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

NCT Number: NCT05064436

Document Date (Date in which document was last revised): 12 April 2024

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 1, OPEN-LABEL, MULTI-PART STUDY TO EVALUATE THE SAFETY, TOLERABILITY, KINETICS, AND BIODISTRIBUTION, AND CNS SIGNAL OF THE PET LIGAND 11C-BMS-986196 IN HEALTHY PARTICIPANTS AFTER INTRAVENOUS ADMINISTRATION AND TO EVALUATE THE SAFETY, TOLERABILITY, KINETICS, AND CNS SIGNAL REPEATABILITY AFTER REPEAT IV ADMINISTRATION IN PARTICIPANTS WITH MULTIPLE SCLEROSIS

PROTOCOL(S) IM038010

VERSION # FINAL 1.0

DATE: 12-APR-2024

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1 BACKGROUND AND RATIONALE

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned final analysis to be completed to support generation of the Clinical Study Report (CSR) for study IM038010 titled "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". [redacted] analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any performed post-hoc or unplanned analyses not identified in this SAP will be clearly identified as such in the CSR. The SAP was prepared in compliance with ICH E9.

Research Hypothesis:

^{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).

This is the first study testing ^{11}C-BMS-986196 as a Positron Emission Tomography (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 multiple sclerosis (MS) to facilitate its use for:

- Assessment of central nervous system (CNS) [redacted] in future clinical studies in patients with 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

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.

Schedule of Analyses:

A final statistical analysis will be conducted after study closure and database lock. No interim analysis is planned for this study.

2 STUDY DESCRIPTION

2.1 Study 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 unbound 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 2.1-1.

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 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.

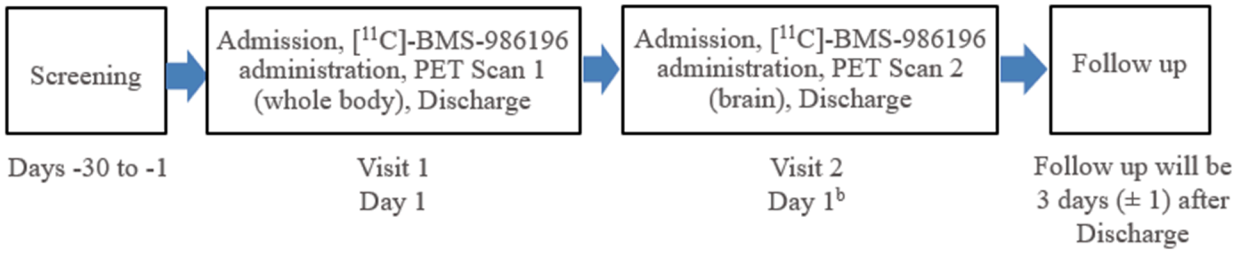
Part C (Quantification of free BTK availability in the humain brain): Up to 12 evaluable healthy adult participants will complete 2 evaluable cranial PET-CT or PET-MRI scans (dependent on equipment availability). The first cranial PET scan will occur on Day 1 after a bolus IV administration of ^{11}C-BMS-986196. After completion of the first evaluable PET scan (on the same day or the day following the PET scan), participants will receive orally adimistered 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-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.

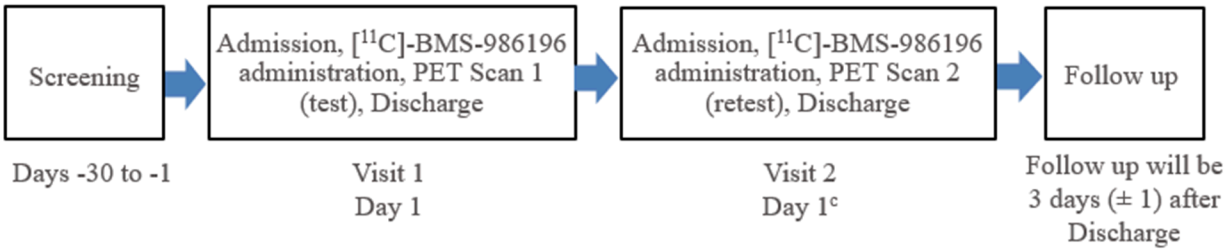
The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schema

