administration) drug or alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM 5), Diagnostic Criteria for Drug and Alcohol Abuse

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w) Use of any tobacco- or nicotine-containing products (including but not limited to cigarettes, pipes, cigars, electronic cigarettes, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 3 months prior to the first dose of tracer administration (Part A and Part C)

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

y) Inability to lie on the scanner for the duration of a PET scan acquisition

z) Current clinical or laboratory evidence of active TB. Participants with a positive QuantiFERON-TB Gold Plus test or 2 successive indeterminate QuantiFERON-TB Gold Plus tests at Screening will be excluded (Part C only).

aa) Participants who answer "yes" to items 4 or 5 of the C-SSRS or who answer "yes" to any suicidal behavior item (excluding non-suicidal self-injurious behavior) within 6 months prior to Day 1 or at Day -1 (See Section 9.4.7 for details on suicidal risk monitoring) (Part C only).

2) Reproductive Status

a) Women who are pregnant

b) Women who are breastfeeding

3) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7 Concomitant Therapy

b) Use of any prescription drugs within 4 weeks or 5 times the elimination half-life (if known), whichever is longer before tracer administration (Part A and Part C)

c) Use of any investigational drugs or placebo within 4 weeks or 5 times the elimination half-life (if known), whichever is longer before tracer administration

d) Systemic steroid medication within 4 weeks prior to tracer administration

e) Disease-modifying therapies for MS (approved, off label, or experimental) except for glatiramer acetate, interferon-β1a, or interferon-β1b (Part B only)

4) Physical and Laboratory Test Findings

a) Evidence of organ dysfunction or any clinically significant deviation from normal in PE, vital signs, ECG, or clinical laboratory determinations beyond what is consistent with the target population, in the opinion of the investigator

b) Positive urine screen for drugs of abuse (Part A and Part C)

c) Positive cotinine test (Part A and Part C)

d) Positive blood screen for hepatitis C antibody, hepatitis B core antibody, hepatitis B surface antigen, or human immunodeficiency virus (HIV)-1 and -2 antibody

e) Estimated renal creatinine clearance < 30 mL/min based on the Cockgroft-Gault formula (Appendix 5)

f) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN)

g) Total bilirubin > 2 x ULN (unless in the context of Gilbert syndrome)

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5) Allergies and Adverse Drug Reaction

a) History of allergy to BMS-986196 or BTKi
b) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity)
c) Known hypersensitivity to ^{11}C-BMS-986196
d) Hypersensitivity to gadolinium-based contrast agents (Part B only)

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been imprisoned may be included or permitted to continue as a participant. Strict conditions apply and BMS approval is required.)
b) Inability to comply with the study protocol including restrictions as listed in Section 6.3, Lifestyle Restrictions
c) Participation in another clinical trial concurrent with this study. Participation in certain non-interventional studies (eg, longitudinal cohort observational studies) or lifestyle and dietary intervention studies (eg, studies testing interventions such as mild to moderate exercise, diets low in carbohydrates, and/or cognitive training) is permitted if, in the assessment of the investigator, concurrent study participation does not pose a safety risk and is not expected to affect the imaging outcomes of the current study.
d) For Participants in the UK (at the London site): Previous participation in another clinical trial involving radiation exposure, which in combination with the radiation exposure from this study, would result in an effective dose of more than 10 mSv in a 1-year period.

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

Restrictions for meals, diet, and lifestyle/activity are described in detail in the following sections.

6.3.1 Meals and Dietary Restrictions

Study participants in Part A and C are required to fast for at least 8.5 hours prior to tracer administration and remain fasted during the PET scan procedure and until at least 1.5 hours after tracer administration. After completion of the PET procedure, meals will be provided by the PET center on the day of each PET scan. Participants who undergo 2 PET scans on 1 day do not have to remain fasted for the second PET scan and can have a light meal after the first tracer administration.

6.3.2 Caffeine, Alcohol, and Tobacco

Part A and Part C participants must meet the eligibility criteria related to alcohol, tobacco, and nicotine use.

1) Participants are not permitted to consume alcohol-containing beverages from 3 days prior to Day 1 until the end of the safety follow-up period.

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2) Participants are not permitted to smoke or use electronic cigarettes, vaporizers, or any nicotine-containing products on tracer administration days.

There are no restrictions on caffeine use outside of the required fasting times.

6.3.3 Activity

Participants are required to remain at the PET center on scanning days until they are discharged. Participants are to refrain from strenuous exercise and contact sports from at least 3 day(s) prior to the first tracer administration until discharge.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population.

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, as applicable, 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

Participant Re-enrollment: This study permits one-time 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) due to reasons that can be reasonably assumed to be of temporary nature. If re-enrolled, the participant must be re-consented.

A one-time retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value). Consultation with the medical monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

The most current result prior to ^{11}C-BMS-986196 tracer administration on Day 1 is the value by which study inclusion will be assessed, because it represents the participant's most current clinical state.

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, procedure(s) or medical device intended to be administered to a study participant according to the study protocol.

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

An IP, also known as IMP 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

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a marketing authorization but used or assembled (formulated or packaged) differently from 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 IPs/AxMPs. Not applicable for this study.

7.1 Study Interventions Administered

Table 7.1-1: Study Interventions

Arm Name	Part A	Part B	Part C	
Intervention Name	^{11}C-BMS-986196	^{11}C-BMS-986196	^{11}C-BMS-986196	BMS-986196
Type	Small molecule PET tracer	Small molecule PET Tracer	Small molecule PET Tracer	Small molecule/OSD
Dose Formulation	Solution for IV injection	Solution for IV injection	Solution for IV injection	Tablet
Unit Dose Strength(s)	Approximately 370 MBq, equivalent to up to 20 µg	Approximately 370 MBq, equivalent to up to 20 µg	Approximately 370 MBq, equivalent to up to 20 µg	15 mg, 30 mg, and 60 mg
Dosage Level(s)	One dose level. Up to 2 doses administered with an interdose interval between 2 hours to 6 days.	One dose level. Two doses administered with an interdose interval between 2 hours to 6 days.	One dose level. Two doses administered with an interdose interval between 2 hours to 6 days.	One tablet per day.
Route of Administration	IV injection	IV injection	IV injection	Oral
Use	Experimental	Experimental	Experimental	Experimental
IMP and Non-IMP/AxMP	IMP	IMP	IMP	IMP
Sourcing	Locally synthesized by the trial site	Locally synthesized by the trial site	Locally synthesized by the trial site	Provided centrally by the Sponsor
Packaging and Labeling	Study intervention will be provided in a sterile glass vial with rubber stopper and aluminum seal. Each container will be labeled as required per country requirement.	Study intervention will be provided in a sterile glass vial with rubber stopper and aluminum seal. Each container will be labeled as required per country requirement.	Study intervention will be provided in a sterile glass vial with rubber stopper and aluminum seal. Each container will be labeled as required per country requirement.	15 mg or 30 mg or 60 mg tablets packaged in bottles of 35 tablets. Single bottles will only contain one dose strength level of tablets. Each bottle will be labeled as required per country requirements.

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Table 7.1-1: Study Interventions

Arm Name	Part A	Part B	Part C	
Current/Former Name(s) or Alias(es)	^{11}C-BMS-986196	^{11}C-BMS-986196	^{11}C-BMS-986196	BMS-986196

Abbreviations: AxMP, auxiliary medicinal product; IMP, Investigational Medicinal Product; IV, intravenous; MBq, megabecquerel; OSD, oral solid dose; PET, positron emission tomography.

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

Restrictions related to food and fluid intake are described in Section 6.3.

