NOVARTIS

Clinical Development

AAA501/NETSPOT®

CAAA501A11301 / NCT06240741

A prospective, open-label, multi-center, single arm, phase III study of [^{68}Ga]Ga-DOTA-TATE in the diagnosis of patients with neuroendocrine neoplasms (NENs) and healthy volunteers in Japan

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment 1 Final
Release date:	02-Sep-2024
Number of pages:	35

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07-Feb-2024	Prior to FPFV	Creation of final version	N/A - First version	NA
02-Sep-2024	Prior to DBL	Creation of amendment 1	1. Updated the list of abbreviations. 2. Added R to analysis software. 3. Specification added on data included in the analysis, i.e. the items to which the way of reporting as 'ongoing' applies, as well as imaging data included in summaries when a participant has multiple assessments. 4. Addition of subgroup of interest (NET grading and primary site of cancer) 5. Based on eCRF update, clarification added regarding Diagnosis of Disease, NET grading, and the definition of subgroups by NEN classification. 6. Specification added regarding how to show rescreened participants in the summary for patient disposition. 7. Added listing of participants included in each analysis set. 8. Limited NET grading to GEP-NET. Accordingly, Table 2-1 updated to define NET grading. 9. Added time since most recent diagnosis or relapse/progression to the summary of diagnosis and extent of cancer. 10. Clarification added on the population for which summary of time since initial diagnosis and time since most recent relapse/progression will be created. 11. Specification added on data included in concomitant medications, non-drug therapies and procedures. 12. The population for which the listing for central imaging assessment will be provided set as the FAS. 13. Clarification added on how to determine an imaging as readable but not optimal in the supplementary analysis. 14. Added summary of transition of intended treatment plan in the analysis of impact on treatment decision. 15. Weight deleted from summary of notable vital sign values since it is collected only at Day 1 post injection. 16. Specification added on the population for which blood concentration data will be listed, i.e. confining to participants with PK concentration in the FAS.	List of abbreviations Sections 2.1, 2.2, 2.3.1, 2.3.2, 2.4.2, 2.5, 2.6.2, 2.7.4.2, 2.8, 4, 5.1.2.1, 5.5, 5.6, and Section 5.7

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			17. Updated the imputation rules for missing dates of initial diagnosis and most recent relapse/progression. Added specification for cases where the imputed date is later than the date of informed consent. 18. Addition of Sections 5.5, 5.6 and 5.7. 19. Grammatical or editorial corrections.	

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CIM	Conventional Imaging
CM	Concomitant Medications
CSR	Clinical Study Report
CT	Computerized Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFF	Efficacy Analysis Set
EG	Electrocardiogram results
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
FU	Follow-Up
HV	Healthy Volunteer
LB	Laboratory test results
LLOQ	Lower Limit of Quantification
MBq	Mega-Becquerel
MedDRA	Medical Dictionary for Regulatory Activities
MiNEN	Mixed Neuroendocrine-non-neuroendocrine Neoplasm
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NEC	Neuroendocrine Carcinoma
NEN	Neuroendocrine Neoplasm
NET	Neuroendocrine Tumor
NPV	Negative Predictive Value
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic(s)
PET	Positron Emission Tomography
PK	Pharmacokinetic(s)
PPV	Positive Predictive Value
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class

SPECT	Single-photon Emission Computerized Tomography
SSTR	Somatostatin Receptor
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TP	True Positive
VS	Vital Signs
WBC	White blood cells
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CAAA501A11301, a prospective, open-label, phase III study of [^{68}Ga]Ga-DOTA-TATE in patients with neuroendocrine neoplasms (NENs) and healthy volunteers in Japan.

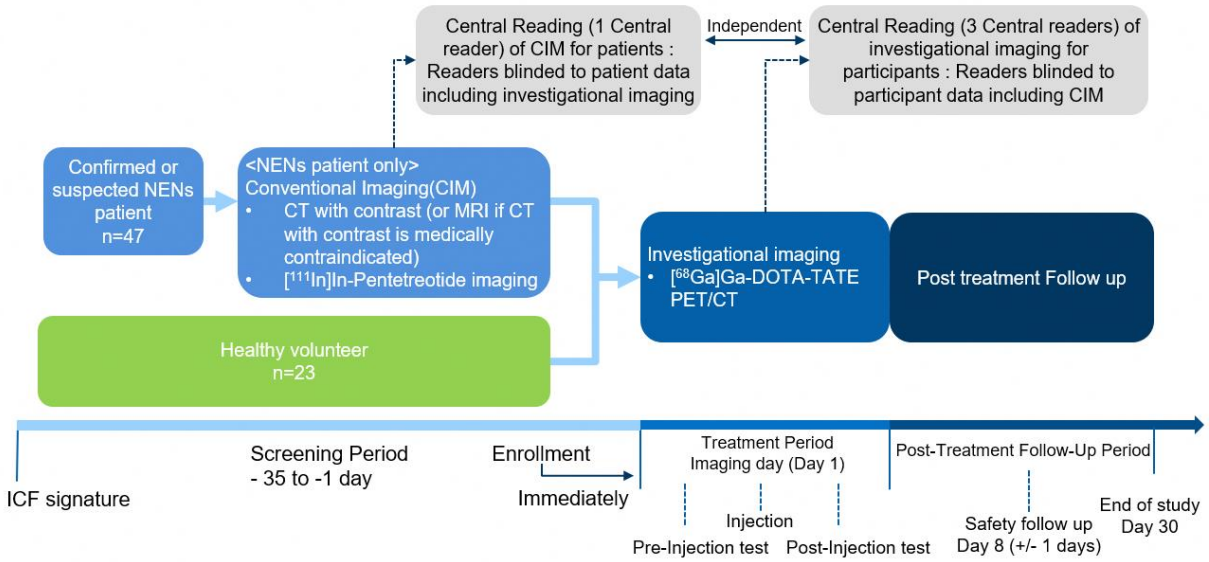
The content of this SAP is based on protocol CAAA501A11301 version 01. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This prospective, open-label, multi-center, single arm, phase III study, will enroll approximately 47 adult male or female participants with NENs and 23 HVs. Of all the participants with NENs, the number of participants with suspected NENs is limited to up to 5 with negative conventional imaging (CIM) result by central read in order to enroll sufficient number of participants with positive result in CIM. Negative CIM result by central read is applicable for patients who do not show any lesions based on CIM by central read. All eligible participants will undergo [^{68}Ga]Ga-DOTA-TATE PET/CT imaging. [^{68}Ga]Ga-DOTA-TATE will be administered intravenously at a single dose of 2 MBq/kg (0.054 mCi/kg) of body weight up to a maximum total dose of 200 MBq (5.4 mCi), and imaging will be acquired 40 to 90 minutes after the intravenous injection of [^{68}Ga]Ga-DOTA-TATE.

