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Clinical Trial Protocol Title:

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

Clinical Trial Protocol Number: CAAA501A11301 / NCT06240741

Version Number: v01 (Clean)

Compound: AAA501

Brief Title: A prospective, open-label study of [^{68}Ga]Ga-DOTA-TATE in patients with neuroendocrine neoplasms (NENs) and healthy volunteers in Japan

Study Phase: III

Sponsor Name: Novartis, Eckert & Ziegler Radiopharma GmbH

Regulatory Agency Identifier Number(s): Not applicable

Approval Date: 29-NOV-2023 (content final)

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Amendment 1 (29-NOV-2023)

As of the release of this protocol amendment, study has not started, and no sites are initiated. No participants are enrolled.

Amendment rationale

The purpose of this amendment is to:

- Correct the components of regions for Regional-Level Assessment.
- Update the clinical laboratory parameters for clarification.

Other editorial changes, reformatting, and corrections are also made throughout the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

List of changes to protocol:

- Section 1.1: Brief Title has been revised to match the Brief Title in the cover page.
- Table 8-4: Chemistry: “Glucose (fasting)” has been updated to “Plasma Glucose (fasting)”.
- Section 8.9.1: Language in the section has been revised to “Not Applicable”.
- Section 9.4.1: Regional-Level Assessment: “duodenum” has been revised into “gastrointestinal”.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

A prospective, open-label study of [^{68}Ga]Ga-DOTA-TATE in patients with neuroendocrine neoplasms (NENs) and healthy volunteers in Japan

Purpose

To evaluate the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging compared with conventional imaging (CIM) as standard of truth in patients with neuroendocrine neoplasms (NENs) and healthy volunteers (HVs)

Study Indication /Medical Condition:

Neuroendocrine neoplasms (NENs)

Treatment type

Drug

Study type

Interventional

Objectives, Endpoints, and Estimands:

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary	
• To evaluate the subject-level sensitivity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs. • To evaluate the subject-level specificity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [^{68}Ga]Ga-DOTA-TATE positive participants (TP participants) among CIM positive participants (TP or FN participants). • Proportion of [^{68}Ga]Ga-DOTA-TATE negative participants (TN participants) among CIM negative participants (TN or FP participants).
Secondary	
• To evaluate subject-level positive predictive values (PPV) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who are positive on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TP participants) among

	participants who are positive on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TP or FP participants).
• To evaluate subject-level negative predictive values (NPV) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who are negative on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TN participants) among participants who are negative on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TN or FN participants).
• To evaluate subject-level accuracy of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who have consistent results (i.e. TP or TN participants) among all participants assessed by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM
• To evaluate region-level sensitivity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [^{68}Ga]Ga-DOTA-TATE positive regions (TP regions) among CIM positive regions (TP or FN regions).
• To evaluate region-level specificity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [^{68}Ga]Ga-DOTA-TATE negative regions (TN regions) among CIM negative regions (TN or FP regions).
• To evaluate region-level positive predictive values (PPV) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions which are positive on both [^{68}Ga]Ga-DOTA-TATE PET/CT imagings and CIM (TP regions) among regions which are positive on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TP or FP regions).
• To evaluate region-level negative predictive values (NPV) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions which are negative on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TN regions) among regions which are negative on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TN or FN regions).
• To evaluate region-level accuracy of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions which have consistent results (i.e. TP or TN regions) among all regions assessed by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM
• To evaluate the number of lesions detected by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and each CIM at region-level.	• Number of lesions detected by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and each CIM at region-level.
• To evaluate the impact of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging on treatment decision.	• Percentage of patients who underwent a change in intended treatment plan attributed to the [^{68}Ga]Ga-DOTA-TATE imaging as assessed by pre and post imaging questionnaires.
• To evaluate inter-reader variability.	• Inter-reader agreement on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.
• To evaluate safety and tolerability of [^{68}Ga]Ga-DOTA-TATE.	• Incidence of Treatment emergent adverse event (TEAE) rate within 8 days after [^{68}Ga]Ga-DOTA-TATE administration.
• To evaluate PK of [^{68}Ga]Ga-DOTA-TATE.	• Pharmacokinetic parameters (AUCinf, AUClast, Cmax, Tmax, T1/2, CL, Vz etc.).

• To evaluate lesion-level concordance for somatostatin receptor (SSTR) between [^{68}Ga]Ga-DOTA-TATE PET/CT imaging local read and local histopathology results.	• Lesion-level concordance rate for SSTR between [^{68}Ga]Ga-DOTA-TATE PET/CT imaging local read and local histopathology result among lesions that local histopathology result are available.
[redacted]	

Trial Design:

This is a prospective, open-label, multi-center, single arm, phase III study to evaluate the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging compared with conventional imaging (CIM) including High Resolution CT with contrast (or MRI if CT with contrast is medically contraindicated) and [^{111}In]In-Pentetreotide SPECT/CT as standard of truth in patients with NENs and HVs.

Approximately 47 patients with NENs and 23 HVs will be enrolled. Of all the participants with NENs, the number of participants with suspected NENs is limited to up to 5 with negative CIM by central read. Negative CIM by central read is applicable for patients who do not show any lesions based on CIM by central read. [^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be read by 3 independent readers who will be blinded to any other participant's data including CIM. In addition, CIM as standard of truth will be read by an independent reader who will be blinded to [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and any other participant's data.

Brief Summary:

The purpose of this study is to evaluate the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging compared with CIM as standard of truth in patients with NENs and HVs. The

data from this study will provide the evidence for diagnosis of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging in patient with NENs in Japan.

All enrolled participants will undergo [^{68}Ga]Ga-DOTA-TATE PET/CT imaging. [^{68}Ga]Ga-DOTA-TATE will be administered intravenously at a 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 PET/CT imaging will be acquired 40 to 90 minutes after the intravenous administration of [^{68}Ga]Ga-DOTA-TATE.

- Duration of screening period is up to 35 days
- Imaging period will be completed within one day followed by safety follow up visit (Day 8) after imaging day (Day 1)

Treatment of interest

[^{68}Ga]Ga-DOTA-TATE will be administered intravenously at a 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 PET/CT imaging will be acquired 40 to 90 minutes after the intravenous injection of [^{68}Ga]Ga-DOTA-TATE.

Number of Participants

Approximately 70 participants (47 patients with NENs and 23 HVs) will be enrolled. Of all the participants with NENs, the number of participants with suspected NENs is limited to up to 5 patients with negative CIM by central read.

Key Inclusion criteria

1. Signed informed consent must be obtained prior to participation in the study

2. Participants must be adults ≥ 18 years of age

3. ECOG performance status 0-2

4. For patient with NENs only: Participants with confirmed NENs based on histopathology, imaging and other relevant examination, or with suspected NENs which localization cannot be confirmed by CIM

5. For HVs only: Male or female participant in good health condition as determined by no clinically significant findings from medical history, physical examination, vital signs, lab test and ECG

Key Exclusion criteria

1. Inability to complete the needed investigational and conventional imaging due to any reason (severe claustrophobia, inability to lie still for the entire imaging time, etc.)

2. Any additional medical condition, serious intercurrent illness, concomitant cancer or other extenuating circumstance that, in the opinion of the Investigator, would indicate a significant risk to safety or impair study participation

3. Known allergy, hypersensitivity, or intolerance to [^{68}Ga]Ga-DOTA-TATE and [^{111}In]In-Pentetreotide

4. Therapeutic use of any somatostatin analogue except for the following washout period
• Short-acting analogs of somatostatin can be used up to 24 hours before injection of [^{68}Ga]Ga-DOTA-TATE.

• Long-acting analogs of somatostatin can be used up to 28 days before injection of [^{68}Ga]Ga-DOTA-TATE.
5. Prior administration of a radiopharmaceutical unless 10 or more half-lives have elapsed before injection of [^{68}Ga]Ga-DOTA-TATE

6. Use of other investigational drugs within 30 days before screening

Treatment Groups:

All screening procedures must be completed within 35 days prior to imaging day. Enrollment should occur within the 35-days screening period once all eligibility criteria are met.

All enrolled participants will undergo [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and come back to the hospital at safety follow up visit (Day 8) after imaging day (Day 1) for safety follow up assessment.