7.2 Method of Study Intervention Assignment

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

In Part C, up to 12 evaluable participants will be enrolled and will receive (unlabeled) BMS986196 at dose levels of 15 mg, 30 mg, or 60 mg QD. Up to 4 evaluable participants will be assigned to each dose level. Initially, participants will be assigned to the 30 mg dose level. After an interim review of PET results from 2 to 4 evaluable participants, the next dose level (15 mg or 60 mg) will be determined. At least 2 evaluable participants should have completed PET imaging at the second dose level before participants are assigned to the last dose level.

Study intervention will be administered at the study visits as listed in Schedule of Activities (Section 2). Participants will not be replaced if they are discontinued due to an AE unless the AE can be determined to be unrelated to treatment. If a participant is replaced after dosing, then the replacement participant will be assigned the original participant's number plus 100. The replacement participant will receive the same treatment as the participant being replaced, but a new participant number will be assigned to him/her. For example, Participant 4 would be replaced by Participant 104. Participants with non-evaluable PET images may be replaced, ie, the total number of enrolled participants may exceed 28 if participants have to be replaced.

7.3 Blinding

This is a nonrandomized, open-label study, and blinding procedures are not applicable.

7.4 Dosage Modification

No dose modifications are allowed in Part A.

In Parts B and C, an initial dose of ^{11}C-BMS-986196 will be administered at approximately 370 MBq (10 mCi) and up to 20 µg, but the radioactive dose and participant preparation may be revised based on results of radiation dosimetry obtained in Part A.

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7.5 Preparation/Handling/Storage/Accountability

The IP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/AxMP is only dispensed to study participants. The IP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention 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 intervention arise, the study intervention should not be dispensed, and BMS should be contacted immediately.

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

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

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Only participants enrolled in the study may receive study intervention, and only authorized staff may supply, prepare, or administer study intervention.

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

Radiosynthesis instructions will be provided separately to the site.

7.6 Treatment Compliance

When participants are dosed at the site, they will receive study intervention directly from qualified site staff under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents and recorded in the case report form (CRF). The specific dose of study intervention and study participant identification will be confirmed at the time of tracer administration by a member of the study site staff other than the person administering the study intervention.

For Part C only, BMS-986196 (unlabeled) study intervention compliance will be periodically monitored by drug accountability (including review of dosing diary). Drug accountability should be reviewed by the site study staff at each visit to confirm treatment compliance. Site staff should discuss discrepancies with each participant at Visit 2.

- When participants are dosed at the site with BMS-986196 (unlabeled), they will receive study intervention directly from authorized site staff. The date and time of each dose received in the clinic will be recorded in the source documents and in the CRF. The dose of study intervention

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and study participant identification will be confirmed at the time of dosing by a member of the study site staff.

- When participants self-administer BMS-986196 (unlabeled) at home, compliance with study intervention will be assessed at Visit 2. Compliance will be assessed by direct questioning, counting of the remaining tablets, and review of the Participant Diary (supplied by the Sponsor) and documented in the source documents and the CRF. Deviations from the prescribed dosage regimen should be recorded in the CRF.
- A record of the quantity of BMS-986196 (unlabeled) dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates will also be recorded in the CRF.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

Prohibited and/or restricted medications taken prior to tracer administration in the study are described below. Medications taken within 4 weeks prior to tracer administration must be recorded on the CRF.

1) Prior exposure to BMS-986196 within 4 weeks of ^{11}C-BMS-986196 tracer administration
2) Exposure to any investigational drug or placebo within 4 weeks or 5 times the elimination half - life (if known), whichever is longer of ^{11}C-BMS-986196 tracer administration
3) Fish oil, aspirin, platelet aggregation inhibitors (including nonsteroidal anti-inflammatory drugs with such activity) and anticoagulants within 10 days prior to and within 7 days after ^{11}C-BMS-986196 tracer administration
4) Use of disease-modifying therapies for MS (approved, off label, or experimental), except for glatiramer acetate, interferon-β1a and interferon-β1b (Part B only)
5) Systemic steroid medication within 4 weeks prior to ^{11}C-BMS-986196 tracer administration.
6) Use of any prescription drugs within 4 weeks or 5 times the elimination half-life (if known), whichever is longer, prior to ^{11}C-BMS-986196 tracer administration. Contraceptive medication is permitted. In Part B, symptomatic therapy for MS (eg, against spasticity) is permitted.
7) Use of any other drugs, including over-the-counter medications and herbal preparations, within 1 week prior to ^{11}C-BMS-986196 tracer administration, except those medications cleared by the medical monitor. Paracetamol (acetaminophen) at daily doses up to 2000 mg for up to 3 days is permissible.

Administration of investigational SARS-CoV-2 vaccines is not allowed during the study. Participants may receive approved SARS-CoV-2 vaccines while continuing on study treatment at the discretion of the investigator.

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Treatment of active SARS-CoV-2 infections or high risk exposures, including use of investigational therapies, is allowed and should be discussed with the medical monitor.

The investigator should contact and confirm agreement with the medical monitor prior to the administration of any concomitant medications that are not explicitly permitted and are not used for the emergency treatment of AEs.

7.7.2 Other Restrictions and Precautions

Participants are prohibited from joining another clinical trial while they are participating in this study. Participation in certain observational studies or lifestyle or dietary intervention studies may be permissible if, in the assessment of the investigator, concurrent study participation does not pose a safety risk and is not expected to affect the imaging outcomes of the current study.

7.7.2.1 Imaging Restriction and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, and renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Renal function should be assessed in study participants receiving gadolinium-based contrast agent with regard to contrast agent dose and appropriateness of any administered contrast agent. Specific to MRI, participants with severe renal insufficiency, defined as estimated glomerular filtration rate (eGFR) < 30 mL/min based on the Cockcroft-Gault formula[20] (Appendix 5), are excluded from the study. In addition, participants may be excluded from MRI and study participation in Part B if they have tattoos, non-MRI compatible metallic implants, pacemakers, etc. This will be outlined in the Imaging Manual. A local safety read of the MRI should be performed and shared with the investigator.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

7.8 Continued Access to Study Intervention after the End of the Study

At the end of the study, BMS will not continue to provide BMS-supplied study intervention to participants/investigators. The investigator should ensure that any patient with MS receives appropriate standard of care to treat the condition under study.

BMS reserves the right to terminate access to BMS-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of ^{11}C-BMS-986196 is terminated for other reasons, including, but not limited to not meeting the study objectives. In all cases, BMS will follow local regulations.

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8 DISCONTINUATION CRITERIA

8.1 Discontinuation from Study Intervention

Participants MUST discontinue IP (and Non-IP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention 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 the participant to provide this information
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Termination of the study by BMS
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness. (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and BMS approval is required.)
- Pregnancy (study treatment must be discontinued immediately. Refer to Section 9.2.5).
- Significant noncompliance with protocol (eg, procedures, assessments, medications, etc). The investigator should discuss such issues with the medical monitor.
- Abnormal liver tests suggestive of potential drug-induced liver injury (DILI) as defined in Section 9.2.7.
- A participant has reported an adverse event meeting the stopping rule defined in Section 8.4.
- A participant has experienced a protocol-defined MS relapse after administration of ^{11}C-BMS-986196 at the Day 1 Visit.

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

All participants who discontinue study intervention 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 (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention 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 per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Post-study Intervention Study Follow-up

Participants who discontinue study intervention may continue to be followed.

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8.2 Discontinuation from the Study

Participants who request to discontinue study intervention 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.
- 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 intervention 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.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- 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 (3)** documented phone calls, faxes, or emails, as well as lack of response by participant to one (1) registered mail letter. All attempts should be documented in the participant's medical records.

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- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.
- If the 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 the 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 AE-defined Stopping Rules

AE-based stopping rules are triggered if an AE of sufficient significance (as judged by the investigator) warrants halting further enrollment and tracer administration. The AE must be considered related to study treatment and must not be an underlying condition of the study participant.