The purpose of this study is to evaluate the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging compared with the CIM as standard of truth in patients with NENs and HVs. The data from this study will provide the evidence for diagnosis use of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging in patient with NENs in Japan.

Figure 1-1 Study design



NENs: Neuroendcrine neoplasms, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, CIM: Conventional Imaging, PET: Positron Emission Tomography

1.2 Study objectives, endpoints and estimands

Endpoints will be evaluated based on central read unless otherwise specified.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the subject-level sensitivity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [68Ga]Ga-DOTA-TATE positive participants (TP participants) among CIM positive participants (TP or FN participants).
• To evaluate the subject-level specificity of [68Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [68Ga]Ga-DOTA-TATE negative participants (TN participants) among CIM negative participants (TN or FP participants).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate subject-level positive predictive values (PPV) of [68Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who are positive on both [68Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TP participants) among participants who are positive on [68Ga]Ga-DOTA-TATE PET/CT imaging (TP or FP participants).
• To evaluate subject-level negative predictive values (NPV) of [68Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who are negative on both [68Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TN participants) among participants who are negative on [68Ga]Ga-DOTA-TATE PET/CT imaging (TN or FN participants).
• To evaluate subject-level accuracy of [68Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who have consistent results (i.e. TP or TN participants) among all participants assessed by [68Ga]Ga-DOTA-TATE PET/CT imaging and CIM.
• To evaluate region-level sensitivity of [68Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [68Ga]Ga-DOTA-TATE positive regions (TP regions) among CIM positive regions (TP or FN regions).
• To evaluate region-level specificity of [68Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [68Ga]Ga-DOTA-TATE negative regions (TN regions) among CIM negative regions (TN or FP regions).
• To evaluate region-level positive predictive values (PPV) of [68Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions which are positive on both [68Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TP regions) among regions which are positive on [68Ga]Ga-DOTA-TATE PET/CT imaging (TP or FP regions).
• To evaluate region-level negative predictive values (NPV) of [68Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions who are negative on both [68Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TN regions) among regions which are negative on [68Ga]Ga-DOTA-TATE PET/CT imaging (TN or FN regions).
• To evaluate region-level accuracy of [68Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions which have consistent results (i.e. TP or TN regions) among all regions assessed by [68Ga]Ga-DOTA-TATE PET/CT imaging and CIM.
• To evaluate number of lesions detected by [68Ga]Ga-DOTA-TATE PET/CT imaging and each CIM at region-level.	• Number of lesions detected by [68Ga]Ga-DOTA-TATE PET/CT imaging and each CIM at region-level.
• To evaluate the impact of [68Ga]Ga-DOTA-TATE PET/CT imaging on treatment decision.	• Percentage of patients who underwent a change in intended treatment plan attributed to the [68Ga]Ga-DOTA-TATE PET/CT imaging as assessed by pre and post imaging questionnaires.

Objective(s)	Endpoint(s)
• To evaluate inter-reader variability.	• Inter-reader agreement on [68Ga]Ga-DOTA-TATE PET/CT imaging.
• To evaluate safety and tolerability of [68Ga]Ga-DOTA-TATE.	• Incidence of Treatment emergent adverse event (TEAE) within 8 days after [68Ga]Ga-DOTA-TATE administration.
• To evaluate PK of [68Ga]Ga-DOTA-TATE.	• Pharmacokinetic parameters (AUCinf, AUClast, Cmax, Tmax, T1/2, CL, Vz etc.).
• To evaluate lesion-level concordance for SSTR between [68Ga]Ga-DOTA-TATE PET/CT imaging local read and local histopathology results.	• Lesion-level concordance rate for SSTR between [68Ga]Ga-DOTA-TATE PET/CT imaging local read and local histopathology result among lesions that local histopathology result are available.

1.2.1 Primary estimand(s)

The primary clinical question of interest is: What is the probability that [^{68}Ga]Ga-DOTA-TATE PET/CT imaging truly detects tumor lesion(s) in subject-level for NENs using CIM (including [^{111}In]In-Pentetreotide SPECT/CT and High Resolution CT with contrast (or MRI if CT with contrast is medically contraindicated) as standard of truth).