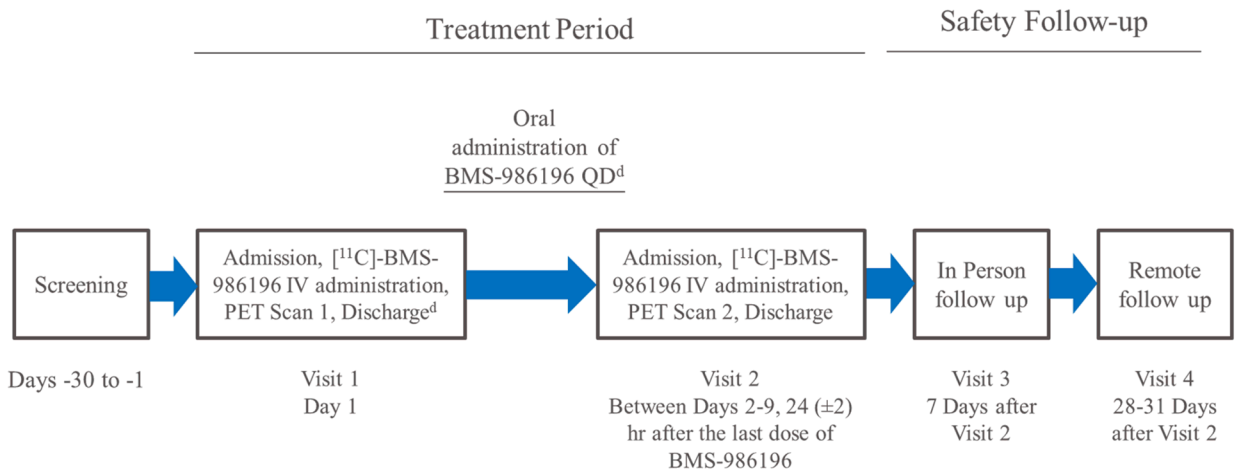
Part A - Safety, Tolerability, and Dosimetry in Healthy Participants[a]



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 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.

2.2 Treatment Assignment

This is a non-randomized, open-label study. Treatment will be assigned to participants in the order of enrolment.

2.3 Blinding and Unblinding

This is a non-randomized, open-label study. Blinding procedures are not applicable.

2.4 Protocol Amendments

Protocol Amendment 1, dated 22-Oct-2021, [redacted] included revisions to the exclusion criteria and to the (S)AE-based stopping rules. These revisions did not affect the statistical analysis outlined in the protocol.

Protocol Amendment 2, dated 02-Nov-2021, [redacted] included revisions to the (S)AE-based stopping rules. These revisions did not affect the statistical analysis outlined in the protocol.

Protocol Amendment 3, dated 21-Feb-2022, included revisions to allow venous blood sampling during cranial PET. These revisions did not affect the statistical analysis outlined in the protocol.

Protocol Amendment 4, dated 09-May-2022, included revisions to accurately account for the radiation exposure resulting from cranial CT scan, to allow a shorter interval between PET scans, to allow a third PET scan in Part B in case of unsuccessful scans, to allow up to 6 cranial CT scans in Part B (1 before and 1 after each PET scan), to specify that fasting requirements are only applicable to Part A participants, and to allow vital signs assessment in sitting position. These revisions did not affect the statistical analysis outlined in the protocol.

Protocol Amendment 5, dated 30-Jun-2023, included revisions to add a novel Part C to the protocol, to quantify free 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.

3 OBJECTIVES

3.1 Primary

The primary objectives of this study are:

- 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.
- To quantify the proportion of free BTK in the brain after administration of unlabeled BMS-986196.

3.2 Secondary

The secondary objective of this study is to assess ^{11}C-BMS-986196 signal characterization.

[redacted]

4 ENDPOINTS

The study endpoints are summarized in Table 4-1.

Table 4-1: Objectives and Endpoints

Objectives		Endpoints
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 • 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 • % Free brain BTK relative to baseline
Secondary	To assess ^{11}C-BMS-986196 signal characterization	• Calculated SUV and V_T in the brain
[redacted]		

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 SAMPLE SIZE AND POWER

The sample size in Parts A to C of the study are 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 and 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.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

Important note: As it was decided to terminate this study earlier and not to follow with the dosing of Part C anymore, the following sections will refer to Parts A and B only. A synoptic CSR will be written for this study.