In addition, the following criteria trigger stopping rules:

- One participant experiences a serious adverse event (SAE) that is considered related to ^{11}C-BMS-986196 or BMS-986196.
- Two participants experience severe AEs that are related to ^{11}C-BMS-986196 or BMS-986196.

If either above listed criteria for stopping rules are met, a review of the safety data will be initiated to assess if the initial assessment of the relevant safety events was accurate.

If the review of the safety data concludes that the stopping rules were not met, then a justification for study restart will be submitted to the IEC/IRB and the study will only restart after IEC/IRB approval for restart has been obtained. If review of the safety data concludes that the stopping rules were met, the study will only restart after submission of a substantial amendment providing the data and justification for the restart.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in the Schedule of Activities (Section 2).
- Protocol waivers or exemptions are not allowed in this study.
- All safety concerns must be discussed with the medical monitor 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 (Section 2), 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 enrollment and tracer administration.

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9.1 Efficacy Assessments

Not applicable; efficacy will not be assessed in this study.

9.1.1 Imaging Assessments

9.1.1.1 PET Assessments

PET procedures will be conducted at the PET center at each site. Female participants will be given a pregnancy test prior to the initiation of any imaging procedures. If the test is positive, the scans will not be conducted.

Participant preparation for PET scanning consists of placement of venous lines and placement of arterial lines. In Part C, no arterial lines will be placed. IV line placement will be performed by the research nurse, certified nuclear medicine technologist, or investigator. The arterial and venous catheters will be placed by experienced staff, before the PET scan. One IV line will be used for tracer administration. The arterial line and, if applicable, a second IV line will be used to draw arterial and venous blood samples, respectively, for metabolite analysis and for determination of the fraction of plasma radioactivity unbound to protein.

The goal of arterial and venous lines is to be able to measure absolute physiological functions by mathematically relating the signal (from the PET scanner) to the tracer availability (from the blood). This approach provides the gold-standard data. If an arterial line cannot be placed, a second IV line may be placed for IV blood sampling. IV blood sampling should occur on the arm opposite of the arm used for ^{11}C-BMS-986196 tracer administration. All processing of blood samples for ^{11}C-BMS-986196 input function determination should occur promptly at the PET center due to the short half-life of C-11 (20 min).

PET scans will be performed and acquired as participants lie supine on the scanner bed.

For each PET scan, approximately 370 MBq (10 mCi) of ^{11}C-BMS-986196 will be administered by a slow IV bolus. Acquisition of emission data will begin shortly after administration and continue for a period of up to 120 minutes. Vital signs (blood pressure, heart rate, respiration rate, and body temperature) will be obtained before ^{11}C-BMS-986196 administration, after completion of the PET scan procedure, and prior to discharge on each scan day. An ECG will be completed before each PET scan and prior to discharge on each scan day.

<u>Part A</u>

Two tracer administrations of ^{11}C-BMS-986196 are each followed by a PET scan. The interval between the first and second tracer administrations must be at least 2 hours and at most 6 days. If the second tracer administration is done on Days 5, 6, or 7, the study site staff must contact the participant remotely (ie, by phone) on Day 4 (ie, 3 days after the first PET scan) and record AEs and concomitant medications.

Before or after the first PET scan, a low-dose whole-body CT scan (from apex to upper-thigh level) will be acquired for attenuation correction. No contrast agent is administered for the CT scan.

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Before and/or after the cranial PET scan, a low-dose cranial CT scan or MRI scan will be acquired (depending on availability of equipment). No contrast agent is administered for the CT or the MRI scan.

The maximal number of tracer administrations in Part A is 2 and the maximal number of whole-body CT scans in Part A is 1. The maximum number of cranial CT scans in Part A is 2 per cranial PET (1 before and 1 after the PET scan). Hence, the maximum number of cranial CT scans is 4 for participants who will not undergo whole-body CT scans. For all other participants in Part A, the maximum number of cranial CT scans is 2. If 2 PET scans are performed on the same day, hematology and clinical chemistry samples, VS, ECG, AEs, and review of concomitant medications are the only safety assessments that must be assessed in duplicate, and the same arterial line may be used for both scans.

If, after completion of dosimetry in Part A participants and based on emerging data from Part B, 2 additional participants are enrolled to Part A, then these 2 participants will only undergo the cranial PET scan of Visit 2, and these participants will have arterial and venous blood samples drawn during the Visit 2 PET scan. For these 2 participants, Visit 2 will be regarded as Day 1.

Part B

Two administrations of ^{11}C-BMS-986196 are each followed by a cranial PET scan. The interval between the first and second tracer administration must be at least 2 hours and at most 6 days. If the second tracer administration is done on Days 5, 6, or 7, the study site staff must contact the participant remotely (ie, by phone) on Day 4 (ie, 3 days after the first PET scan) and record AEs and concomitant medications. Participants who had a MS relapse within 30 days prior to Day 1 must start Scan 2 on Day 1 or Day 2.

Before or after each tracer administration, a low-dose cranial PET-CT or PET-MRI scan will be performed (depending on equipment availability). No contrast agent will be administered for the PET-CT scan. To account for potential significant movement during the PET scan, it is permissible to perform 1 cranial CT or MRI scan before and 1 CT or MRI scan after a cranial PET scan. At the discretion of the investigator, gadolinium-based contrast agents may be administered if a PET-MRI is performed. Participants in Part B must have at least one cranial PET-MRI scan performed with gadolinium-based contrast agent. Gadolinium-based contrast agent may be administered either at Screening or during PET-MRI.

Before a PET-MRI scan, participants will be asked for the presence of contra-indications against MRI or application of gadolinium-based contrast agents and asked to remove magnetic objects before entering the scanner.

The maximal number of tracer administrations in Part B is 3 and the maximal number of CT scans in Part B is 6. If 2 PET scan visits are performed on the same day, vital signs (VS), ECG, AEs, and review of concomitant medications are the only safety assessments that must be assessed in duplicate, and the same arterial line may be used for both scans.

In Part B, every effort must be made to perform the re-test PET scan under identical conditions as the test scan (eg, same scanning machines, same imaging procedures).

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If, based on emerging data from Part B, simultaneous sampling of venous and arterial blood sampling is considered warranted to facilitate future studies without arterial blood sampling, up to 6 participants in Part B may undergo simultaneous venous and arterial blood sampling only during one PET scan procedure. Preferably, the simultaneous and arterial blood sampling is performed during Visit 1.

Part C

Two administrations of ^{11}C-BMS-986196 will each be followed by a cranial PET scan. The second tracer administration will occur approximately 24 hours after the last administration of (unlabeled) BMS-986196.

Before or after each tracer administration, a low-dose cranial PET-CT or PET-MRI scan will be performed (depending on equipment availability). No contrast agent will be administered for the PET-CT scan. To account for potential significant movement during the PET scan, it is permissible to perform 1 cranial CT or MRI scan before and 1 CT or MRI scan after a cranial PET scan. No gadolinium-based contrast agents will be administered if a PET-MRI is performed.

Before a PET-MRI scan, participants will be asked for the presence of contraindications against MRI and asked to remove magnetic objects before entering the scanner.

The maximal number of tracer administrations in Part C is 3, and the maximal number of CT scans in Part C is 6.

In Part C, every effort must be made to perform the second PET scan under identical conditions as the first scan (eg, same scanning machine, same imaging procedures).

9.1.1.2 MRI Imaging During Screening

Participants in Part B will undergo cranial MRI scanning during the Screening period. Participants will only undergo cranial MRI scanning if they are eligible for the study based on the other assessments performed during screening. A Screening MRI should be performed within 14 days of Day 1. Imaging should be performed on a 3T MRI machine and at a minimum T1 and T2 sequences are performed, including T1 sequences with and without enhancement by gadolinium-based contrast agent. However, if use of gadolinium-based contrast agent is planned during PET-MRI, gadolinium-based contrast agent is not required during screening MRI. Before screening, MRI participants will be asked for the presence of contra-indications against MRI or application of gadolinium-based contrast agents and asked to remove magnetic objects before entering the scanner. The details of the MRI scanning conditions will be detailed in an Imaging Charter. A local safety read of the MRI should be performed and provided to the investigator for review.