The justification for the primary estimand is that it will capture the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging in detecting tumor lesion(s) in NENs subjects. For this reason, participants with confirmed or suspected NENs will be investigated with CIM obtained on or before screening phase (HVs will be categorized as CIM negative without performing CIM) and confirmed or suspected NENs and HVs will be investigated with [^{68}Ga]Ga-DOTA-TATE PET/CT imaging on treatment phase, and the results of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be compared against the results of CIM as standard of truth. The primary estimands are described by the following attributes:

Primary estimand 1:

1. Population: Patients who show at least one lesion based on CIM by central read, received [^{68}Ga]Ga-DOTA-TATE, completed a PET/CT scan and had a central read of the [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.
2. Variable: The result of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (positive (i.e., showing at least one lesion) or negative (i.e., not showing any lesion)). In the population above, a participant with positive on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging corresponds to True positive (TP) and a participant with negative on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging corresponds to False negative (FN).
3. Treatment of interest: [^{68}Ga]Ga-DOTA-TATE injected as a single intravenous dose of 2 MBq/kg (0.054 mCi/kg) of body weight up to a maximum total dose of 200 MBq (5.4 mCi).
4. Intercurrent events: None
5. Summary measure: Estimate of proportion of participants who test positive on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TP) among those who are CIM positive (TP+FN according to [^{68}Ga]Ga-DOTA-TATE PET/CT imaging) (subject-level sensitivity), along with 95% confidence interval.

Primary estimand 2:

1. Population: Participants who do not show any lesions based on CIM by central read or are HVs, received [^{68}Ga]Ga-DOTA-TATE, completed a PET/CT imaging and had a central read of the [^{68}Ga]Ga-DOTA-TATE PET/CT imaging. The population selection depends on the results of central read, therefore patients with NENs can be included if applicable, in addition to HVs who will be categorized as CIM negative without performing CIM.
2. Variables: The result of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (positive or negative). In the population above, a participant who test positive on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging corresponds to False positive (FP) and a participant who test negative on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging corresponds to True negative (TN).
3. Treatment of interest: [^{68}Ga]Ga-DOTA-TATE injected as a single intravenous dose of 2 MBq/kg (0.054 mCi/kg) of body weight up to a maximum total dose of 200 MBq (5.4 mCi).
4. Intercurrent events: None.
5. Summary measure: Estimate of proportion of participants who test negative on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TN) among those who are CIM negative (TN+FP according to [^{68}Ga]Ga-DOTA-TATE PET/CT imaging) (subject-level specificity), along with 95% confidence interval.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis. SAS version 9.4 or later and R version 4.3.1 or later will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

Only one final analysis is planned for the co-primary endpoints. All statistical analyses will be performed using all data collected in the database up to the database lock date. The database lock date for the final analysis of study data will be established after all enrolled participants have completed End of study visit (Last Patient Last Visit).

All events with start date before or on the database lock date and not having documented end date will be reported as 'ongoing'. This approach applies, in particular, to adverse events, prior anti-neoplastic medication/ anti-neoplastic radiotherapies, and concomitant medication/ non-drug therapies/ non-drug procedures reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

For participants who have both High Resolution CT with contrast and MRI imaging as CIM, the results of MRI will be used for summaries. For participants who have multiple imaging assessments of the same modality on different imaging dates, the results on the latest assessment date will be used for summaries.

Participant categorization

For some efficacy analyses (subject/region-level sensitivity, specificity, PPV, NPV and accuracy), HVs will be categorized as CIM negative population (TN or FP) without CIM. If there are participants enrolled as patients with suspected NENs but founded not to have NENs based on CIM, they will be also categorized in this population.

Other than those above:

Analyses will be conducted by patients with confirmed/suspected NENs and HVs. Results will be presented by population unless otherwise specified.

General analysis conventions

Qualitative data (e.g., gender, race, etc.) will be summarized by frequencies and percentages; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. N, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum).

2.1.1 General definitions

Study treatment/ drug

Study treatment/ drug is [^{68}Ga]Ga-DOTA-TATE administered intravenously at a dose of 2 MBq/kg (0.054 mCi/kg) of body weight up to a total maximum dose of 200 MBq (5.4 mCi) even if no [^{68}Ga]Ga-DOTA-TATE PET/CT scan was acquired.

Study day

The study day describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

Baseline

The last available assessment including unscheduled assessments before injection of study drug is taken as "baseline" value or "baseline" assessment.

If participants have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before dosing of investigational drug.
2. On-treatment period: from day of dosing of investigational drug to 8 days after dosing of investigational drug. (i.e. Day 1 – Day 9)
3. Post-treatment period: starting 9 days after dosing of investigational drug. (i.e. start from Day 10)

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all enrolled participants.

Enrollment will take place at the time when all eligibility requirements are confirmed.

Efficacy Analysis Set

The Efficacy Analysis Set (EFF) comprises all enrolled participants who were administered with [^{68}Ga]Ga-DOTA-TATE. Patients with confirmed/suspected NENs must have both results of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM. HVs must have result of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging. If at least 1 central reader cannot judge results for all CIM or

[^{68}Ga]Ga-DOTA-TATE PET/CT imaging due to imaging quality, the results are considered as "Not evaluable". Those participants will be excluded from the EFF.

A result considered “Not evaluable” if the following scenarios happened:

- There is no subject-level result due to poor imaging quality or insufficient coverage.
- There is no accurate subject-level result because one or more region-level result are not readable and all other region-level result are negative.

Safety Set

The Safety Set comprises all participants who received any dose of [^{68}Ga]Ga-DOTA-TATE.

Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PAS) includes all participants who provided at least one evaluable PK concentration. A profile is considered evaluable if all of the following conditions are satisfied:

- Participant received the study drug
- Participant provided at least one primary PK parameter

2.2.1 Subgroup of interest

Subgroup analyses will be conducted when the co-primary objectives of subject-level sensitivity and specificity are met.

The objective of the efficacy subgroup analysis is to demonstrate homogeneity of diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT in the following subgroups.

For CIM positive population,

- NEN classification (NET, NEC, MiNEN, Other NEN)*
- NET grading (NET G1, NET G2, NET G3 (GEP-NET patients only))
- Functionality (Functional_All/ Carcinoid/ Gastrinoma/ Glucagonoma/ Insulinoma/ VIPoma/ Other, Non-functional)**
- Primary site of cancer***

* For NET and NEC, results will be presented regardless of the number of patients within each category. For MiNEN and Other NEN, only subgroup category results including 5 or more patients will be presented.