Data Monitoring/Other Committee:

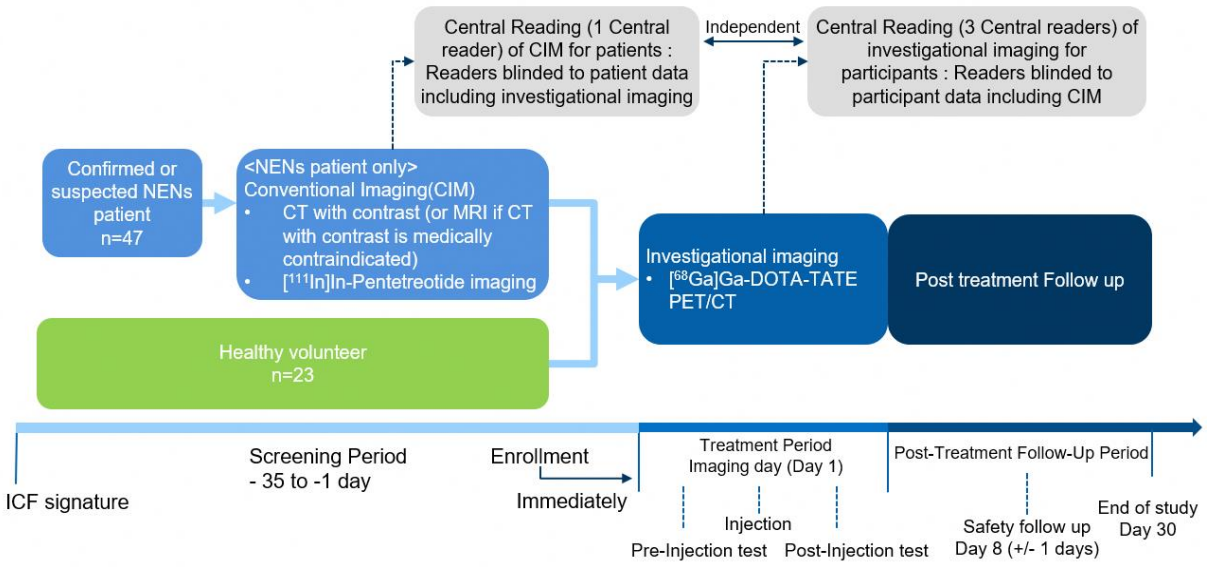
Not applicable.

Key words

[^{68}Ga]Ga-DOTA-TATE, Neuroendocrine Neoplasms (NENs), PET/CT, Diagnostic performance, Sensitivity, Specificity

1.2 Schema

Figure 1-1 Study design



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

1.3 Schedule of activities (SoA)

The SoA lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, the adverse events and concomitant medications not previously reported must be recorded on the electronic Case Report Form (eCRF).

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, while patient is at rest, followed by vital signs, and blood sampling.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	**Screening**	**Treatment**			**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Imaging day**			**Safety follow up**	**EOS**
Days	**-35 to -1**	**1**			**8 ±1**	**30**
Time (post-dose)	**-**	**Pre-injection**	**Injection**	**Post-injection**	**-**	**-**
Informed consent	X					
Inclusion / Exclusion criteria	X					
Medical history/current medical conditions	X					
Demography	X					
Diagnosis and Extent of cancer	X[1,2]					
Enrollment	X					
Physical Examination	S			S	S	
ECOG performance score	X					
Body Height	X					
Body Weight		X				
Vital Signs	X	X		X	X	
Electrocardiogram (ECG)	X			X		
Hematology	X	X			X	
Clinical Chemistry	X	X			X	
Urinalysis	X	X			X	
Coagulation	X	X			X	
Pregnancy testing (Serum / Urine), if applicable	S					
PK blood collection		X[3]		X[3]		
[^{111}In]In-Pentetreotide SPECT/CT	X[1,4,5]					

Period	**Screening**	**Treatment**			**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Imaging day**			**Safety follow up**	**EOS**
Days	**-35 to -1**	**1**			**8 ±1**	**30**
Time (post-dose)	**-**	**Pre-injection**	**Injection**	**Post-injection**	**-**	**-**
High Resolution CT with contrast (or MRI if CT with contrast is medically contraindicated)	X[1,4]					
[^{68}Ga]Ga-DOTA-TATE injection			X			
[^{68}Ga]Ga-DOTA-TATE PET/CT imaging				X[6]		
Histopathology, if applicable	X[1,7]					X[1,8]
Patient Management Questionnaire	2 times: Before and until Safety follow up after having the results of the [^{68}Ga]Ga-DOTA-TATE PET/CT imaging assessment in local read of PET/CT imaging. [1]					
Adverse Events	All (S) AE monitoring and (S) AE recording and reporting will begin at the time pf consent and will continue up to 8 days after [^{68}Ga]Ga-DOTA-TATE injection (i.e. Day 9). On and after Day10, SAEs should be reported only if the investigator suspects a causal relationship to study treatment. The presence of study treatment related SAE can be confirmed by phone at EOS.					
Prior/Concomitant Medication	Collected until 8 days after [^{68}Ga]Ga-DOTA-TATE injection (i.e. Day 9). On and after Day10, when the investigator suspects that SAEs are related to study treatment, their relevant medications should be also reported.					
Prior/Concomitant Non-drug therapies	Collected until 8 days after [^{68}Ga]Ga-DOTA-TATE injection (i.e. Day 9). On and after Day10, when the investigator suspects that SAEs are related to study treatment, their relevant therapies should be also reported.					
Prior/Concomitant Non-drug Procedures	Collected until 8 days after [^{68}Ga]Ga-DOTA-TATE injection (i.e. Day 9). On and after Day10, when the investigator suspects that SAEs are related to study treatment, their relevant procedures should be also reported.					
Prior antineoplastic therapy(Medication, Radiation, Surgery)	X[1]					

Period	**Screening**	**Treatment**			**Post-Treatment Follow-Up**	
Visit Name	**Screening**	**Imaging day**			**Safety follow up**	**EOS**
Days	**-35 to -1**	**1**			**8 ±1**	**30**
Time (post-dose)	**-**	**Pre-injection**	**Injection**	**Post-injection**	**-**	**-**
Disposition	X			X		X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Only for the patients with NENs
[2] In case definitive diagnosis has not been confirmed at Screening, this will be performed at Treatment, Post-Treatment Follow-Up and even after EOS and documented in eCRF.
[3] Please refer to Table 8-5 regarding the time points.
[4] CIM assessment performed as a part of clinical practice within 2 months prior to imaging day even before informed consent, can be used as standard reference as long as imaging quality meets study defined criteria.
[5] If SPECT/CT is not available in the clinical site, SPECT can be acceptable.
[6] Imaging will be acquired 40 to 90 minutes after the intravenous administration
[7] In case pathology from retrospective biopsy even before informed consent is available, the result can be evaluated.
[8] If indicated, biopsy/surgery should be performed within 30 days after Imaging day.

2 Introduction

2.1 Study rationale

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

2.2 Background

NENs are malignant tumors that develop in the lungs, gastrointestinal tract, and other organs and show various clinical symptoms. The most common primary site varies by race, with the lung being the most common in white patients, and the rectum being the most common in Asian patients (Yao et al 2008). Gastroenteropancreatic NENs are common in the Japanese population and the age-adjusted incidence rate of gastroenteropancreatic NENs was approximately 3.5 cases/year per 100,000 people in Japan (Masui et al 2020). Neuroendocrine markers (synaptophysin, chromogranin A, etc.), various diagnostic imaging technologies (ultrasonography, CT, MRI, FDG-PET/CT, somatostatin receptor (SSTR) scintigraphy), and histopathologies are used in diagnosis of NENs (Clinical Practice Guidelines for Gastroenteropancreatic Neuroendocrine Neoplasms 2019). The treatment of NENs is mainly radical surgery and drug therapy, and the first-line curative treatment is surgical resection when tumors are localized. Hence, accurate localization diagnosis and disease staging are important to determine the indication for surgery.

A distinct feature shared by NENs is the over-expression of SSTRs, particularly SSTR type 2 (SSTR2), on the membrane's plasma, which makes SSTRs suitable molecular targets for specific diagnostic and therapeutic ligands (Reubi 2003, Volante et al 2007). This has led to the approval of [^{177}Lu]Lu-DOTA-TATE, a radioligand therapy targeting SSTR, in Japan in 2021 for the indication of "somatostatin receptor-positive neuroendocrine tumors". In order to select appropriate patients for this new drug therapy, it is important to confirm the SSTR expression.