9.1.1.3 Central Image Analysis

PET, CT, and MRI images will be submitted to a central imaging vendor for independent central review at any time during the study. Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

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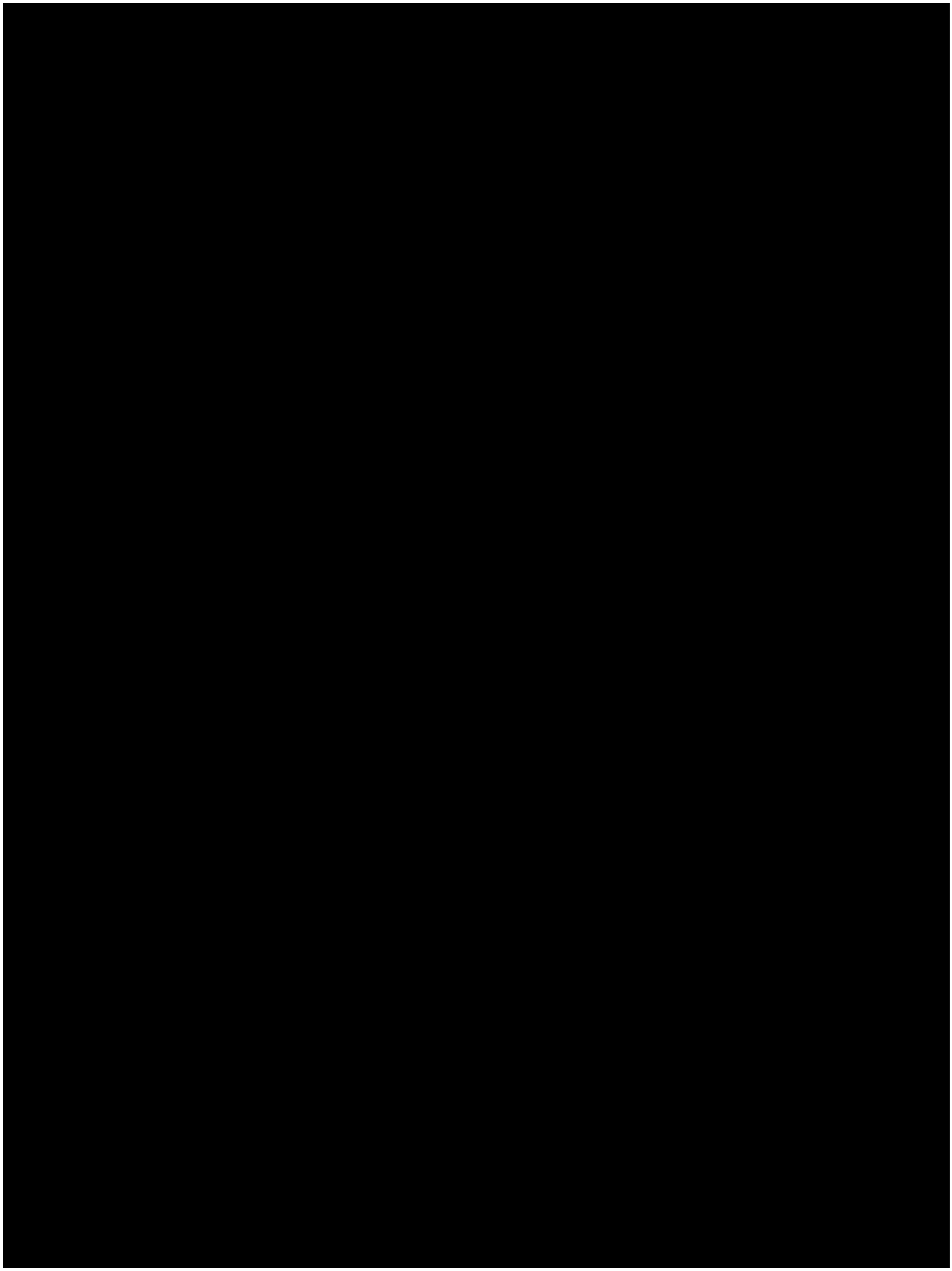

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[redacted]

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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

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

Refer to Appendix 3 for SAE reporting.

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs must be collected from the time of signing the consent, including those thought to be associated with protocol-specified procedures, and within 10 days following discontinuation of dosing in Parts A and B, and within 28 days following discontinuation of dosing in Part C.

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study intervention or protocol-specified procedure (eg, a follow-up skin biopsy).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the appropriate section of the CRF module.
- 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 or designee within 24 hours of updated information 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 intervention 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.

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9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgement in the context of known AEs, when appropriate for the program or protocol.

9.2.3 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 intervention and for those present at the end of study intervention 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.

All SAEs 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.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward 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 (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A SUSAR (suspected, unexpected serious adverse reaction) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

This section is not applicable for WNOCBP in Part C.

If, following initiation of the study intervention in Parts A or B, it is subsequently discovered that a participant is pregnant or may have been pregnant at the time of study drug exposure, including at least 30 hours after study product administration, the investigator must immediately notify the BMS medical monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the BMS designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Appendix 3.

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

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and at least for 30 hours after tracer administration in Parts A and B and at least for 10 days after the last dose of unlabeled study drug administration in Part C, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE CRF, 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 intervention 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 (eg, anemia vs low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (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 DILI is defined as 1 of the following 3 conditions:

- Condition 1:
  - Aminotransaminase (AT [ALT or AST]) elevation > 3 times upper limit of normal (ULN)

  AND

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

  AND

  - 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.

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- Condition 2
  - AT (ALT or AST) elevation > 3 times upper limit of normal (ULN) in the presence of clinical symptoms (eg, upper abdominal quadrant pain, brown colored urine)

  AND

  - 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.
- Condition 3
  - Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) and clinical symptoms (eg, icteric conjunctiva or skin)

  AND

  - No other immediately apparent possible causes of aminotransaminase (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.

9.2.8 Other Safety Considerations

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

9.3 Overdose

For this study, any dose of ^{11}C-BMS-986196 greater than 100 µg within a 24-hour time period will be considered an overdose. Overdoses that meet the regulatory definition of SAE will be reported as an SAE (see Appendix 3).

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately
- Closely monitor the participant for AEs/SAEs and laboratory abnormalities until ^{11}C-BMS-986196 can no longer be detected systemically. The specific follow up duration will be determined after consultation with the medical monitor and will depend on the actual tracer dose administered. Because 50% recovery of BTK is projected to occur within 7 days, in-person follow-up beyond 7 days in the absence of AEs is not required.
- Document the quantity of the excess dose as well as the duration of the overdose in the CRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

9.4 Safety

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2).

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9.4.1 Physical Examinations

A complete PE includes examination of head, eyes, ears, nose, and throat (HEENT), heart, lungs, abdomen, extremities, skin and in Parts A and C only, a limited neurological exam. In Part B, the [redacted] serves as neurological examination. A partial PE will be symptom-oriented and include areas with previously noted abnormalities and/or newly emergent symptoms.

Complete and/or partial PEs may be performed by a Doctor of Medicine, or someone who is authorized to perform the examinations by training and has been delegated this task by the investigator. Every effort should be made to ensure the same evaluator will complete the examination for each participant at all visits throughout the study. Documentation of the person who performed the examination is to be recorded in source notes.

9.4.2 Height and Weight

Height and body weight will be measured per the Schedules of Activities (Section 2). BMI will be calculated using the equation: BMI = weight (kg)/(height[m]^2).