** Only subgroup category results including 5 or more patients will be presented.

*** Results of each category including 5 or more patients will be presented.

For CIM negative population,

- Population (patients, HV)****

**** Analysis will be conducted only if 5 or more patients are included.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Screen phase disposition will be summarized for all screened participants. The number (%) of screened/ enrolled/ not enrolled participants and the primary reason for not completing screen phase will be summarized. For rescreened participants, only status of rescreening will be included in the summaries.

Information of informed consent from each screened participant will be listed.

For enrolled participants in the FAS, all disposition information will be summarized and listed.

Protocol deviations

Protocol deviations will be summarized for the FAS.

The number (%) of participants with any reportable protocol deviation will be tabulated by deviation category (as specified in the Edit Check Specifications).

All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized for the FAS.

Participants included in each analysis set will be listed.

2.3.2 Demographics and other baseline characteristics

Demographics and other baseline data including disease characteristics will be summarized descriptively for the FAS and the EFF.

Basic demographic and baseline characteristics

All demographic and baseline disease characteristics data will be summarized and listed.

Categorical data (age groups: 18 – < 65 and ≥ 65 years, gender, race, ECOG performance status) will be summarized by the number (%) of participants with missing data.

Continuous data (age, weight, body mass index (BMI)) will be summarized by descriptive statistics (N, mean, standard deviation, median, 25th percentile, 75th percentile, minimum, and maximum).

Diagnosis and extent of cancer

Diagnosis and extent of cancer including tissue biopsy assessment will be summarized and listed. Categorical data and continuous data will be summarized by same method with demographics.

The summary includes:

- Diagnosis of Disease

- NEN classification
- NET grading
- Time since initial diagnosis (months)
- Primary Site of Cancer
- Stage at Initial Diagnosis
- Stage at Time of Study Entry
- Time since Most Recent Relapse/Progression (months)
- Time since most recent diagnosis or relapse/progression (months)
- Histological Grade
- Result of Ki67 proliferation index (%)
- Functionality
- SSTR expression status

Diagnosis of Disease consists of NEN and Other. NEN classification consists of NET, NEC, MiNEN, and Other NEN. NET grading will be summarized only for GEP-NET as per Table 2-1. Primary Site of Cancer corresponding to GEP-NET is described in Section 5.6.

Table 2-1 NET grading

Grading	Histological Grade	Ki67 (%)
NET G1	Well differentiated	< 3%
NET G2		3-20%
NET G3		>20%
Unknown	Well differentiated	Missing
	Poorly differentiated Undifferentiated Unknown	-

Time since initial diagnosis (months) will be calculated as (the date of study informed consent – the date of initial diagnosis of NEN +1)/ 30.4375. Summary will be done for participants with definitive diagnosis on or before the date of informed consent.

Time since most recent relapse/progression (months) will be calculated as (the date of study informed consent – the date of most recent relapse/progression of NEN +1)/ 30.4375. Summary will be done for participants with relapse/progression with definitive diagnosis on or before the date of informed consent.

Time since most recent diagnosis or relapse/progression (months) will be calculated as:

- For participants with primary onset: (the date of study informed consent – the date of initial diagnosis of NEN +1)/ 30.4375,
- For participants with relapse/progression*: (the date of study informed consent – the date of most recent relapse/progression of NEN +1)/ 30.4375.

  * This includes participants who have both values of the date of initial diagnosis and the date of most recent relapse/progression.

Medical history

Medical history and current medical conditions will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listing.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The actual received [^{68}Ga]Ga-DOTA-TATE dose (MBq), [^{68}Ga]Ga-DOTA-TATE dose per 1 kg (MBq/kg) and time interval (minutes) from injection of [^{68}Ga]Ga-DOTA-TATE to PET/CT acquisition start will be summarized by descriptive statistics using the Safety Set.

All dose administration records will be listed.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

Prior anti-cancer therapy analyses will be performed for the FAS and the EFF.

The number (%) of participants who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy and prior anti-neoplastic surgery will be summarized.

Prior anti-neoplastic medications will be summarized by total number of regimens and setting by lowest ATC class and preferred term (PT).

Prior anti-neoplastic radiotherapies will be summarized by setting.

Prior anti-neoplastic surgeries will be summarized by type of surgery and presence of residual disease.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery. Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding WHO-DD and MedDRA version will be included in the footnote in the tables/listings.

Concomitant medications, non-drug therapies and procedures

Concomitant medications analyses including non-drug therapies and procedures will be performed for the Safety Set.

Concomitant medications, non-drug therapies and procedures starts on or after the day of dosing of investigational drug but not more than 8 days after dosing of investigational drug (i.e. Day 1 – Day 9) or starts prior to and continues after the start of study treatment.

Only medications, non-drug therapies and procedures collected in the eCRF 'Prior or Concomitant Medications' and 'Prior or Concomitant Non-drug therapies and Procedures' will be included in concomitant medications, non-drug therapies and procedures; those collected in

the eCRF 'Prior Anntineoplastic Medications', 'Prior Antineoplastic Radiotherapies', and 'Prior Antineoplstic Surgeries' will not be included.

Concomitant medications will be coded using the WHO-DD and summarized by lowest ATC class and PT. Non-drug therapies and procedure will be coded using MedDRA and summarized by SOC and PT. Details regarding WHO-DD and MedDRA version will be included in the footnote in the tables/listings.

The listing includes all prior and concomitant medications, non-drug therapies and procedures will be provided. Any concomitant therapies starting and ending prior to the start of study treatment or starting 9 days after dosing of investigational drug (i.e. start from Day 10) will be flagged in the listing.

2.5 Analysis supporting primary objectives

All analyses supporting primary objectives will be performed for the EFF unless otherwise specified.