SSTR imagings are widely used to identify SSTR-positive lesions or to evaluate the expression of SSTR in lesions. [^{111}In]In-Pentetreotide was firstly approved in US in 1994 and had been used around the world over the past decades. Recently, the metallic positron emitter, gallium (^{68}Ga), has become of great interest because of its suitable radiophysical properties; its positron yield is high and accounts for 89% of all disintegrations. The radionuclide has a half-life of 68 min matching the pharmacokinetics of many peptides and other small molecules which have rapid blood clearance, quick diffusion and target localization. ^{68}Ga-labeled somatostatin analogues such as, [^{68}Ga]Ga-DOTA-TOC, [^{68}Ga]Ga-DOTA-NOC and [^{68}Ga]Ga-DOTA-TATE, have been largely tested in preclinical and clinical settings, showing high binding affinity to SSTR2 and good uptake in SSTR2-expressing NENs (Reubi et al 2000, Froidevaux et al 2002, Antunes et al 2007) , and became the gold standard imaging for the patient with SSTR positive NENs (Ambrosini et al 2022, NCCN Guidelines 2022, Pavel et al 2020, Sundin et al 2017, Hope et al 2023). In Japan, [^{111}In]In-Pentetreotide was approved as a radiopharmaceutical for

the indication of "somatostatin receptor scintigraphy in the diagnosis of neuroendocrine neoplasms" in 2015, but any ^{68}Ga-labeled somatostatin analogues has not been approved yet.

[^{68}Ga]Ga-DOTA-TATE

[^{68}Ga]Ga-DOTA-TATE is a radiolabeled somatostatin analog that has high affinity for SSTR2. It is composed of the somatostatin peptide analog Octreotate, coupled to the metal-ion chelating moiety DOTA. It can be radiolabeled with ^{68}Ga for molecular imaging with PET and binds to cells expressing SSTR. NetSpot® (Gallium Ga 68 dotate (USAN)) is a kit for radiopharmaceutical preparation of [^{68}Ga]Ga-DOTA-TATE, approved in the USA, Canada and Switzerland for the localization of SSTR-positive neuroendocrine tumors (NETs) after radiolabeling with ^{68}Ga.

Several clinical studies with [^{68}Ga]Ga-DOTA-TATE have been published. Srirajaskanthan et al. (Srirajaskanthan et al 2010) demonstrated that in patients with negative or equivocal [^{111}In]In-Pentetreotide findings, [^{68}Ga]Ga-DOTA-TATE PET identifies additional lesions and may alter management in many cases. Kabasakal et al. (Kabasakal et al 2012) compared [^{68}Ga]Ga-DOTA-TATE and [^{68}Ga]Ga-DOTA-NOC, which were found to have similar diagnostic accuracy. However, [^{68}Ga]Ga-DOTA-TATE seems to have a higher lesion uptake and may have a potential advantage. In another study, Wild et al. (Wild et al 2013) indicated that [^{68}Ga]Ga-DOTA-NOC had greater sensitivity for detecting liver metastases, but [^{68}Ga]Ga-DOTA-TATE showed greater sensitivity detecting bone metastases. Furthermore, the investigators found that [^{68}Ga]Ga-DOTA-TATE had lower background activity, resulting in better imaging properties (ability to detect faint lesions). Hofman et al. and Walker et al. (Hofman et al 2012, Walker et al 2013) described the dosimetry of [^{68}Ga]Ga-DOTA-TATE and demonstrated that patient radiation exposure from [^{68}Ga]Ga-DOTA-TATE is lower than that from [^{111}In]In-Pentetreotide for a whole-body scan. [^{68}Ga]Ga-DOTA-TATE also provides superior image quality compared to [^{111}In]In-Pentetreotide while significantly shortening examination time by a full day.

Schmid-Tannwald et al. (Schmid-Tannwald et al 2013) demonstrated the superior sensitivity of [^{68}Ga]Ga-DOTA-TATE PET/CT compared to MRI in the detection of pancreatic NETs.

A study from Sandström et al. (Sandström et al 2013) explored the biodistribution and radiation dosimetry of [^{68}Ga]Ga-DOTA-TATE compared to [^{68}Ga]Ga-DOTA-TOC. The study found that the effective radiation dose for a 100 MBq administration was identical for both compounds. With respect to biodistribution, there was little difference between the two compounds, with [^{68}Ga]Ga-DOTA-TATE showing a somewhat slower washout from liver (possibly due to the result of slightly greater retention in liver metastases which were present in the majority of patients).

Further details on [^{68}Ga]Ga-DOTA-TATE can be found in the Investigator's Brochure (IB).

2.3 Benefit/Risk assessment

Various retrospective and prospective studies provided the evidence of significant diagnostic benefit for [^{68}Ga]Ga-DOTA-TATE (Refer to Section 2.2 and Investigator's Brochure).

The published data and report from commercial use consistently demonstrates that imaging with [^{68}Ga]Ga-DOTA-TATE is well tolerated. No serious or severe adverse events were observed,

and no participants had a trial related event requiring additional medical care (Deppen et al 2016b). The number of patients exposed to [^{68}Ga]Ga-DOTA-TATE can be estimated as 171,613 cumulatively until 30-Nov-2022 in the post marketing experience. There is no new or changing safety signal; the benefit/risk assessment was considered to remain favorable and unchanged.

[^{68}Ga]Ga-DOTA-TATE contributes to a participant's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

As this is a diagnostic study participants enrolled are not expected to derive direct benefit even though it is expected that new lesions maybe identified in some participants as a consequence of this study and these participants may benefit from a more appropriate management plan.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Appropriate eligibility criteria are included in this protocol.

The risk-benefit ratio is expected to be favorable to [^{68}Ga]Ga-DOTA-TATE. Additional details of the nonclinical and clinical experience with [^{68}Ga]Ga-DOTA-TATE are provided in the IB.

3 Objectives, endpoints, and estimands

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

Table 3-1 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 [^{68}Ga]Ga-DOTA-TATE positive participants (TP participants) among CIM positive participants (TP or FN participants).
• To evaluate the subject-level specificity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [^{68}Ga]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 [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who are positive on both [^{68}Ga]Ga-DOTA-TATE PET/CT imagings and CIM (TP participants) among participants who are positive on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TP or FP participants).
• To evaluate subject-level negative predictive values (NPV) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who are negative on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TN participants) among participants who are negative on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TN or FN participants).
• To evaluate subject-level accuracy of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of participants who have consistent results (i.e. TP or TN participants) among all participants assessed by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM.

Objective(s)	Endpoint(s)
• To evaluate region-level sensitivity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [^{68}Ga]Ga-DOTA-TATE positive regions (TP regions) among CIM positive regions (TP or FN regions).
• To evaluate region-level specificity of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging for NENs.	• Proportion of [^{68}Ga]Ga-DOTA-TATE negative regions (TN regions) among CIM negative regions (TN or FP regions).
• To evaluate region-level positive predictive values (PPV) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions which are positive on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TP regions) among regions which are positive on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TP or FP regions).
• To evaluate region-level negative predictive values (NPV) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions who are negative on both [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM (TN regions) among regions which are negative on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (TN or FN regions).
• To evaluate region-level accuracy of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.	• Proportion of regions which have consistent results (i.e. TP or TN regions) among all regions assessed by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM.
• To evaluate number of lesions detected by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and each CIM at region-level.	• Number of lesions detected by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and each CIM at region-level.
• To evaluate the impact of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging on treatment decision.	• Percentage of patients who underwent a change in intended treatment plan attributed to the [^{68}Ga]Ga-DOTA-TATE PET/CT imagings as assessed by pre and post imaging questionnaires.
• To evaluate inter-reader variability.	• Inter-reader agreement on [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.
• To evaluate safety and tolerability of [^{68}Ga]Ga-DOTA-TATE.	• Incidence of Treatment emergent adverse event (TEAE) within 8 days after [^{68}Ga]Ga-DOTA-TATE administration.
• To evaluate PK of [^{68}Ga]Ga-DOTA-TATE.	• Pharmacokinetic parameters (AUCinf, AUClast, Cmax, Tmax, T1/2, CL, Vz etc.).
• To evaluate lesion-level concordance for SSTR between [^{68}Ga]Ga-DOTA-TATE PET/CT imaging local read and local histopathology results.	• Lesion-level concordance rate for SSTR between [^{68}Ga]Ga-DOTA-TATE PET/CT imaging local read and local histopathology result among lesions that local histopathology result are available.
[redacted]	

3.1 Primary estimands

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 [^{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.