6.1 Study Periods

Study Day 1 will be defined as the day of first administration of tracer ^{11}C-BMS-986196. The day before the first administration will be defined as Study Day -1, there is no Study Day 0.

For statistical analysis, the following analysis periods will be defined:

- Pre-treatment period: starts at signing of informed consent (ICF) and lasts up to first dosing date/time on Study Day 1 .
- On treatment period: starts at first dosing date/time on Study Day 1 and lasts in each study part.

6.2 Treatment Regimens

Parts A and B of this study are designed as non-randomized, single-arm studies; therefore, participants in each study part will be analyzed as treated for all imaging and safety analyses.

6.3 Populations for Analyses

For analysis, analysis populations as defined in Table 6.3-1 will be used.

Table 6.3-1: Analysis Populations

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.
Response-Evaluable	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 (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 Part B (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 Part B (Per-Protocol 3)

Abbreviations: PET, positron emission tomography.

7 STATISTICAL ANALYSES

SAS® version 9.4 or higher will be used for statistical analyses, tabulations, and graphical presentations.

7.1 General Methods

Unless otherwise noted, descriptive summaries will be presented for continuous variables using number of participants (N), mean, standard deviation (SD), median, minimum, and maximum. Frequency summaries for categorical variables will utilize counts and percentages. Percentages will be rounded to one digit after the decimal and, therefore, may not always sum up to exactly 100%.

Baseline is defined as the last non-missing result prior to first dosing of study treatment (Day 1). Note: For assessments with multiple measurements on Day 1, the value with relative time recorded as “pre-dose”, “pre-infusion” or similar, as appropriate per parameter, will be considered as baseline.

If not otherwise stated and as appropriate per analysis population, summary statistics will be calculated for participants in Part A, participants in Part B, and overall (Parts A and B combined) as appropriate. This will also serve the purpose of directly comparing results from healthy participants and participants with MS.

7.2 Study Conduct

Not appropriate.

7.3 Study Population

7.3.1 Participant Disposition

Participant disposition of the enrolled participants and Safety population (enrolled, entered, completed, discontinued, along with primary reasons for discontinuation, as apropriate) will be summarized separately for the pre-treatment and treatment and study, as appropriate.

7.3.2 Demographic Characteristics

The demographic characteristics will be summarized for the Safety population.

7.3.3 Medical History and Specific Disease History

Not applicable.

7.3.4 Prior and Concomitant Medications and Procedures

Not applicable.

7.4 Extent of Exposure

The time between the first and the second administration of the PET tracer will be derived from the administration dates and times recorded in the CRF and presented in hours.

Exposure in terms of administered dose will be recorded as drug mass as well as radioactive dose. The planned radioactive dose will be recorded in the CRF as well. Summary statistics will be presented for the administered dose per visit for drug mass and radioactive dose, for the cumulative

administered dose for drug mass and radioactive dose, for the cumulative planned radioactive dose, and for the relative radioactive dose intensity. Relative radioactive dose intensity will be derived as:

Relative radioactive dose intensity (%) = Cumulative administered radioactive dose / Cumulative planned radioactive dose *100%.

Treatment exposure will be summarized for the Safety population as follows:

- Number (%) of participants receiving PET tracer ^{11}C-BMS-986196 (1 dose, 2 doses, 3 doses, >3 doses)
- Time (hours) between last administration of ^{11}C-BMS-986196 at Visit 1 and first administration of ^{11}C-BMS-986196 at Visit 2
- Total administered mass (µg) of ^{11}C-BMS-986196 per visit
- Cumulative administered mass (µg) of ^{11}C-BMS-986196
- Total administered radioactive dose (MBq) of ^{11}C-BMS-986196 per visit
- Cumulative administered radioactive dose (MBq) of ^{11}C-BMS-986196
- Cumulative planned radioactive dose (MBq) of ^{11}C-BMS-986196
- Relative radioactive dose intensity (%) of ^{11}C-BMS-986196

7.5 Imaging

Imaging endpoints will be analyzed using descriptive statistics and tables will not include the total column. Two-sided 95% confidence intervals may be presented for some analyses as defined in the following and will be considered descriptive measures of association only. No formal testing for statistical significance will be conducted in this analysis.