9.4.3 Vital Signs

After resting quietly in a supine position for at least 5 minutes, vital signs (oral or tympanic body temperature, respiration rate, blood pressure [BP], and heart rate [HR]) will be recorded as per Schedules of Activities (Section 2). At Visits 1 and 2, the vital signs assessment prior to discharge can be performed in sitting or supine position.

For BP, the participant's arm should be supported at the level of the heart, and BP should be recorded to the nearest mmHg. Preferably, the same arm should be used throughout the study. The same size BP cuff, which has been properly sized and calibrated, will be used to measure BP each time. The use of automated devices for measuring BP, respiration rate, and HR are acceptable. However, manual HR (if used) will be measured by palpitation in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and HR should be obtained prior to the nominal time of the blood collection.

9.4.4 Allen's Test (Part A and Part B only)

The Allen's test is a clinical assessment of arterial blood flow supply to the hand. For the test, the participant raises the extended arm, ideally from a supine position, such that the hand is above the heart level. The participant then clinches a fist for at least 30 seconds, and the assessor places manual pressure on the radial and ulnar artery to limit the blood flow for several seconds. The participant then opens the fist and the palm of the hand should look pale. The assessor then releases the manual pressure from the ulnar artery and watches the palm of the hand, which should return to its normal color within approximately 5 to 15 seconds for a normal test result.

9.4.5 Electrocardiograms

Single 12-lead ECGs in the supine position will be performed as per the Schedule of Activities (Section 2). Participants will have rested in the supine position for at least 5 minutes prior to each ECG. A local ECG read will be performed. Clinically significant abnormal findings will be recorded as AEs.

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9.4.6 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.

A local laboratory will perform the analyses and will provide reference ranges for these tests.

Participants in Parts A and C are required to fast for at least 10 hrs prior to specimen collection.

Results of clinical laboratory tests performed on Day -1 must be available and reviewed for study eligibility, if applicable, prior to tracer administration.

Specimens will be collected at least 1.5 hrs after the first tracer administration and at least 1.5 hours after the second tracer administration.

Table 9.4.6-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Chemistry	
Aspartate aminotransferase Alanine aminotransferase Total bilirubin Direct bilirubin Alkaline phosphatase Amylase Lipase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Fasting or non-fasting glucose	Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance (Screening only)
Coagulation (Screening only)	
INR aPTT	
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
pH	

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Table 9.4.6-1: Clinical Laboratory Assessments

Microscopic examination of the sediment if blood, protein or leukocyte esterase are positive on the dipstick
Serology
Serum for hepatitis C antibody, hepatitis B core antibody, hepatitis B surface antigen, HIV-1 and -2 antibody (Screening only)
Other Analyses
Test for drugs of abuse (urine; Screening and prior to Day 1 tracer administration; Parts A and C only) Alcohol test (urine or breath; Screening and prior to Day 1 tracer administration) Cotinine test (urine; Screening and prior to Day 1 tracer administration; Parts A and C only)
Urine or serum pregnancy test (Parts A and B only; WOCBP only; Screening and prior to Day 1 tracer administration)
FSH test (women < 55 years for confirmation of postmenopausal status; refer to Appendix 4)
QuantiFERON-TB Gold Plus (Screening; Part C only)

Abbreviations: aPTT, activated partial thromboplastin time; FSH, follicle stimulating hormone; HIV, human immunodeficiency virus; INR, international normalized ratio; WOCBP, women of childbearing potential.

9.4.7 Suicidal Risk Monitoring (Part C only)

BMS-986196 is CNSpenetrant. It is unknown whether BMS-986196 affects mood and/or suicidal ideation/behavior. In Part C, study participants will be assessed for suicidal ideation/behavior with the C-SSRS (baseline version at Screening and since last visit/last assessment version afterwards).

Participants treated with BMS-986196 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. Consideration should be given to discontinuing BMS-986196 in participants who experience signs of suicidal ideation or behavior.

9.4.8 Other Safety Assessment

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the investigator and/or the qualified neurologist as per standard medical/clinical judgment.

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[redacted]

9.6 Immunogenicity Assessments

Not applicable.

9.7 Genetics

Not applicable.

9.8 Biomarkers

No blood samples for [redacted] or downstream target engagement as pharmacodynamics (PD) analysis will be collected or analyzed in Parts A and B. Blood collection for measuring blood [redacted] will occur in Part C, as detailed in the Schedule of Assessments (Table 2-4).

Table 9.8-1: Biomarker Sampling Schedule for All Participants in Parts A and B (IM038010)

Study Day	Time (Event) Hour	Time (Relative To Dosing) Hour: Min	[redacted]	SARS-CoV-2 Serum Sample (Parts A and B only)
Screening	Not applicable	Not applicable		X
Visit 1	Not applicable	Not applicable		Not applicable
Visit 2	Not applicable	Not applicable		Not applicable
Visit 3	Not applicable	Not applicable		Not applicable

Abbreviations: Min, minutes; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 9.8-2: Target Engagement as Pharmacodynamics Sampling Schedule for Part C (IM038010)

Study Day of Sample Collection	Event	Time Relative to Last BMS-986196 Dose (hr:min)	BMS-986196 Whole Blood Sample for PD
Visit 1	Predose	-00:30	X
Visit 2	Postdose	24:00	X

Abbreviations: hr, hour; min, minute; PD, pharmacodynamic. ,

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For Parts A and B, serum samples will be collected from all participants and shipped to the Sponsor for potential evaluation of [redacted], if warranted. Results will not be used to determine eligibility.

TE as PD whole blood sample collection, labeling, processing, storage, and shipping will be provided to the site in the laboratory/procedure manual.

9.9 Additional Research

This protocol will not include sample collection and/or residual sample storage for additional research.

Additional research is intended to expand the research and development capability at Bristol Myers Squibb and will support as yet undefined research aims that will advance our understanding of disease and options for treatment. This may also include genetic/genomic exploration aimed at exploring disease pathways, progression and response to treatment etc.

9.10 Other Assessments

Not applicable.

9.11 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 Statistical Hypotheses

Not applicable.

10.2 Sample Size Determination

The sample size in Parts A to C of the study is not based on statistical power considerations or formal sample size calculations. In Part A, up to 8 healthy participants (at least 2 females and 2 males are planned) will be enrolled, in Part B, up to 8 participants with MS will be enrolled, and in Part C, up to 12 healthy participants will be enrolled, such that in this study, up to approximately 28 participants will have evaluable PET scans. Participants with non-evaluable PET scans may be replaced, ie, the total number of enrolled participants may exceed 28 if participants have to be replaced.

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who provide written (signed) informed consent.
Safety	All participants who received at least 1 dose of tracer administration.
PET	All participants who received at least 1 dose of tracer administration and have any available PET scan data.

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Population	Description
Response-Evaluable	All participants who receive at least 1 dose of tracer administration, and: 1) 1 evaluable whole-body PET scan in Part A (Response-Evaluable 1) 2) At least 1 evaluable cranial PET scan in Part A or B (Response-Evaluable 2) 3) 2 evaluable cranial PET scans in Parts B and C (Response-Evaluable 3)
Per Protocol	All participants who receive at least 1 dose of tracer administration, and: 1) 1 evaluable whole-body PET scan without major important protocol deviations in Part A (Per-Protocol 1) 2) At least 1 evaluable cranial PET scan without major important protocol deviations in Part A or B (Per-Protocol 2) 3) 2 evaluable cranial PET scans without major important protocol deviations in Parts B and C (Per-Protocol 3)
[redacted]	

Abbreviations: PET, positron emission tomography.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the selection of participants to be included in the analyses and procedures for accounting for missing, unused, and spurious data.

10.4.1 General Considerations

Details on statistical considerations will be included in the SAP. Statistical analyses in this study will be detailed in the SAP.