3.2 Secondary estimands

Not applicable.

4 Study design

4.1 Overall design

Refer to Section 1.2 Schema for study design figure.

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 CIM by central read in order to enroll sufficient number of participants with positive result in CIM. Negative CIM 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.

Screening

Participants must sign an informed consent form (ICF) prior to any study specific screening evaluations. All screening procedures must be completed within 35 days prior to Imaging day. All procedures described in the Assessment Schedule Table 1-2 must be carried out to confirm the eligibility.

Enrollment

Until Imaging day in the Treatment period, all participants will be assessed for eligibility. Enrollment will take place when all eligibility requirements described in the Assessment Schedule Table 1-2 are confirmed, prior to Imaging day in the Treatment period. After the registration, the tests which are defined in the Table 1-2 as pre-injection should be performed. To calculate the volume of the medication, the weight should be measured. All enrolled participants will be administered intravenously at a 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 after 40-90 minutes from the injection, the participants will undergo [^{68}Ga]Ga-DOTA-TATE PET/CT imaging. This visit should be completed within one day.

Post-Treatment Follow-Up

After the injection of [^{68}Ga]Ga-DOTA-TATE, all participants will be followed for safety with a post imaging follow-up visit (Day 8 +/- 1 day).

A participant may choose to discontinue follow-up components of the study at any time.

4.2 Scientific rationale for study design

The design of this imaging study was chosen to evaluate diagnostic performance (subject/region-level sensitivity, specificity, PPV, NPV, accuracy) of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging compared with CIM as standard of truth (SoT).

[^{111}In]In-Pentetreotide has sufficient diagnostic capability for NENs. Subject-level sensitivity in patients with at least one positive lesions identified by CIM such as CT or MRI and with no positive lesions identified by CIM was 73.7-100% and 66.7-100%, respectively. In addition, [^{111}In]In-Pentetreotide imaging has high concordance with the octreotide suppression test and immunohistological examination of SSTR (Review Report for OctreoScan I.V. Injection Set).

Patients with NENs are often diagnosed with metastases, and it's not ethically and medically feasible to obtain biopsy sample from all lesions for histopahological confirmation. Given [^{111}In]In-Pentetreotide imaging as well as CT and/or MRI are established diagnostic procedure for SSTR positive NENs, these CIM read can be used as SoT to evaluate diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging.

CIM for patients with NENs must include [^{111}In]In-Pentetreotide SPECT or SPECT/CT and High Resolution CT with contrast (or MRI if CT with contrast is medically contraindicated). A centralized reading of CIM for NENs patient will be submitted to a designated CRO. An independent reader who will be blinded to patient data (including clinical condition, histopathology and [^{68}Ga]Ga-DOTA-TATE PET/CT imaging results). This central read result of CIM will be SoT and HVs will be categorized as CIM negative without performing CIM.

[^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be performed for all participants including HVs and PET/CT imaging will be submitted to a designated CRO for independent central read. 3 independent readers, who will be blinded to patient data (including clinical condition, histopathology and CIM results) will read PET/CT imaging. Central read results will not be provided to the treating physician/Clinical Study Investigator.

4.3 Justification for dose

[^{68}Ga]Ga-DOTA-TATE will be administered intravenously at a 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 pharmacokinetics of [^{68}Ga]Ga-DOTA-TATE in blood has not been assessed.

Estimated radiation absorbed dose per injected activity for organs and tissues of adult patients following an intravenous injection of [^{68}Ga]Ga-DOTA-TATE were derived from different sources from literature (Sandström et al 2013; Josefsson et al 2018). The absorbed doses for the tissues with higher absorbed dose per unit activities (adrenals, kidney, liver, gall bladder wall, urinary bladder wall, pituitary gland) are those reported by Josefsson (2018), obtained using updated and more formalized methodologies based on ICRP 110 reference voxel phantoms. For the other tissues, the estimated absorbed doses are those reported by Sandstrom (2013), which were obtained using standard phantom-based dosimetry (Stabin 2006).

Estimated radiation effective dose per injected activity for adult and pediatric patients following an intravenous injection of [^{68}Ga]Ga-DOTA-TATE were calculated starting from available [^{68}Ga]Ga-DOTA-TATE biokinetics data for adults (Sandström et al 2013), using Cristy-Eckerman age-dependent phantoms provided by OLINDA/EXM software. The effective radiation dose resulting from the administration of 150 MBq (4.05 mCi) (within the range of the recommended [^{68}Ga]Ga-DOTA-TATE injection dose) to adult weighing 75 kg, is about 3.45 mSv. For an administered activity of 150 MBq (4.05 mCi) the typical radiation absorbed dose to the critical organs, which are the urinary bladder wall, the spleen and the kidneys/adrenals, are about 6, 37.5, 21 and 16.5 mGy, respectively. Because the spleen has one of the highest physiological uptakes, higher uptake and radiation dose to other organs or pathologic tissues may occur in patients with splenectomy.

SNMMI Procedure Standard/EANM Practice Guideline (Hope et al 2023), which take into account the Directive 97/43/EURATOM (Council Directive 97/43/Euratom), recommends a dose range of 100-200 MBq of [^{68}Ga]Ga-somatostatin analogue depending on patient's weight. Thus, the recommended dosage of 2 MBq/kg for [^{68}Ga]Ga-DOTA-TATE is in line with international guidelines and found to be an acceptable dose to have adequate performance and safety. In addition, [^{68}Ga]Ga-DOTA-TATE dose of 2 MBq/kg appears to give a considerably lower total radiation dose to the patients as compared to [^{111}In]In-Pentetreotide. For instance, the effective dose for [^{68}Ga]Ga-DOTA-TATE dose of 150 MBq to an adult weighing 75 kg was estimated to be approximately 3.15 mSv, while the effective dose for [^{111}In]In-Pentetreotide dose of 111 MBq was estimated to be 13 mSv. Numerous publications and post-marketing experience have consistently demonstrates that imaging with [^{68}Ga]Ga-DOTA-TATE at this dose range is well tolerated.

The effect of radiation would be minimal for microdose nature of [^{68}Ga]Ga-DOTA-TATE and it not be variable between patients and HVs. As the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging should be evaluated in HVs for specificity assessment at same dose level with dosing to patients, this recommended dose of [^{68}Ga]Ga-DOTA-TATE for patients is applicable for HVs.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

4.5 Rationale for public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

4.6 Purpose and timing of interim analyses/design adaptations

Not applicable

4.7 End of study definition

Study completion is defined as when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

5 Study population

The study population will consist of approximately 47 eligible female or male adult participants with confirmed or suspected NENs, and 23 HVs. The number of participants with suspected NENs is limited to up to 5 with negative CIM by central read.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Participants must be adults ≥ 18 years of age
3. Eastern Cooperative Oncology Group (ECOG) performance status 0-2
4. For patient with NENs only: Participants with confirmed NENs based on histopathology, imaging and other relevant examination, or with suspected NENs which localization cannot be confirmed by conventional imaging

5. For HVs only: Male or female participant in good health condition as determined by no clinically significant findings from medical history, physical examination, vital signs, lab test and ECG
6. Women of childbearing potential must have a negative urine or blood pregnancy test.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Any additional medical condition, serious intercurrent illness, concomitant cancer or other extenuating circumstance that, in the opinion of the Investigator, would indicate a significant risk to safety or impair study participation.
2. Inability to complete the needed investigational and conventional imaging due to any reason (severe claustrophobia, inability to lie still for the entire imaging time, etc.)
3. Known allergy, hypersensitivity, or intolerance to [^{68}Ga]Ga-DOTA-TATE and [^{111}In]In-Pentetreotide
4. Therapeutic use of any somatostatin analogue except for the following washout period
   - Short-acting analogs of somatostatin can be used up to 24 hours before injection with [^{68}Ga]Ga-DOTA-TATE
   - Long-acting analogs of somatostatin can be used up to 28 days before injection of [^{68}Ga]Ga-DOTA-TATE
5. Prior administration of a radiopharmaceutical unless 10 or more half-lives have elapsed before injection of [^{68}Ga]Ga-DOTA-TATE
6. Use of other investigational drugs within 30 days before screening
7. Participants who are pregnant.
8. Participants who are lactating.