Sensitivity analyses of primary and secondary imaging endpoint may be carried out, if deemed necessary, based on the corresponding per-protocol populations as defined in Section 6.3.

In addition to the statistical analysis covered in the SAP, an imaging report will be provided by the imaging vendor at time of final analysis. The imaging report may be reported as an appendix to the synoptic CSR. The imaging report will provide further analyses and results to guide interpretation of the imaging data. In particular, primary imaging endpoints relating to the analysis of radiation dosimetry data and recommendation of the optimal image acquisition window after administration of ^{11}C-BMS-986196 in Part A will only be provided in the imaging report and are therefore not included in the SAP.

Results for relevant quantitative PET parameters will be presented separately for regions of interest (ROI) as appropriate in this study. The list below includes expected ROIs but may not be exhaustive. ROIs to be evaluated in this study will be further specified in the vendor imaging report and the transferred quantitative data.

- Cortical grey matter, Normal appearing white matter, Whole brain (Parts A and B)
- T2 lesions, T2 lesion-free areas (Part B only)

A short description of imaging-related endpoints in this study is provided in Table 7.5-1.

Table 7.5-1: Description of Imaging Endpoints

Parameter	Definition
Radiation dosimetry	Measurement and assessment of radiation exposure and absorption of ionizing radiation in body tissue.
Image acquisition window after tracer administration	Period of time required to collect the imaging data during a scan.
Standardized uptake value (SUV)	Semi-quantitative measurement of tracer uptake in body tissue defined as ratio of radioactivity per unit volume of a region of interest to the radioactivity per unit volume of the whole body.
Volume of distribution (V_T)	Ratio of the radioligand concentration in a region of interest to the radioligand concentration in plasma at equilibrium.

7.5.1 Primary Imaging Endpoints

Radiation dosimetry calculated from PET-CT images in healthy participants: As noted in Section 7.5 above, analysis of radiation dosimetry will be provided in the imaging report and is not included in the SAP.

Image acquisition window after administration of ^{11}C-BMS-986196: As noted in Section 7.5 above, the determination of the image acquisition window after administration of the PET tracer will be provided in the imaging report and is not included in the SAP.

Test-retest repeatability based on standardized uptake value (SUV) of CNS PET images in participants with MS: The test-retest repeatability will be based on a quantitative analysis of cranial PET images and will be evaluated for the Response-Evaluable 3 population (Part B only). Calculated SUV (g/mL) in the brain will be summarized using descriptive statistics and will be presented by visit and for each appropriate ROI.

For each participant in the Response-Evaluable 3 population, the difference between test and retest values will be derived as well as the test-retest repeatability (%), which is defined based upon the absolute value of the difference between test and retest values normalized by their mean:

$$\text{Test-retest difference} = RT - T,$$

$$\text{Test-retest repeatability (\%)} = 100\% - 2 \times \left|\frac{RT-T}{RT+T}\right| \times 100\%,$$

with T being the calculated value for the parameter measured at Visit 1 (test) and RT being the calculated value for the same parameter measured at Visit 2 (retest). Summary statistics of the test-retest difference and test-retest repeatability will be presented for each appropriate ROI.

In addition, the 95% limits of agreement for the difference will be derived for each appropriate ROI as the corresponding mean difference ±1.96 times the standard deviation of the difference.

As sensitivity analysis, tabulation of test-retest analysis of calculated SUV may be repeated, if deemed appropriate, for the Per-Protocol 3 population (Part B only).

Test-retest repeatability based on volume of distribution (V_T) of CNS PET images in participants with MS: The test-retest repeatability of calculated V_T (mL/cm^3) in the brain will be evaluated in the same manner as described for calculated SUV above.

7.5.2 Secondary Imaging Endpoint

To characterize the ^{11}C-BMS-986196 tracer signal, summary statistics will be provided for calculated SUV and V_T in the brain and presented by visit and each appropriate ROI for the Response-Evaluable 2 population (Parts A and B). As sensitivity analysis for the secondary imaging endpoint, the analysis may be repeated, if deemed appropriate, for the Per-Protocol 2 population (Parts A and B).