2.5.1 Primary endpoint(s)

The co-primary endpoints of the study are subject-level sensitivity and specificity.

Subject-level sensitivity

Subject-level sensitivity is defined as the proportion of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging positive participants (i.e. TP participants) among CIM positive participants (i.e. TP or FN participants).

Subject-level specificity

Subject-level specificity is defined as the proportion of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging negative participants (i.e. TN participants) among CIM negative participants (i.e. TN or FP participants).

Table 2-2 Sensitivity and Specificity

		Conventional Imaging (CIM)	
		Positive	Negative
[^{68}Ga]Ga-DOTA-TATE PET/CT imaging	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)
Sensitivity: TP / (TP + FN), Specificity: TN / (TN + FP)			

Where TP, FP, TN, FN participants are defined as follows:

- TP participants are those who show at least one lesion based on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM by central read.
- FP participants are those who show at least one lesion based on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging but do not show any lesion based on CIM by central read.
- TN participants are those who do not show any lesion based on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM by central read.

- FN participants are those who do not show any lesion based on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging but show at least one lesion based on CIM by central read.

2.5.2 Statistical hypothesis, model, and method of analysis

To address the co-primary objectives, following analyses will be conducted.

Subject-level sensitivity and its 95% exact confidence interval (CI) will be calculated based on the binomial distribution. The lower bound of the 95% exact CI for subject-level sensitivity should be greater than 0.7 to attain the first co-primary objective.

Subject-level specificity and its 95% exact CI will be calculated based on the binomial distribution. The lower bound of the 95% exact CI for subject-level specificity should be greater than 0.6 to attain the second co-primary objective.

Listing for central imaging assessments will be provided for the FAS.

2.5.3 Handling of intercurrent events

Not applicable.

2.5.4 Handling of missing values not related to intercurrent event

This is a diagnostic study and primary endpoints are calculated on the basis of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM assessments. The primary analysis will be conducted for the EFF and missing data related to primary endpoints will not occur in the population.

2.5.5 Sensitivity analyses

Not applicable.

2.5.6 Supplementary analyses

If the primary endpoints of subject-level sensitivity and specificity are met, following supplementary analyses will be conducted.

- TP, FP, FN, TN, sensitivity, specificity and corresponding exact 95% CIs will be shown for each of the 3 central readers.
- If there are participants who are excluded from the EFF, those participants' results will be assumed all positive or all negative respectively and each analysis will be performed for primary endpoints. Assumption of handling as all negative will be conservative for sensitivity and assumption of handling as all positive will be conservative for specificity.
- If there are participants with readable but not optimal [^{68}Ga]Ga-DOTA-TATE PET/CT imaging, analysis excluding those participants will be repeated for primary endpoints. If at least one reader reports readable but not optimal, then the imaging of the participant will be considered readable but not optimal.
- The subgroup analyses estimating subject-level sensitivity or specificity with corresponding exact 95% CIs will be performed. Subgroups of interest are specified in Section 2.2.1.

2.6 Analysis supporting secondary objectives

All analyses supporting secondary objectives will be performed for the EFF.

2.6.1 Secondary endpoint(s)

Subject-level assessments

Subject-level positive predictive values (PPV) is defined as the proportion of TP participants among [^{68}Ga]Ga-DOTA-TATE PET/CT imaging positive participants (i.e. TP or FP participants).

Subject-level negative predictive values (NPV) is defined as the proportion of TN participants among [^{68}Ga]Ga-DOTA-TATE PET/CT imaging negative participants (i.e. TN or FN participants).

Subject-level accuracy is defined as the proportion of TP and TN participants among all patients in the EFF (i.e. TP+TN+FP+FN participants).

Region-level assessments

Region-level sensitivity is defined as the proportion of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging positive regions (TP regions) among CIM positive regions (i.e. TP or FN regions).

Region-level specificity is defined as the proportion of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging negative regions (TN regions) among CIM negative regions (i.e. TN or FP regions).

Region-level PPV is defined as the proportion of regions which are positive on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TP regions) among [^{68}Ga]Ga-DOTA-TATE PET/CT imaging positive regions (i.e. TP or FP regions).

Region-level NPV is defined as the proportion of regions which are negative on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TN regions) among [^{68}Ga]Ga-DOTA-TATE PET/CT imaging negative regions (i.e. TN or FN regions).

Region-level accuracy is defined as the proportion of regions which are CIM and [^{68}Ga]Ga-DOTA-TATE PET/CT imaging positive (TP regions) or negative (TN regions) among regions detected by CIM and [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (i.e. TP+TN+FP+FN regions).

Where TP, FP, TN, FN regions are defined as follows:

- TP regions are the regions which show at least one lesion based on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM by central read.
- FP regions are the regions which show at least one lesion based on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging but do not show any lesion based on CIM by central read.
- TN regions are the regions which do not show any lesion based on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM by central read.
- FN regions are the regions which do not show any lesion based on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging but show at least one lesion based on CIM by central read.

Number of lesions detected by imaging

Number of lesions is defined as number of lesion identified at [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and each CIM (i.e. [^{111}In]In-Pentetreotide SPECT/CT and High Resolution CT with contrast (or MRI if CT with contrast is medically contraindicated)).

Impact on treatment decision

Impact on treatment decision is defined as change of intended treatment plan collected from physician at pre and post [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.

Inter-reader variability

Inter-reader variability for [^{68}Ga]Ga-DOTA-TATE PET/CT imaging is defined as agreement rate among reader determinations assessed by Fleiss' Kappa statistics.

Lesion-level concordance rate for SSTR

Lesion-level concordance rate for SSTR is defined as the proportion of lesions which are positive or negative on both local read of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and local histopathology among lesions detected by local histopathology.