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable eCRF. The demographic information, informed consent, Visit Date, subject Status at Screening, Inclusion/Exclusion, Assignment, Withdrawal of Informed Consent (if applicable), Death (if applicable) and Screening Phase Disposition pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see SAE section for reporting details). Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition eCRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Each case must be discussed and agreed with Novartis, Eckert & Ziegler Radiopharma GmbH on a case-by-case basis.

Re-screening is only allowed once. There is no restriction on how much time must pass from the date of screen failure to the date of re-screening.

If a participant re-screens for the study, then they must sign a new ICF. The investigator/qualified site staff will record if the participant was re-screened on the re-screening eCRF and any applicable screening numbers the participant was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the informed consent eCRF to correspond to the new screening subject number. For re-screening, all screening assessments must be performed per protocol.

5.3.1 Replacement policy

Participants will not be replaced.

5.3.2 Participant numbering

Upon signing the informed consent form, the participant is assigned to the next sequential Participant Number (No.) available. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential number suffixed to it, so that each participant is numbered uniquely across the entire database. This number will be retained throughout participation in the trial. If the participant is rescreened, then a new Participant No. will be assigned.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

In this study, the term “study treatment” used in the protocol refers to the investigational radioligand imaging compound [^{68}Ga]Ga-DOTA-TATE, which after radiolabeling with ^{68}Ga, serves as a radioactive PET diagnostic agent for localization of SSTR-positive tumors, and to the ^{68}Ge/^{68}Ga generator used to obtain ^{68}Ga as a ^{68}Ga chloride solution. Both study treatments have no therapeutic effect.

Due to short radioactive half-life of ^{68}Ga, [^{68}Ga]Ga-DOTA-TATE cannot be supplied as ready-to-use radiopharmaceutical. Therefore, [^{68}Ga]Ga-DOTA-TATE will be manufactured directly at clinical trial sites immediately prior to administration into participants by chelation of ^{68}Ga with DOTA-TATE supplied as a cold kit for the radiopharmaceutical preparation. The ^{68}Ga used for chelation will be eluted from the ^{68}Ge/^{68}Ga generator as ^{68}Ga chloride. [^{68}Ga]Ga-DOTA-TATE will be prepared as a sterile solution.

[^{68}Ga]Ga-DOTA-TATE will be 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) (refer to Section 6.2 for details on handling, preparation and administration).

[^{68}Ga]Ga-DOTA-TATE used for PET imaging must be prepared only with the use of DOTA-TATE cold kit for the radiopharmaceutical preparation and the ^{68}Ge/^{68}Ga generator.

Sponsors or their designee will provide ^{68}Ge/^{68}Ga generator and DOTA-TATE cold kit for the radiopharmaceutical preparation of [^{68}Ga]Ga-DOTA-TATE.

Table 6-1 Investigational and control drug

Treatment Title	DOTA-TATE	^{68}Ge/^{68}Ga Generator
Type	drug	drug
Dose Formulation	Kit for radiopharmaceutical preparation	Radionuclide generator
Unit Dose Strength(s)	40 mcg per kit	1850 MBq (50 mCi)
Dosage Level(s)	[^{68}Ga]Ga-DOTA-TATE will be administered at a dose of 2 MBq/kg (0.054 mCi/kg) of body weight up to a maximum total dose of 200 MBq (5.4 mCi)	NA
Route of Administration	Intravenous use (After radiolabeling with Ga-68)	NA
Use	experimental	experimental
IMP	Yes ([^{68}Ga]Ga-DOTA-TATE, after radiolabeling with Ga-68)	Yes, Radionuclide generator
Sourcing	Provided centrally by the sponsor (global)	Provided centrally by the sponsor (global)
Packaging and Labeling	Study treatment will be provided as a kit. Each kit will be labeled as required per country requirement.	The ^{68}Ge/^{68}Ga Generator is presented as a stainless-steel case

6.1.1 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.2 Treatment arms/group

Not applicable for this study because there is only one treatment arm.

6.1.3 Guidelines for continuation of treatment

Not applicable for this study.

6.1.4 Treatment duration

[^{68}Ga]Ga-DOTA-TATE will be administered intravenously at a dose of 2 MBq/kg (0.054 mCi/kg) of body weight up to a maximum total dose of 200 MBq (5.4 mCi) at the imaging day.

6.1.4.1 Treatment beyond disease progression

Not applicable.

6.1.5 Medical devices

Not applicable.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs section.

The DOTA-TATE as a sterile two-vials kit and the $^{68}Ge/^{68}Ga$ Generator will be supplied by Sponsors to hospital's radiopharmacies. The elution of the $^{68}Ge/^{68}Ga$ Generator and the reconstitution of the kit with the eluate for radiolabeling will be performed at clinical trial sites.

[^{68}Ga]Ga-DOTA-TATE must be prepared and administered by qualified/authorized personnel only in accordance with pharmaceutical quality requirements and radiation safety regulations.

After reconstitution, [^{68}Ga]Ga-DOTA-TATE solution will be administered by intravenous injection.

The instructions and explanations for ordering, delivery, elution of the $^{68}Ge/^{68}Ga$ Generator, radiolabeling procedure and dispensing of [^{68}Ga]Ga-DOTA-TATE, as well as cautionary notes, analytical controls and stability information for the radiolabeled product will be provided to each site (please refer to the Pharmacy Manual).

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements. They will include storage conditions for the study treatment but no information about the participant.

The Investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial. It must be possible to reconcile delivery records with those of used and unused medication. Any discrepancies must be accounted for and explained. Appropriate forms of deliveries and returns must be signed and dated by the responsible person at the clinical site and maintained as records. The return or disposal of all study medication will be documented appropriately.

For more details about technical complaints, the handling of [^{68}Ga]Ga-DOTA-TATE refer to the Pharmacy Manual.

6.2.2 Handling of other treatment

Not applicable.

6.2.3 Instruction for prescribing and taking study treatment

For further details on the [^{68}Ga]Ga-DOTA-TATE administration refer to Section 6.1 and to Pharmacy Manual.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

Not applicable.

6.3.2 Treatment blinding

The following blinding is applicable in this study:

- [^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be submitted to a CRO for independent centralized read by 3 independent readers blinded to CIM and patient data collected in clinical database.
- CIM will be submitted to a CRO for independent centralized read by 1 independent reader, blinded to [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and patient data collected in clinical database.

6.3.3 Emergency breaking of assigned treatment code

Not applicable.

6.4 Study treatment compliance

All participants will have the study treatment administered during site visits on imaging day. All study treatments must be recorded in the Drug Accountability Log and in the corresponding eCRF pages.

6.5 Dose modification

Dose modifications are not applicable in this study for the investigational imaging agent which is administered intravenously as a single dose.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Dose modifications

Not applicable.

6.5.3 Follow-up for toxicities

Not applicable.

6.5.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Not applicable.

6.6 Continued access to study treatment after the end of the study

Not applicable.

6.6.1 Post trial access

Not applicable.

6.7 Treatment of overdose

In the event of administration of a radiation overdose with investigational agent, the radiation absorbed dose to the participant should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective radiation dose that was applied.

In the event of an overdose, the Investigator/treating physician should:

- Contact the medical monitor immediately.
- Document the quantity of the excess dose as well as the duration of the overdose.
- Follow standard clinical practice for overdose of diagnostic radiopharmaceuticals.

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

- Use of diuretics (e.g. furosemide) to help the subject voiding before PET/CT acquisition is allowed in case of need, upon the discretion of the Investigator, and should be captured in the eCRF like other concomitant medications.

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis, Eckert & Ziegler Radiopharma GmbH medical monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis, Eckert & Ziegler Radiopharma GmbH to determine if the participant should continue participation in the study.

Use of diuretics (e.g. furosemide) to help participants voiding before PET/CT acquisition is allowed in case of need, upon the discretion of the Investigator.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Some evidence exists that corticosteroids can induce down-regulation of SSTR2. Repeated administration of high-doses of corticosteroids prior to [^{68}Ga]Ga-DOTA-TATE administration may cause insufficient SSTR2 expression for adequate visualization of SSTR-positive tumors.