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10.4.2 Primary Endpoint(s)

Table 10.4.2-1: Endpoints

Primary Endpoint	Description	Timeframe
Incidence, severity, seriousness, type of AEs. (Safety Population)	Incidence of AEs, SAEs, severe, type of AEs. AEs listed by frequency	Treatment emergent during the study
Incidence of clinically significant abnormal findings. (Safety Population)	Incidence of clinically significant abnormal findings in ECG, laboratory values, VS, physical examination	Treatment emergent during the study
Radiation dosimetry (Part A only). (Response-Evaluable 1 Population)	Organ absorbed dose and whole-body effective dose	After ^{11}C-BMS-986196 tracer administration at Visit 1
Window of acquisition. (Response--Evaluable 2 Population)	Time during which peak PET signal is detected	Part A Visit 2, and Part B Visit 1 and Visit 2 after ^{11}C-BMS-986196 tracer administration
Test-Retest Repeatability (Part B only). (Response-Evaluable 3 Population)	Quantitative analysis of PET signal in CNS between 2 evaluable PET sessions	Visit 1 and Visit 2 after ^{11}C-BMS-986196 tracer administration
% Free brain BTK relative to baseline (Part C only)	Proportion of free brain BTK at Visit 2 relative to Visit 1	Visit 1 and Visit 2

Abbreviations: AE, adverse event; CNS, central nervous system; ECG, electrocardiogram; PET, positron emission tomography; SAE, serious adverse event; VS, vital signs.

All recorded AEs will be listed according to system organ class and preferred term and tabulated by study part. ECGs as reported on the ECG CRF (including abnormality) will be reported separately. Vital signs as reported on the VS CRF will be reported separately. Physical examinations as recorded on the PE CRF will be reported separately. Clinical laboratory test results as reported on Lab CRF will be reported separately. Vital signs, ECGs, and laboratory test results will be summarized.

For test-retest repeatability in Part B, descriptive statistics will be reported by measurement. A scatter plot of test versus retest with the line of equality will be created. A plot of differences between retest and test versus the mean of the test and retest may also be constructed. The estimated limits of agreement will be also presented on this plot.

The proportion of free brain BTK relative to baseline will be summarized for Part C.

Descriptive statistics and plots may be provided for the other endpoints. Other details may be added in the SAP as appropriate.

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10.4.3 Secondary Endpoint(s)

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Timeframe
^{11}C-BMS-986196 signal characterization. (Response-Evaluable 1 Population)	SUV, $V_{T,}$ and other relevant quantitative PET measures as applicable in the brain	Visit 1 and Visit 2

Abbreviations: PET, positron emission tomography; SUV, standardized uptake value; VT, volume of distribution.

Descriptive statistics will be provided for the secondary endpoint. Plots may be also created.

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10.4.5 Other Safety Analysis

Not applicable.

10.4.6 Other Analyses

Not applicable.

10.5 Interim Analyses

Not applicable.

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[redacted]

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12 APPENDICES

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APPENDIX 1 ABBREVIATIONS AND TRADEMARKS

Term	Definition
[redacted]	
AE	adverse event
ALT	alanine aminotransferase
Anti-HBc	hepatitis B core antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminase
AUC	area under the concentration-time curve
AUC(0-24h)	area under the plasma concentration-time curve from time zero to 24 hours postdose
AxMP	auxiliary medicinal product
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
C_{Cr}	creatinine clearance
CD	cluster of differentiation
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
Cmax	maximum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	Case Report Form, paper or electronic
CRU	clinical research unit
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CTAg	Clinical Trial Agreement
[redacted]	
DCBB	daily covalent binding burden

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Term	Definition
DILI	drug-induced liver injury
DSM 5	Diagnostic and Statistical Manual of Mental Disorders (5th Edition)
EAE	experimental autoimmune encephalomyelitis
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EDSS	Expanded Disability Status Scale
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
[redacted]	
FSH	follicle-stimulating hormone
g	gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GSH	glutathione
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV Ab	hepatitis C virus antibody
HEENT	head, eyes, ears, nose, and throat
[redacted]	
hERG	human ether a go go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
hrs	hours
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
IgG	immunoglobulin G

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Term	Definition
IKr	rapid delayed rectifier potassium channel current
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	international normalized ration
IP	Investigational Product
IRB	Institutional Review Board
IT	information technology
IUS	intrauterine hormone-releasing system
IV	intravenous
kg	kilogram
KLH	keyhole limpet hemocyanin
L	liter
LAM	lactational amenorrhea method
MAD	multiple ascending dose
MBq	megabecquerel
mg	milligram
min	minute
mL	milliliter
MoA	mechanism of action
MRI	magnet resonance imaging
MS	multiple sclerosis
mSv	millisievert
µg	microgram
ng	nanogram
Non-IMP	Non-investigational Medicinal Product
NOAEL	no-observed-adverse-effect level
NTCP	sodium taurocholate cotransporting polypeptide
OATPs	organic anion transporting polypeptides
PCR	polymerase chain reaction
PD	pharmacodynamic
PE	physical examination
PET	positron emission tomography
PET-CT	positron emission tomography - computed tomography

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Term	Definition
PET-MRI	positron emission tomography - magnetic resonance imaging
PK	pharmacokinetic
PO	oral
QD	quaque die, once daily
RANK	receptor activator of nuclear factor kappa-B
RSC	Radiation Safety Committees
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
S_{Cr}	serum creatinine
SUSAR	suspected, unexpected serious adverse reaction
SUV	standardized uptake value
T	time
TB	tuberculosis
TMF	trial master file
UK	United Kingdom
ULN	upper limit of normal
VS	vital signs
V_T	volume of distribution
WOCBP	women of childbearing potential

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APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws, regulations, and requirements

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

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a Quality Issue (eg, protocol deviation) that is likely to affect, to a significant degree, one or more of the following: (1) the rights, physical safety or mental integrity of one or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

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

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

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, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

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- ICH guidelines,
- United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)
- European Union Directive 2001/20/EC; or
- European Regulation 536/2014 for clinical studies (if applicable),
- European Medical Device Regulation 2017/745 for clinical device research (if applicable),
- the IRB/IEC
- and all other applicable local regulations.

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 the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

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
- 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 the local Health Authority, must be sent to Bristol-Myers Squibb (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF 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 participants 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 participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with 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 participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

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The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant or participant's legally acceptable representative and answer all questions regarding the study.
- Inform participant that his/her participation is voluntary. Participant or participant's legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for participant or participant's legally acceptable representative to inquire about the details of the study.

Obtain an ICF signed and personally dated by participant or participant's legally acceptable representative and by the person who conducted the informed consent discussion.

- Include a statement in participant's medical record that written informed consent was obtained before participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent participant to the most current version of the ICF(s) during his/her participation in the study, as applicable.

Revise the ICF 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 participant's legally acceptable representative 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 participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA Authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

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

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyber attacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible

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adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of information technology (IT) Personnel
2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic CRF (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definitions of what constitutes source data can be found in hospital records, clinic and office charts, laboratory notes, memoranda, evaluation checklists and dispensing records.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten 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 records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an 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 INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention 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.

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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 (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, 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 treatment integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its 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 (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be

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reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants 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 and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

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

MONITORING

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

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

In addition, the study may be evaluated by the 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 the 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 its 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 its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

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

RETURN OF STUDY TREATMENT

For this study, study treatments (those supplied by BMS or 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 interventions 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 (eg, cytotoxics or biologics). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. But unused IMP must be reconciled by site monitor/Clinical Research Associate prior to destruction. 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; eg, study treatments sourced from the site's 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 of study interventions, 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 standard operating procedures and a copy provided to BMS upon request.

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- 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 (eg, 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 Study 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.