2.6.2 Statistical hypothesis, model, and method of analysis

Subject-level assessments

Subject-level PPV, NPV, accuracy will be summarized with corresponding exact 95% CI.

Region-level assessments

Region-level sensitivity, specificity, PPV, NPV, accuracy will be summarized respectively with corresponding exact 95% CI by regions.

Region consists of liver, pancreas, gastrointestinal, lymph nodes and others.

Number of lesions detected by imaging

Descriptive statistics for number of lesions will be provided by region-level and subject-level.

Regarding [^{68}Ga]Ga-DOTA-TATE PET/CT imaging, descriptive statistics of number of lesions for each of the 3 central reader , and 3 readers' mean number of lesions will be presented.

Regarding CIM, descriptive statistics of number of lesions detected by [^{111}In]In-Pentetreotide SPECT/CT and High Resolution CT with contrast (or MRI if CT with contrast is medically contraindicated) will be presented respectively.

Listing for number of lesions will be provided.

Impact on treatment decision

The number (%) of participants for intended treatment plan at pre and post [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and the number (%) of participants for whom the intended treatment plan has changed and for whom it has not changed will be summarized. The number (%) of

participants will also be summarized for each combination of transition of intended treatment plan.

Listing for intended treatment plan will be provided.

Inter-reader variability

Each central read subject-level result (positive or negative), inter-reader variability (%) and its 95% CI will be presented.

Inter-reader variability will be assessed by Fleiss' Kappa (κ_1) statistic (Fleiss 1971). Refer to Section 5.4.2 for details on Fleiss' Kappa.

An additional table will be presented to show the distribution of agreements with the number (%) of scans agreed by two readers and the number (%) of scans agreed by all three readers.

If one of the central readers is changed during the study and the total amount of its read is more than 30% of the total number of participants who have evaluable [^{68}Ga]Ga-DOTA-TATE PET/CT, inter-reader variability for each combination (before the change and after the change) and its normality 95% CI will be presented additionally. The distribution of agreements with the number (%) of scans agreed by two readers and the number (%) of scans agreed by all three readers will be also presented for each combination.

Lesion-level concordance rate for SSTR

For patients who have histopathology assessments, total number of patients, result of local histopathology (lesion-level positive or negative), result of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging by local read (lesion-level positive or negative), numbers (%) of lesion-level concordance and its exact 95% CI will be presented.

All local histopathology assessments will be listed.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

This is a diagnostic study and secondary endpoints (subject-level PPV/ NPV/ accuracy and region-level sensitivity/ specificity/ PPV/ NPV/ accuracy) are calculated on the basis of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM assessments. The secondary analyses will be conducted for the EFF and missing data related to these endpoints will not occur in the population.

For other secondary endpoints, missing data will not be imputed.

2.6.5 Sensitivity analyses

No sensitivity analyses are planned for the secondary endpoints.

2.6.6 Supplementary analyses

No supplementary analyses are planned for the secondary endpoints.

2.7 Safety analyses

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by group (i.e. Patients with confirmed/suspected NENs and HVs).

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries).

2.7.1 Adverse events (AEs)

Adverse events are coded using MedDRA terminology. The latest MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

AE summaries will include all AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. All AEs collected in the 'AE' eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number (%) of subjects having at least one AE, having at least one AE in each primary SOC and for each PT using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PT will be sorted within primary SOC in descending frequency. The sort order for the PT will be based on their frequency in patient's arm.

The following adverse event summaries will be produced;

- Overview of AEs
- AEs regardless of study treatment relationship by SOC and PT
- AEs regardless of study treatment relationship by PT
- AEs with suspected relationship to study treatment by SOC and PT
- AEs with suspected relationship to study treatment by PT
- Serious Adverse Events (SAEs) regardless of study treatment relationship by SOC and PT
- SAEs regardless of study treatment relationship by PT
- SAEs with suspected relationship to study treatment by SOC and PT
- SAEs with suspected relationship to study treatment by PT
- AEs requiring additional therapy by SOC and PT

For the legal requirements of ClinicalTrials.gov, two required tables of on-treatment AEs which are non-SAEs with an incidence greater than 5%, and on-treatment death and SAEs will be provided by SOC and PT.

If for the same patient, several consecutive AEs (regardless of study treatment relationship, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.7.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest are not set for [^{68}Ga]Ga-DOTA-TATE PET/CT.

2.7.2 Deaths

All deaths (on-treatment and post-treatment) will be summarized.

All deaths will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

2.7.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries will be generated separately for hematology, and biochemistry tests:

For laboratory tests where grades are defined by CTCAE version 5.0:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value.

For laboratory tests where grades are not defined by CTCAE version 5.0:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

Listing of laboratory data will be produced with values flagged to show the corresponding CTCAE version 5.0 grades if applicable and the classifications relative to the laboratory normal ranges.

All urinalysis and coagulation data will be listed.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Number (%) of participants with abnormality will be provided by time-point (Screening and Day1_post-injection). All ECG data will be listed.

2.7.4.2 Vital signs

Notable vital sign values in participants with non-notable values at baseline (e.g. systolic blood pressure (BP) >90 and <180 mmHg for analysis of systolic BP) will be summarized by time-point (Day1_post-injection and Safety FU (i.e. Day 8)). A listing of all vital signs' assessments will be produced, and notable values will be flagged.

Table 2-3 Notable vital sign values

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Systolic blood pressure (mmHg)	≥180 with increase from baseline of ≥20	≤90 with decrease from baseline of ≥20
Diastolic blood pressure (mmHg)	≥105 with increase from baseline of ≥15	≤50 with decrease from baseline of ≥15
Pulse rate (bpm)	≥100 with increase from baseline of >25%	≤50 with decrease from baseline of >25%
Respiratory rate (breaths per minute)	> 22	<14
Body temperature (°C)	≥39.1	-

2.8 Pharmacokinetic endpoints

Descriptive summary statistics of [^{68}Ga]Ga-DOTA-TATE blood concentration data will be provided by participant, and visit/sampling time point, including the frequency of concentrations below the LLOQ and reported as zero.