6.8.1.2 Use of bone modifying agents

Not applicable.

6.8.2 Prohibited medication

HV participants

Except for protocol allowed concomitant medication and/or any medication which may be required to treat adverse events [and permitted oral or injectable contraceptives for female participants], no medication other than study treatment will be allowed from the date participant signs the inform consent until all of the study completion evaluations have been performed.

NENs patients

Somatostatin analogues competitively bind to the same SSTR as [^{68}Ga]Ga-DOTA-TATE. Refer to Section 5.2 for washout period prior to [^{68}Ga]Ga-DOTA-TATE imagings.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Since [^{68}Ga]Ga-DOTA-TATE is administered as a single intravenous injection, discontinuation of [^{68}Ga]Ga-DOTA-TATE is not applicable.

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be made as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue, the Investigator must document "due diligence" steps taken to contact the participant, e.g. dates of telephone calls, registered letters in the source documents. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis, Eckert & Ziegler Radiopharma GmbH at any time.

Reasons for early termination (but not limited to)

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development in this indication

In taking the decision to terminate, Novartis, Eckert & Ziegler Radiopharma GmbH will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment (e.g. safety follow up period must be completed if applicable with required visits to be performed). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis, Eckert & Ziegler Radiopharma GmbH depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in Section 1.3 Schedule of Activities. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Novartis, Eckert & Ziegler Radiopharma GmbH upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

Screening

Written informed consent must be obtained prior to any screening procedures. Please refer to Section 10.1.2 for the Informed Consent procedures.

All screening assessments should occur within 35 days prior to imaging day. CIM assessment performed as a part of clinical practice within 2 months prior to imaging day even before informed consent, can be used as standard reference as long as imaging quality meets study defined criteria. Refer to Imaging Manual for details.

It is permissible to re-screen (only once) a participant if he or she fails the initial screening (screen failure); however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Re-screening should not be performed for avoiding the eligibility criteria, putting the participant at safety risk. Re-screened participants will need to be re-consented and a new Participant Number will be assigned. Re-screening tests should be repeated as per

inclusion/exclusion requirements and re-screening should be documented in the source documents.

8.1.1 Eligibility screening

- For HVs: The investigator or his/her delegate will confirm that the participant fulfills all the inclusion/exclusion criteria

For NEN patients: The Investigator or his/her delegate will contact the registration center after confirming that the participant fulfills all the inclusion/exclusion criteria. The registration center will confirm the result of CIM by central read and notify the registration to investigators. The registration center will limit the enrollment of patients with negative CIM up to 5. Details will be provided in the registration manual.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with the eCRF.

Participant demographics: age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, we will assess the diversity of the study population as required by Health Authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See protocol Section 10.1.5 for further details on what information must be recorded on the appropriate page of the eCRF.

Participant demographic and baseline characteristic data to be assessed on all participants include:

- Demographic information: Age, Gender, Race and ethnicity
- ECOG Performance status scale
- Height and Weight
- Vital signs: Body temperature, Blood pressure, Pulse rate, Respiratory rate measurements
- 12 Lead ECG
- Laboratory evaluations: Hematology, Chemistry, Urinalysis, Coagulation, and Pregnancy testing (if applicable)
- Conventional Imaging (Patients with NENs only)
- Patient Management Questionnaire (Patients with NENs only)
- Adverse Events
- Medical history:
    - Ongoing medical conditions, symptoms and diseases which are recorded on the Medical History eCRF should include the toxicity grade when applicable.
    - Concomitant medications of the last 30 days prior to imaging day

  - Other important medical, surgical, and allergic conditions that could have an impact on the participant's evaluation, and current medical conditions (e.g. all relevant current medical conditions which are present at the time of signing informed consent).
- Diagnosis and Extent of Cancer (if applicable for patients with NENs): Date of initial diagnosis, Date of the last relapse/progression, Extent of disease, Functional test, Histopathology result (Diagnosis of disease, Ki67 proliferation index, Histological grade, SSTR expression status). Any assessments after biopsy will be documented on the appropriate eCRF.
- Prior Antineoplastic Medications/Radiotherapy/Surgery

ECOG Performance status scale will be used as described in Table 8-1.

Table 8-1 ECOG performance status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

8.3 Efficacy assessments

Efficacy assessments in this study include diagnostic assessment of disease using CIM (NENs patients only) at screening as well as assessments of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging. In addition, disease assessment using histopathology will be collected for the participants whose histopathology assessment is available. Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities.

8.3.1 Imaging for tumor assessment

The imaging assessment collection plan for this study is presented in Table 8-2.

Table 8-2 Imaging Assessment Collection Plan

Imaging procedure	Mandatory or Optional	Imaging Acquisition Timing
[^{111}In]In-Pentetreotide SPECT/CT**	Mandatory - NENs patients only	screening*
High Resolution CT with contrasts (or MRI if CT with contrast is medically	Mandatory - NENs patients only	screening*

Imaging procedure	Mandatory or Optional	Imaging Acquisition Timing
contraindicated) of at least Chest, Abdomen and Pelvis (and any additional region as clinically indicated)		
[^{68}Ga]Ga-DOTA-TATE PET/CT	Mandatory - all participants	Imaging day

*CIM assessment performed as a part of clinical practice within 2 months prior to imaging day, even before informed consent, can be used as long as imaging quality meets study defined criteria.

**If SPECT/CT is not available in the clinical site, SPECT can be acceptable.

[^{68}Ga]Ga-DOTA-TATE PET/CT imaging

[^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be performed for all participants including HVs and PET/CT imaging will be submitted to the designated central CRO for independent central review. Three independent reviewers, who will be blinded to CIM and other patient data collected in clinical database will review PET/CT images. Central read results will not be provided to the treating physician/Clinical Study Investigator. If applicable for histopathology assessments detailed in Section 8.3.2, local read results of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be used for the assessment.

CIM for NENs patient

CIM for patients with NENs must include [^{111}In]In-Pentetreotide SPECT/CT and High Resolution CT with intravenous and oral contrasts (or MRI if CT with contrast is medically contraindicated). A centralized reading of CIM for patients with NENs will be performed by a central independent reader who will be blinded to [^{68}Ga]Ga-DOTA-TATE PET/CT imaging results and other patient data collected in clinical database. Further details will be provided in the Imaging Manual.

8.3.2 Histopathology assessments

From prospective biopsy or surgery performed within 30 days after imaging day : In the cases where pathology will be available, histopathology assessments by the local pathologists, who are not blinded to [^{68}Ga]Ga-DOTA-TATE PET/CT imaging results, CIM and other patient data collected in clinical database, will be performed as per standard clinical practice, and results are to be provided within 2 weeks of the biopsy or surgery.

From retrospective biopsy performed before imaging day : In case if pathology is available, the result will be collected.

Pathology data collected for histopathology assessments can be documented in eCRF (e.g. Diagnosis and Extent of Cancer).

8.3.3 Appropriateness of imaging assessments

CIM including [^{111}In]In-Pentetreotide SPECT/CT and High Resolution CT with contrasts (or MRI if CT with contrast is medically contraindicated) is considered as the SoT to assess the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging. CIM and [^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be read by independent central reviewers, who will be

blinded to patient data (including clinical condition, histopathology and each other imaging result).

Since patients with NENs are often metastatic at the time of diagnosis, it is ethically impossible to make a histological diagnosis by biopsy of all lesions, and since CIM including [^{111}In]In-Pentetreotide SPECT/CT and High Resolution CT with contrasts (or MRI if CT with contrast is medically contraindicated) have been established for SSTR-positive NENs, it is considered appropriate to evaluate the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging using CIM as the SoT.

8.4 Safety assessments

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 1-2.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an adverse event must be recorded as an adverse event.

8.4.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure (Systolic and diastolic), respiratory rate) will be monitored as per Section 1.3 Schedule of Activities.

8.4.3 Electrocardiograms

Figure 8-1 Timing of study procedures

Single local 12 lead ECGs are collected.

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date and time, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening should be reported on the appropriate eCRF. Clinically significant findings must be discussed with Novartis prior enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

The original ECG appropriately signed must be collected and archived at the study site. If heat sensitive paper is used, a certified copy on non-heat sensitive paper must be also collected and archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated.