STUDY AND SITE START AND CLOSURE

The Sponsor/designee reserves the right to close the study site or to terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

In order to benefit potential study participants, patients, healthcare providers and researchers, and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public as per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

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CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- Involvement in trial design

SCIENTIFIC PUBLICATIONS

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

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered by BMS for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

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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 pre-existing medical condition in a clinical investigation participant administered study treatment 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 treatment, whether or not considered related to the study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal lab tests or other safety assessments should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE, even if serious conditions are met.

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SERIOUS ADVERSE EVENTS

A 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 Bristol-Myers Squibb (BMS) clinical studies: • A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery, planned prior to signing consent. • Admissions as per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
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 [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm and 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 9.2.7 for the definition of potential DILI.)

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Pregnancy and DILI must follow the same transmission timing and processes to BMS as used for SAEs. (See Section 9.2.5 for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or product information for marketed products in his/her assessment. • For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 treatment 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 treatment, and pregnancies must be reported to BMS (or designee) immediately within 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.
  - The required method for SAE data reporting is through the electronic case report form (eCRF).
  - The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or designee).
    - In this case, the paper form is transmitted via email or confirmed facsimile transmission.
    - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed facsimile transmission.

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SAE Email Address: [redacted]

SAE Facsimile Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

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APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Woman of Childbearing Potential and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1 of the protocol. Only the contraception methods as described in Section 6.1 are acceptable for this study.

DEFINITIONS

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal 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. Suggested guidelines for the duration of the washout periods for HRT types are presented below. 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

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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.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the timepoint where the Investigational Medicinal Product (IMP) or any active major metabolites have decreased to a concentration that is no longer considered to be relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the IMP to pass.

METHODS OF CONTRACEPTION

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 and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b]
  - Oral (birth control pills)
  - Intravaginal (rings)
  - Transdermal
- Combined (estrogen-and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.

- Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b]
  - Oral
  - Injectable
- Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b]
- Intrauterine device.
- Intrauterine hormone-releasing system (IUS). (This method of contraception can only be used by WOCBP participants in studies where hormonal contraception is permitted by the study protocol.)[b,c]

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• Bilateral tubal occlusion.
• Vasectomized partner Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is already pregnant or breastfeeding.
• 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 treatment. 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.* • Continuous abstinence must begin at least 30 days prior to initiation of study therapy. • 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 participant chooses to forego complete abstinence. • Periodic abstinence (including, but not limited to, calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study.
NOTES: [a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. [b] Hormonal contraception may be susceptible to interaction with the study treatment, 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. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol. [c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Sections 6.1 INCLUSION CRITERIA and 7.7.1 PROHIBITED AND/OR RESTRICTED TREATMENTS of the protocol.

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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. (This method of contraception cannot be used by WOCBP participants in studies where hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, postovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

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 Appendix 3.

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APPENDIX 5 COCKCROFT GAULT FORMULA

Males: C_{Cr} = (140 - age) x body weight/(72 x S_{Cr})

Females: C_{Cr} = (140 - age) x body weight x 0.85/(72 x S_{Cr})

C_{Cr} = creatinine clearance [milliliter per minute]

S_{Cr} = serum creatinine [in milligram per deciliter]

Body weight in kilograms

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

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APPENDIX 6 PROTOCOL AMENDMENT SUMMARY OF CHANGE HISTORY

Overall Rationale for Protocol Amendment 04, 09-May-2022

The primary purpose for this amendment is to:

- Accurately account for the radiation exposure resulting from a cranial computed tomography (CT) scan.
- To facilitate operational conduct of the study by:
  - Allowing for a shorter interval between positron emission tomography (PET) scans.
  - Allowing a third PET scan in Part B in case 1 PET scan procedure is not successful.
  - Allowing up to 6 cranial CT scans in Part B (1 before and 1 after each PET scan) to account for potential movement during the PET procedure.
  - Specifying that fasting requirements are only for Part A participants.
  - Allowing vital sign assessment in sitting position.

Minor changes, corrections, and edits to improve accuracy, clarity, and formatting of the protocol have also been included.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

This protocol amendment applies to future participants.

Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Screening Procedural Outline for Parts A and B (IM038010); Table 2-3: Imaging Procedural Outline for Part B (IM038010); Table 3.3.1-1: Risk Assessment; Section 6.3.1: Meals and Dietary Restrictions; Section 9.4.6: Clinical Safety Laboratory Assessments	Specified that fasting is only required for Part A participants.	To reduce study burden for participants with multiple sclerosis (MS) in the study.
Table 2-2: Imaging Procedural Outline for Part A (IM038010); Table 2-3: Imaging Procedural Outline for Part B (IM038010); Section 5.1: Overall Design; Figure 5.1-1: Study Design Schema; Table 7.1-1: Study Interventions;	Reduced minimum interval between 2 PET scans from 3.5 hours to 2 hours.	Facilitate operational conduct and allow for shorter visit duration if 2 PET scans are done on the same day.

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Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 9.1.1.1: PET Assessments		
Table 2-3: Imaging Procedural Outline for Part B (IM038010)	Added footnote "e" to ^{11}C-BMS-986196 tracer administration on Visit 2.	To clarify that third administration is permissible if a PET scan has to be repeated.
Section 3.3 Benefit/Risk Assessment; Section 5.5 Justification for Dose; Table 5.5-1: Radiation Exposure from PET Tracer Administration and CT Scans; Section 9.1.1.1: PET Assessments	• Added text to allow for 2 cranial CT scans (1 before and 1 after each cranial PET scan) in Parts A and B, and specified the maximum number of cranial CT scans in Parts A and B. • Added text to allow for a third PET scan and up to 6 cranial CT scans in Part B.	Facilitate operational conduct by providing the option for an additional PET scan in case 1 PET scan procedure is not successful, and by providing the option for up to 6 CT scans (1 before and 1 after each PET scan) to account for movement of participants with MS during the PET procedure.
Section 3.3 Benefit/Risk Assessment; Table 3.3.1-1: Risk Assessment; Section 5.5 Justification for Dose; Table 5.5-1: Radiation Exposure from PET Tracer Administration and CT Scans	• Estimation of radiation exposure from cranial CT scan was reduced from 1.5 mSv to approximately 0.3 mSv. • In Parts A and B, cumulative exposure from PET and CT scans was updated to account for added options of a third PET scan (Part B only) and additional cranial CT scans before and after each cranial PET scan. • Equivalent duration of average United Kingdom (UK) background radiation was changed to account for maximum new cumulative exposure total. • Increased maximum [redacted] from 5.4% to 8.1%.	• The cranial CT scan sequences used at participating sites result in radiation exposure of approximately 0.3 mSv, not 1.5 mSv, resulting in lower radiation exposure than originally estimated and facilitating up to 3 PET scans and 6 cranial CT scans without increasing maximum radiation exposure relative to the prior versions of the protocol. • The option of a third PET scan adds to the maximum radiation exposure derived from PET tracer. • The cumulative exposure values in Parts A and B change due to lower exposure derived from cranial CT scan and option of a third PET scan. • To account for increased [redacted] following a third PET scan.
Section 5.1 Overall Design, Figure 5.1-1: Study Design Schema	• Corrected spelling to specify that 2 PET-CT or PET-MRI scans must be evaluable in up to 8 study participants (not that study participants must be evaluable).	• To improve accuracy of protocol language.