[redacted]

7.6 Safety

For the calculation of the changes from baseline, baseline will be defined as the last non-missing observation including unscheduled measurements recorded before the first dosing of study treatment.

Data collected from sampling at unscheduled visits or time-points at post-dose will be excluded from summary tables by visit or time-point.

7.6.1 Deaths

All reported deaths after enrolment (i.e., participant has signed the informed consent) will be listed for the Enrolled population.

7.6.2 Adverse Events

All AEs will be coded and grouped into Preferred Terms (PT) by System Organ Class (SOC), using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent adverse events (TEAEs) will be defined as any AEs that start on or after administration of study treatment and until 10 days after last dose of study treatment or date of last study visit, whichever is later.

Only TEAEs will be tabulated. Events will be assigned to the study treatment administered to the participant. For tabulating incidence of TEAEs, the proportion of participants having an TEAE will be calculated as the number of participants experiencing the event, divided by the total number of participants in the Safety population. TEAEs will be summarized by SOC, PT, treatment, and overall.

AE counting rule:

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

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

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

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

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

- Severity/Intensity of event
- Onset date and time

Listings of all recorded AEs will be provided for the Enrolled population.

7.6.3 Serious Adverse Events

All reported serious adverse events (SAEs) if any will be summarized by SOC, PT, treatment, and overall.

7.6.4 Clinical Laboratory Evaluations

A listing of pregnancy test results will be created.

7.6.5 ECG

Summary statistics will be presented for each ECG parameter (heart rate, PR interval, QRS duration, QT interval, QTcF interval) and the corresponding changes from baseline by visit and time-point, for each study part.

7.6.6 Vital Signs and Physical Measurements

Not applicable.

7.6.7 Physical Examination Findings

Frequency and percentage of participants with an abnormal physical examination will be provided by visit.

7.6.8 Allen's Test

Not applicable.

[redacted]

8 CONVENTIONS

8.1 Decimal Places

Unless otherwise specified, minimum and maximum will be reported to the precision as the data collected, and with one more decimal place for the mean, median, and standard deviation. Data recorded or derived with more than 2 digits after the decimal will be displayed with minimum and maximum rounded to 2 decimal places and mean, median, and standard deviation rounded to 3 decimal places in summary tables, and with all decimal places in listings (or as space allows).

8.2 Imputation of Missing Dates for Adverse Events

8.2.1 Incomplete Start Date

Missing day and month:

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only:

- If the month and year are the **same** as the year and month of first dosing date, then the first dosing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day, month, and year:

- No imputation is needed, the corresponding AE will be included as TEAE.

8.2.2 Incomplete Stop Date

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month:

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only:

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

9 CONTENT OF REPORTS

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

10 CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

The statistical analysis of the secondary imaging endpoint will be carried out for the Response-Evaluable 2 population. The protocol erroneously refers to the Response-Evaluable 1 population here, however, this subset would apply to endpoints based on whole body scan data, not cranial scan data.

11 DOCUMENT HISTORY

Table 11-1: Document History

Version Number	Author(s)	Description
1.0	[redacted]	Original Issue

APPENDIX 1 ABBREVIATIONS

Table 11-2: List of Abbreviations

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BMS	Bristol Myers Squibb
BTK	Bruton's Tyrosine Kinase
CNS	Central Nervous System
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CT	Computed Tomography
%CV	Coefficient of Variation
DPP	Data Presentation Plan
ECG	Electrocardiogram
EDC	Electronic Data Capture
[redacted]	[redacted]
GdE	Gadolinium Enhancing
GLP	Good Laboratory Practices
ICH	International Conference on Harmonization
[redacted]	[redacted]
IND	Investigational New Drug
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NCI-CTC	National Cancer Institute - Common Terminology Criteria
PDAP	Protocol Deviation Assessment Plan
PET	Positron Emission Tomography
PT	Preferred Term
ROI	Region of Interest
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	Standard Deviation

Table 11-2: List of Abbreviations

Abbreviation	Description
SE	Standard Error
SI	International System of Units
SOC	System Organ Class
SUV	Standardized Uptake Value
TEAE	Treatment-Emergent Adverse Event
VS	Vital Signs
V_T	Volume of Distribution
WHO-DD	World Health Organization's Drug Dictionary