Table 8-3 Local ECG collection plan

Week (or Cycle)	Day	Time	Number of ECG Replicates
Screening	-35 to -1	Screening	12 Lead Single
Imaging day	1	Post dose 2 hours	12 Lead Single
Unscheduled or Unplanned sample		Anytime	12 Lead Single

8.4.3.1 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable.

8.4.3.2 Cardiac enzymes

Not applicable.

8.4.4 Clinical safety laboratory tests

Local laboratory will be used for analysis of hematology, chemistry, urinalysis, coagulation, and pregnancy testing (if applicable) according to the schedule of assessments as described in Table 1-2. The samples need to be taken prior to the injection of the [^{68}Ga]Ga-DOTA-TATE.

Urine samples will be collected at screening, at imaging day and safety follow-up by dipstick and analyzed locally at the clinical site if dipstick results are abnormal.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria: 1) they induce clinical signs or symptoms, 2) they are considered clinically significant, or 3) they require concomitant therapy or procedures. Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit.

At any time during the study, abnormal laboratory parameters which are clinically relevant, whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Section 10.3.1). Additional analyses are left to the discretion of the Investigator.

Novartis must be provided with a copy of the local laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation.

The Investigator is responsible for reviewing all laboratory reports for participants in the study and evaluating any abnormalities for clinical significance.

Table 8-4 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Mean Corpuscular Hemoglobin (MCH), Platelets, Erythrocytes, Leukocytes, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils (absolute value preferred, percentages are acceptable))
Chemistry	Albumin, Alkaline phosphatase, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-glutamyl transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate*, Calcium, Magnesium, Phosphate (inorganic phosphorus), Chloride, Sodium, Potassium, Creatinine, Creatine kinase (CK), Direct Bilirubin, Total Bilirubin, Blood Urea

Test Category	Test Name
	Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Plasma Glucose (fasting)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If Dipstick is abnormal, Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) will be added (only needs to be recorded in the source documentation).
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Pregnancy testing	Serum / Urine pregnancy testing (refer to 'Pregnancy testing' Section 8.4.5)

*Total carbon dioxide or equivalent is acceptable for Bicarbonate

8.4.5 Pregnancy testing

All women of childbearing potential will have pregnancy testing. Serum or urine pregnancy testing depending on Investigator's preference will be performed at screening visit.

A woman is considered of childbearing potential from menarche until becoming post-menopausal unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

Permanent sterilization methods include hysterectomy, bilateral tubal ligation, bilateral salpingectomy and bilateral oophorectomy. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered to be not of child-bearing potential.

Medical documentation of permanent method of sterilization must be retained as source documents.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the Investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.6 Suicidal ideation and behavior risk monitoring

Not applicable.

8.4.7 Other safety evaluations

Not applicable.

8.4.8 Appropriateness of safety measurements

Not applicable.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Not applicable.

8.5.2 Imaging

Not applicable.

8.5.3 Other assessments

Patient Management questionnaire (NENs patients only) will be completed by the treating physician/Clinical Study Investigator before and until Safety follow up after having the local read results of the [^{68}Ga]Ga-DOTA-TATE PET/CT imaging (total 2 times). The results must be recorded on the appropriate eCRF.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The Investigator and any qualified designees are responsible for managing the safety of individual participants. They are also responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and for following up all AEs and SAEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided below (Section 8.6.1, Section 8.6.2, and Section 8.6.3).

For the investigational product and for non-authorized AxMPs (when applicable), information about adverse drug reactions and how to manage them can be found in the Investigator's Brochure (IB) or equivalent documentation. Information about adverse drug reactions can also be found in the product information for marketed products.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

8.6.1 Adverse events

Definition of AEs

An adverse event (AE) is any untoward medical occurrence (e.g., any occurrence of unfavorable and unintended sign(s), symptom(s) or medical condition, including abnormal laboratory findings, or worsening of any pre-existing sign(s), symptom(s) or medical condition) in a participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of any treatment used in this study. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms

- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values considered to be non-typical in participant with the underlying disease.

Collecting and assessing AEs

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

The investigator will attempt to establish a diagnosis of the event (including lab abnormalities that constitute AEs) based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE.

For each AE, the investigator must assess:

The Common Toxicity Criteria (CTC).

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

The causality

The investigator is obligated to assess the relationship between any treatment used in the study (study treatment) and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be ‘Not suspected.’ The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Handling of AEs

All adverse events must be treated appropriately. More information about how to manage AEs can be found in the IB. Information about adverse drug reactions can also be found in product information for marketed products.

Once an AE is detected, the Investigator must pro-actively followed up the participant, until resolution of the AE, or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), or until stabilization, or until the participant is lost to follow-up. Any change in severity or suspected relationship to study treatment must be assessed at each visit (or more frequently, if necessary).

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event, except if the Investigator considers that progression of malignancy is related to study treatment.

Adverse events separate from the progression of malignancy (for example deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding causality to the study treatment.

Timeframe of recording of AEs

AE recording for each participant should be continued until 8 days after the last dose of study treatment (i.e. Day 9) (On and after Day 10, SAEs should be reported only if the investigator suspects a causal relationship to study treatment).

8.6.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening
  Life-threatening in the context of a SAE refers to a medical occurrence in which the participant was at risk of death at the time of the reaction; it does not refer to a medical occurrence that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction. All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent until 8 days after the last dose of study treatment (i.e. Day 9) must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (On and after Day 10, SAEs should be reported only if the investigator suspects a causal relationship to study treatment). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. All applicable sections of the form must be completed in order to provide a clinically thorough report.

The investigator must review and provide an assessment of causality for each SAE. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Novartis. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Novartis. The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information.

Any SAEs experienced after the 30-day period after dosing of investigational drug should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

If an SAE is not previously documented in the IB or product information for marketed products and is thought to be related to any study treatment, Novartis may urgently require further information from the investigator for HA reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment. SUSARs will be reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries, including EU Clinical Trial Regulation 536/2014.

8.6.4 Pregnancy

Pregnancies

Contraception measures are not required. However, if a female trial participant becomes pregnant, the pregnancy consent form should be presented to the trial participant.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis/Sponsor as described in Section 8.6.3. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Pregnancies
If a female trial participant becomes pregnant, the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Reporting of study treatment errors, study treatment misuse/abuse and overdose

Study treatment errors are unintentional errors in the prescribing, dispensing, and administration of study treatment.

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of study treatment, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, must be reported on the AE CRF.

8.6.6 Adverse events of special interest

Not applicable.

8.7 Pharmacokinetics

PK samples will be collected at the visits defined in Section 1.3 Schedule of Activities. Follow instructions outlined in the Laboratory Manual regarding sample collection, numbering, processing and measurement. See the potential use of residual samples for more information. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PK samples will be obtained and evaluated in 4-6 participants (preferably in patients) enrolled in the selected clinical sites on the imaging day.

Blood samples will be counted at the investigational site in an accurately calibrated gamma counter (e.g. NaI spectrometer) with a suitable reference source of ^{68}Ga of known activity counted in the same geometry as that of the biological samples (e.g. 1 mL in a vial). Samples will be collected at the timepoints described in Table 8-5. Further details about sample collection and radioactivity measurement are provided in the Laboratory Manual.

All data including but not limited to actual date and time of blood sampling, date and time of measurement by gamma counter, exact volume of sample measured (including any dilutions if applicable) and activity counted by gamma counter must be recorded in the appropriate blood collection eCRF page.

Radioactivity concentrations will be expressed in mass per volume units and, if deemed necessary, other units (e.g. radioactivity per volume). In order to determine specific activity for the time of injection, the total peptide content, radioactivity after radiolabeling, and date and time of measurement must be recorded in the appropriate eCRF.

8.7.1 Pharmacokinetic blood collection and handling

Refer to the [AAA501A11301 Laboratory Manual] for detailed instructions for the collection, handling, and shipment of PK samples.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. At specified time points described in Table 8-5, 1 mL blood will be transferred

to the tube or plate for the measurement of radioactivity by gamma counter. The exact date and time of dosing, as well as the date and actual time of blood sampling must be recorded on the appropriate eCRF page.