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Summary of key changes for Protocol Amendment 04		
Section Number & Title	**Description of Change**	**Brief Rationale**
	• Added footnote "a" to Figure 5.1-1. • Added text on maximum blood volume for participants undergoing arterial sampling only, arterial and venous sampling, and undergoing 3 PET scans.	• To ensure that Figure 5.1-1 is consistent with the study design language and that up to 2 participants may be enrolled in Part A, after Part B has been initiated. • To provide more detailed information of the different scenarios and account for the addition of a third PET scan.
Section 9.1.1.1: PET Assessments	• Updated the maximum number of whole-body CT scans to 1. • Removed duplicate assessment of hematology and clinical chemistry for participants in Part B if 2 PET scan visits are performed on the same day.	• To clarify the limits for number of whole-body CT scans in Part A. • To align with footnote in Table 2-3.
Section 9.4.3: Vital Signs	Added sitting position as a new option for assessing Visits 1 and 2 vital signs prior to discharge.	To facilitate site operations.
Section 10.4.2: Primary Endpoint(s)	Changed the window acquisition time frame from Part A Visit 1 to Part A Visit 2.	Correction.
Appendix 2: Study Governance Considerations	Added 2 new sections: BMS Commitment to Diversity in Clinical Trials and Data Protection, Data Privacy, and Data Security.	Added to align with BMS commitment to diversity in clinical trials and to comply with European Union Clinical Trials Regulation (EU-CTR) requirement.
Throughout the protocol	Minor language and formatting changes.	To improve clarity of the protocol.

Overall Rationale for Protocol Amendment 03, 21-Feb-2022

The primary purpose for this amendment is to allow venous blood sampling during cranial positron emission tomography (PET). This would be necessary if emerging data from this ongoing study indicate that a (pseudo) reference region cannot be reliably established, therefore making future studies with ^{11}C-BMS-986196 without arterial input function challenging. This change is being implemented to facilitate future studies with ^{11}C-BMS-986196 without arterial line.

Additional revisions, including to sections of the Protocol Summary, have been made to align the protocol with respect to these changes.

This protocol amendment applies to future participants.

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Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-2: Imaging Procedural Outline for Part A (IM038010)	• Added pregnancy test for Visit 2 • Added venous line placement procedure for venous blood sampling • Added footnote "a" regarding visits for Part A participants prior to and after initiation of Part B	• Pregnancy test was added to Visit 2 to improve consistency with eligibility criteria • Enable venous blood sampling in up to 2 participants of Part A • Clarified visit sequence of newly added participants
Table 2-3: Imaging Procedural Outline for Part B (IM038010)	Added venous line placement procedure for venous blood sampling	Enable venous blood in up to 6 participants of Part B
Section 5: Study Design	• Increased total evaluable participants to up to 16 • Deleted the following text: "Part A must be completed before initiation of Part B" • Increased total Part A participants to up to 8 • Added text to Part A treatment period on when 2 additional participants can be enrolled due to emerging data from Part B • Updated amount of blood to be drawn from Part A and Part B • Updated the maximum amount of blood to be drawn in 24 hours to 420 mL	• Protocol amendment increases maximum total number of participants and maximal number of Part A participants by 2 • Clarified that addition of 2 additional Part A participants is based on emerging data from Part B • Updated maximal blood volume collected, accounting for additional venous blood samples
Table 7.1-1: Study Interventions	Added "up to" 2 doses	Address number of doses administered in Part A participants that have been added as part of the amendment
Section 7.2: Method of Study Intervention Assignment	Updated the total number of enrolled participants to exceed 16 if participants have to be replaced	Protocol amendment increases maximum total number of participants and maximal number of Part A participants by 2
Section 9.1: Efficacy Assessments	• Added text about venous lines for PET assessments • Clarified that 2 additional participants enrolled to Part A will undergo the cranial PET scan with arterial and venous blood samples drawn during the procedure • Added text on when up to 6 participants in Part B may undergo venous and arterial blood sampling	Clarify procedure for collecting venous blood samples in Parts A and B

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Summary of Key Changes for Protocol Amendment 03		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 10.2: Sample Size Determination	• Increased total Part A participants to up to 8 • Increased evaluable participants to up to 16 • Updated the total number of enrolled participants to exceed 16 if participants have to be replaced	Protocol amendment increases maximum total number of participants and maximal number of Part A participants by 2

Overall Rationale for Protocol Amendment 02, 02-Nov-2021

This protocol amendment is being produced [redacted] for the following reasons:

5) Revisions to AE-based stopping rules

- Updated the procedures for study restart after stopping rules have been met.

Revisions apply to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of Key Changes for Protocol Amendment 02		
Section Number & Title	**Description of Change**	**Brief Rationale**
Section 8.4 AE-defined Stopping Rules	Updated the procedure for study restart after stopping rules are met.	Revision was made [redacted]

Overall Rationale for Revised Protocol 01, 22-Oct-2021

This protocol amendment is being produced [redacted] for the following reasons:

6) Revisions to Exclusion Criteria

- Removal of required consultation with the BMS clinical trial physician regarding the eligibility of a participant with any sequelae from a prior SARS-CoV-2 infection.
- Removal of participants with malaria falciparum infection.
- Removal of any exception granted by the Sponsor medical monitor regarding the use of any prescription drugs within 4 weeks or 5 times the elimination half-life (if known), whichever is longer before tracer administration.
- Removal of any exception granted by the Sponsor medical monitor regarding the use of any investigational drugs or placebo within 4 weeks or 5 times the elimination half-life (if known), whichever is longer before tracer administration.

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- Removal of any exception granted by the Sponsor medical monitor with regards to the participant's participation in another clinical trial concurrent with this study. Addition of the investigator assessment on whether or not to enroll the participant meeting this criterion.

7) Revisions to (S)AE-based stopping rules

- Specifying stricter criteria for triggering (S)AE-based stopping rules and specifying the procedures for study restart after stopping have been met.

Revisions apply to future participants enrolled in the study, and where applicable, to all participants currently enrolled.

Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Synopsis	Updated Key Exclusion Criteria	Updated to include changes to exclusion criteria 1l and 1p in Section 6.2.
Section 3.3 Benefit/Risk Assessment, Risks Associated with Use of an Arterial Catheter Section 9.1.1.1 PET Assessments	Changed "experienced physician" to "experienced staff"	Incorporated Administrative Letter 01 that clarified that arterial line placement will be performed by experienced staff. This clarification ensures that arterial line placement is performed according to the standard practice at the participating sites.
Summary and Section 6.2: Exclusion Criterion: 1l	Exclusion criterion 1l was modified to remove the consultation with the BMS clinical trial physician and add examples of sequelae.	Exclusion criterion criteria was updated [redacted]
Summary and Section 6.2: Exclusion Criterion: 1p	Exclusion criterion 1p was modified to remove the exclusion of falciparum.	Exclusion criterion was updated [redacted]
Section 6.2: Exclusion Criterion: 3b Section 7.7.1: Prohibited and/or Restricted Treatments	Exclusion criterion 3b and Section 7.7.1 were modified to remove the exception of any drugs cleared by the Sponsor medical monitor.	Exclusion criterion was updated [redacted]. Section 7.7.1 was updated to be consistent with exclusion criterion.
Section 6.2: Exclusion Criterion: 3c	Exclusion criterion 3c was modified to remove the exception of any drugs	Exclusion criterion was updated [redacted]

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Summary of Key Changes for Protocol Amendment 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
	cleared by the Sponsor medical monitor.	
Section 6.2: Exclusion Criterion: 6c Section 7.7.2: Other Restrictions and Precautions	Exclusion criterion 6c and Section 7.7.2 were revised to remove the exception of any drugs cleared by the Sponsor medical monitor and add the investigator assessment for safety. Examples for non-interventional and lifestyle and dietary intervention studies were also added to the exclusion criterion.	Exclusion criterion was updated [redacted] Section 7.7.2 was updated to be consistent with exclusion criterion.
Section 8.4 AE-defined Stopping Rules	Revised (S)AE-based stopping rules (section title was also updated) and specified the procedure for study restart after stopping rules are met. A minor update was made to Section 8.1 to reflect the changes to Section 8.4.	Revision was made [redacted]

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