Summary statistics will include n, mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.

Drug concentrations below LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%, and as zero for all other calculations including calculation of PK parameters.

All individual and overlaid concentration-time profiles for [^{68}Ga]Ga-DOTA-TATE blood concentration will also be represented graphically (including spaghetti plots and mean plots with SD) on the linear and semi-log view based on nominal time.

All individual [^{68}Ga]Ga-DOTA-TATE blood concentration data will be listed by time point for participants with PK concentration in the FAS.

The PAS will be used in all pharmacokinetic data analysis and PK summary statistics.

Pharmacokinetic variables:

The following pharmacokinetic parameters will be determined using the actual recorded sampling time s and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher):

AUCinf, AUClast, Cmax, Tmax, T1/2, Lambda_z, CL and Vz.

In addition, the following pharmacokinetic parameters may be determined, if deemed appropriate, using the actual recorded sampling time s and two-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher):

V1, K10, K12, K21, AUC, K10 T1/2, Alpha, Beta, Alpha T1/2, Beta T1/2, V2, CL.

Bio-fluid concentrations will be expressed in mass per volume units and, if deemed necessary, other units (e.g. radioactivity per volume). All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics. Refer to Section 5.7 for the derivation of mass-based dose and concentrations.

Pharmacokinetic parameters will be provided by participants. Descriptive statistics of all pharmacokinetic parameters will include n, arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum, and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter. These summaries will be presented for PK parameters from non-compartmental method(s) and two-compartmental method(s), separately.

PK parameters data will be listed (including AUC %extrapolated) by participant and for PK parameters from non-compartmental method(s) and two-compartmental method(s), separately.

Table 2-4 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time^{-1}) may also be used for terminal elimination rate constant (time^{-1})
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume x time^{-1})
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

Not applicable.

[redacted]

[redacted]

2.13 Interim analysis

Not applicable.

3 Sample size calculation

The primary endpoints of the study are subject-level sensitivity and specificity based on central read.

The sample size was calculated based on the following assumptions for primary endpoints.

- Assumptions for subject-level sensitivity: expected sensitivity of 90% and threshold of 70%
- Assumptions for subject-level specificity: expected specificity of 90% and threshold of 60%

The expected sensitivity and specificity are respectively set as 90% based on the systematic review publication on [^{68}Ga]Ga-DOTA-TATE (Deppen et al 2016). The thresholds of 70% for sensitivity and 60% for specificity are set by referring to phase III study of [64Cu]Cu-DOTA-TATE (Delpassand et al 2020)and the thresholds will be considered reasonable to show clinical relevant diagnostic performance in this study. For sensitivity, 47 participants with positive result in CIM are required to reject the null hypothesis of sensitivity ≤ 70% with 1-sided alpha level of 2.5% and ≥ 90% power with exact binomial test. For specificity, 23 participants with negative result in CIM are required to reject the null hypothesis of specificity ≤ 60% with 1-sided alpha level of 2.5% and ≥ 90% power with exact binomial test. Therefore, 47 confirmed/suspected NEN patients (expected to be positive in CIM) and 23 HVs (negative in CIM) are required. As a result, 70 participants are required as Efficacy Analysis Set (EFF) in total. The study enrollment will continue until 70 participants in the EFF.

Table 3-1 Sensitivity of power to changes in number of participants

N_Sensitivity	Power for Sensitivity	N_Specificity	Power for Specificity
42	87.9%	28	94.5%
43	86.7%	27	95.3%
44	85.4%	26	96.0%
45	92.4%	25	90.2%
46	91.6%	24	91.5%
47	90.7%	23	92.7%

The N for sensitivity is based on NEN patients with positive result in CIM. The N for specificity is based on NEN patients with negative result in CIM in addition to HVs (i.e., some NEN patients out of 47 patients will be used for specificity estimation instead of sensitivity if the result in CIM is negative).

4 Change to protocol specified analyses

Analyses related to AESI are not planned since AESI are not set for [^{68}Ga]Ga-DOTA-TATE PET/CT (Section 2.7.1.1).

Supplementary analysis for the primary endpoints which excludes participants with readable but not optimal [^{68}Ga]Ga-DOTA-TATE PET/CT imaging judged by central read is added since the readability categories was updated (Section 2.5.6).

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The complete date of dose administration is required for this study. Completely or partially missing date will not be imputed and should be considered as a data issue and the statistician should contact the data manager of the study.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date, then
	  • If stop date contains a full date and stop date is earlier than date of dose administration, then set start date = 01JanYYYY
	  • Else set start date = date of dose administration.
	• If available year > year of date of dose administration, then 01JanYYYY
	• If available year < year of date of dose administration, then 01JulYYYY

day	• If available month and year = month and year of date of dose administration, then
	  • If stop date contains a full date and stop date is earlier than date of dose administration, then set start date= 01MONYYYY.
	  • Else set start date = date of dose administration.
	• If available month and year > month and year date of dose administration, then 01MONYYYY
	• If available month and year < month year of date of dose administration, then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=date of dose administration plus 8 days not > (death date, database lock date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data database lock will be shown as ‘ongoing’ rather than the end date provided.

5.1.2.1 Other imputations

For the date of initial diagnosis and the date of most recent relapse/progression, missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan. When the imputed date is later than the date of informed consent, it will be re-imputed with the date of informed consent.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (specify version used in the RAP). The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, these data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as ‘<X’ (i.e. below limit of detection) or ‘>X’, prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential.

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mmol/L) = Calcium (mmol/L) + 0.02 [40 (g/L) - Albumin (g/L)]

For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Subject-level sensitivity, subject-level specificity and corresponded 95% CI will be calculated based on the binomial distribution (implemented using SAS procedure FREQ with EXACT statement for one-way tables) (Clopper and Pearson 1934).

5.4.2 Analysis supporting secondary objective(s)

For subject-level assessments and region-level assessments, their estimation and 95% CI will be calculated based on the binomial distribution (implemented using SAS procedure FREQ with EXACT statement for one-way tables) (Clopper and Pearson 1934).

For inter-reader variability, it will be assessed by Fleiss' Kappa (κ_1) statistic (Fleiss 1971) defined below:

$$\kappa_1 = \frac{\bar{P}-\bar{P}_e}{1-\bar{P}_e}.$$

Let N represent the total number of participants who have evaluable [^{68}Ga]Ga-DOTA-TATE PET/CT, n the number of central readings per participants received ($n = 3$), and k the number of outcome categories ($k = 2$). Participants are indexed by $i = 1, \ldots, N$ and categories are indexed by $j = 1, \ldots, k$. Let n_{ij} represent the number of readers who assigned the ith participant to the jth category. Then

$$P_i = \frac{1}{n(n-1)}\sum_{j=1}^{k} n_{ij}\left(n_{ij}-1\right) \text{ and } \bar{P} = \frac{1}{N}\sum_{i=1}^{N} P_i \,;$$

$$p_j = \frac{1}{Nn}\sum_{i=1}^{N} n_{ij} \text{ and } \bar{P}_e = \sum_{j=1}^{k} p_j^2.$$

A contingency table of N row by 2 (the number of outcome categories) will be obtained to summarize the frequency of agreements among the 3 readers for each case and each patient-level outcome (i.e. positive, negative). The counts across each of the N rows will sum up to 3 (number of readers).

Based on the contingency table as described above, a Fleiss's Kappa statistic and corresponding 95% confidence interval will be estimated based on asymptotic estimation of the standard error (i.e. $\widehat{se}(\kappa_1) = \frac{\sqrt{2}}{\sum_{j=1}^{k} p_j(1-p_j)\sqrt{Nn(n-1)}}\sqrt{\left(\sum_{j=1}^{k} p_j\ \left(1-p_j\right)\right)^2 - \sum_{j=1}^{k} p_j(1-p_j)(1-2p_j)}$

(Fleiss, Nee, Landis 1979; Fleiss J, Levin B, Paik MC 2003) and the normality assumption (i.e. 95% CI can be calculated as: $\kappa_1 \pm 1.96\widehat{se}(\kappa_1)$).

5.5 Classification of NEN

Entries as Other in the eCRF Diagnosis of Disease are classified as NET, NEC, or Other NEN based on specified terms according to the Table 5-3. NENs not specified in Table 5-3 will be classified as Other NENs, and a separate .xlsx file will be created to specify the details as needed. Diseases other than NEN will be classified as Other.

Table 5-3 Classification of NEN

Terminology	Classification of NEN
Carcinoid	NET
Merkel cell carcinoma	NEC
Mixed Neuroendocrine-non-neuroendocrine Neoplasm (MiNEN)	MiNEN
Paraganglioma	Other NEN

5.6 Primary Site of Cancer corresponding to GEP-NET

GEP-NET to which NET grading will be applied is defined as patients with following Primary Site of Cancer in the eCRF Diagnosis of Disease.

- Anal canal
- Appendix
- Cecum
- Colon
- Colon, ascending
- Colon, descending
- Colon, sigmoid
- Duodenum
- Esophagus
- Fundus of the stomach
- Gastroesophageal junction
- Greater curvature of the stomach
- Ileum
- Ileum, terminal
- Jejunum
- Left colon
- Lower third of the esophagus
- Middle third of the esophagus
- Pancreas
- Pancreatic duct
- Rectum

- Right colon
- Small intestine
- Stomach
- Stomach lesser curvature
- Transverse colon
- Upper third of the esophagus

5.7 Derivation of Mass-Based Dose and Concentrations

Blood concentration and dose values will be determined by radioactivity measurements performed at the clinical sites. Radioactivity-based concentration values will be converted to mass-based concentration values using the specific activity of the dosing solution (MBq of radioactivity/µg of ligand), taking into account the times at which the specific activities are measured, doses are administered, samples are collected and samples are measured. Radioactivity-based dose values will be converted to mass-based dose values using the fixed amount of mass dose of DOTA-TATE cold kit (40 µg) and radioactivity values after radiolabeling, taking into account the times at which radioactivity values are measured and doses are administered. All necessary information needed to perform these conversions will be captured in the dose preparation, study treatment, gamma counter calibration and blood collection eCRFs. The detailed instructions for how to perform these conversions will be described in a separate document (supplement to SAP).

6 Reference

Clopper CJ, Pearson ES (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.

Delpassand ES, Ranganathan D, Wagh N, et al (2020) 64Cu-DOTATATE PET/CT for Imaging Patients with Known or Suspected Somatostatin Receptor-Positive Neuroendocrine Tumors: Results of the First U.S. Prospective, Reader-Masked Clinical Trial. J Nucl Med; 61(6):890-6.

Deppen SA, Blume J, Bobbey AJ, et al (2016) 68Ga-DOTATATE Compared with 111In-DTPA-Octreotide and Conventional Imaging for Pulmonary and Gastroenteropancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. J Nucl Med; 57(6):872-8.

Fleiss J. L. (1971). Measuring nominal scale agreement among many raters. Psychological bulletin; 76(5): 378-382.

Fleiss J, Levin B, Paik MC (2003) Statistical Methods for Rates and Proportions, 3rd Ed, Wiley Series in Probability and Statistics.

Fleiss J, Nee J, Landis J (1979) . The large sample variance of kappa in the case of different sets of raters. Psychological bulletin; 86(5): 974-977.

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.