Table 8-5 Pharmacokinetic blood collection log

Treatment Period or Cycle	Day	**Scheduled Time Point (min)**	Time range
1	1	Pre-dose / 0	-
1	1	5	± 3 min
1	1	15	± 5 min
1	1	30	± 5 min
1	1	45	± 5 min
1	1	60	± 10 min
1	1	120	± 30 min
1	1	180	± 30 min

8.7.2 Analytical method

Radioactivity in blood for [^{68}Ga]Ga-DOTA-TATE will be measured at the investigational site, with a properly calibrated gamma counter or similar system and must be recorded on the appropriate eCRF. Both lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) will be determined for each analytical instrument at the investigational sites and must be recorded with the calibration factor on the appropriate eCRF.

8.8 Biomarkers

Not applicable.

8.9 Immunogenicity assessments

Not applicable.

8.9.1 Immunogenicity blood sample collection and handling

Not applicable.

8.9.2 Immunogenicity analytical method(s)

Not applicable.

8.10 Health economics OR Medical resource utilization and health economics

Not applicable.

9 Statistical considerations

Efficacy and safety analyses will be conducted for each analysis set respectively at the time all participants will have completed the study.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

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

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.

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

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

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

9.2 Statistical analyses

9.2.1 General considerations

Grouping strategy

For some efficacy analyses (subject/region-level sensitivity, specificity, PPV, NPV and accuracy), HVs will be categorized in 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.

Descriptive statistics

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

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.

9.2.2 Participant demographics and other baseline characteristics

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC) and preferred term (PT) for the FAS and the EFF.

9.2.3 Treatments

The actual received [^{68}Ga]Ga-DOTA-TATE dose and time interval 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.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for the FAS.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary objectives of the study are described in Table 3-1.

Efficacy analyses will be performed for the EFF.

9.3.1 Definition of 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 9-1 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.

9.3.2 Statistical model, hypothesis, 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.

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

Not applicable.

9.3.4 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 be occurred in the population.

9.3.5 Multiplicity adjustment (if applicable)

Not applicable.

9.3.6 Sensitivity analyses

Not applicable.

9.3.7 Supplementary analysis

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 corresponded exact 95% CI will be shown for each 3 central readers respectively.
- If there are participants with not evaluable [^{68}Ga]Ga-DOTA-TATE PET/CT imaging, those participants' results will be assumed all positive or all negative respectively and each analysis will be performed for primary endpoints.
- The subgroup analyses using descriptive statistics and 95% CI to assess the homogeneity of the diagnostic performance of [^{68}Ga]Ga-DOTA-TATE PET/CT imaging across demographic and baseline disease characteristics will also be performed. Important subgroups will be specified in the SAP.

9.4 Secondary endpoint(s)/estimand(s) analysis

The secondary objectives of the study are described in Table 3-1.

Efficacy analyses will be performed for the EFF.

9.4.1 Efficacy and/or pharmacodynamic 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).

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

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.

Region-level sensitivity, specificity, PPV, NPV, accuracy will be summarized respectively with corresponded exact 95% CI by regions. Region consists of liver, pancreas, gastrointestinal, lymph nodes and others.

Number of lesions detected by imaging

For region-level, number of lesion detected by [^{68}Ga]Ga-DOTA-TATE PET/CT imaging and CIM will be counted. Regarding [^{68}Ga]Ga-DOTA-TATE PET/CT imaging, individual and mean number of lesions detected by each 3 central readers will be presented. Regarding CIM, each 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.

Impact on treatment decision

Numbers and percentages of participants for each intended treatment plan collected from physician at pre and post [^{68}Ga]Ga-DOTA-TATE PET/CT imaging will be summarized. Summary statistics of participants for the change of intended treatment plan will also be presented.

Inter-reader variability

Inter-reader variability for [^{68}Ga]Ga-DOTA-TATE PET/CT imaging is defined as agreement rate among reader determinations and will be assessed by Fleiss' Kappa statistics. Inter-reader variability (%) and its normality 95% CI will be presented.

Lesion-level concordance rate for SSTR

The lesion-level concordance rate for SSTR between [^{68}Ga]Ga-DOTA-TATE PET/CT imaging local read and local histopathology result among legions which is available, will be calculated. The rate 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.

9.4.2 Safety endpoints

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). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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.
3. Post-treatment period: starting 9 days after dosing of investigational drug.

Adverse events

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated.

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

All AEs, deaths, and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Vital signs

Notable vital sign values will be summarized by visit/time.

12-lead ECG

ECG abnormalities will be summarized.

Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (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.

9.4.3 Pharmacokinetics

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 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.

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

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.

Pharmacokinetic parameters will be provided by participants. Descriptive statistics of all pharmacokinetic parameters will include 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.

Table 9-2 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)

[redacted]

[redacted]

9.6 (Other) Safety analyses

Not applicable.

9.7 Other analyses

Not applicable.

9.8 Interim analysis

Not applicable.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

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 2016a). The thresholds of 70% for sensitivity and 60% for specificity are set by referring to phase III study of [^{64}Cu]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 9-3 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).

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study was designed and will be implemented, executed and reported in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Tripartite Guidelines for Good Clinical Practice (GCP)
- Applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21)

The protocol, protocol amendments, ICF, Investigator's Brochure, [IDFU], and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated at that specific site.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis, Eckert & Ziegler Radiopharma GmbH monitors, auditors, Novartis, Eckert & Ziegler Radiopharma GmbH Quality Assurance representatives, designated agents of Novartis, Eckert & Ziegler Radiopharma GmbH, IRBs/IECs, and regulatory authorities as required
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Taking any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis/Sponsor must be notified of this action and the IRB/IEC at the study site must be informed according to local regulations.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- Informing Novartis, Eckert & Ziegler Radiopharma GmbH immediately if an inspection of the clinical site is requested by a regulatory authority

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, the participant must indicate agreement by personally signing and dating the written informed consent document.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Common side effects already known about the study treatment will be included in the ICF and must be discussed with the participant upon obtaining consent and during the study as needed. Any new information related to the safety profile that is identified between IB updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the ICF and discussion with the participant.

The following informed consents are included in this study:

- Main study consent, included:
  - A subsection with a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants

As applicable, information sheet for female partners of male participants

A copy of the approved version of all consent forms must be provided to Novartis, Eckert & Ziegler Radiopharma GmbH after IRB/IEC approval.

10.1.3 Data protection

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to Novartis, Eckert & Ziegler Radiopharma GmbH will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis, Eckert & Ziegler Radiopharma GmbH in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, Eckert & Ziegler Radiopharma GmbH, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis and Eckert & Ziegler Radiopharma GmbH have appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Data Monitoring Committee

Not applicable.

10.1.4.2 Steering Committee

Not applicable.

10.1.4.3 Adjudication committee

Not applicable.

10.1.5 Data quality assurance

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

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis and Eckert & Ziegler Radiopharma

GmbH. No records may be transferred to another location or party without written notification to Novartis and Eckert & Ziegler Radiopharma GmbH.

10.1.5.1 Data collection

Data not requiring a separate written record will be defined in the protocol and Section 1.3 Schedule of Activities and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (CRF). The CRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been certified as trained. Automatic validation programs check for data discrepancies in the CRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data entered into CRF is complete, accurate, and that entry and updates are performed in a timely manner e.g. within 5 days of visit. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness, accuracy and scientific/medical plausibility. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be medically coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician.

10.1.6 Source documents

Data reported on the CRF or entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

Study monitors will perform source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or CTIS public website. In addition, after study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis, Eckert & Ziegler Radiopharma GmbH clinical trial results website and all required health authority websites (e.g. Clinicaltrials.gov, EudraCT or CTIS public website etc.).

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided.

Any data analysis carried out independently by the Investigator must be submitted to Novartis/Sponsor before publication or presentation.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and Eckert & Ziegler Radiopharma GmbH and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be

considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and Eckert & Ziegler Radiopharma GmbH and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Eckert & Ziegler Radiopharma GmbH, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis and Eckert & Ziegler Radiopharma GmbH should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AxMP	Auxiliary Medicinal Product
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
CIM	Conventional Imaging
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
COA	Clinical Outcome Assessment
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CT	Computerized Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CV	coefficient of variation
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
EANM	European Association of Nuclear Medicine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report/Record Form
ED	Effective Dose
EDC	Electronic Data Capture
EFF	Efficacy Analysis Set
EMA	European Medicines Agency
EOS	End Of Study
EU	European Union
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FN	False Negative
FP	False Positive

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
kg	kilogram
L	Liter
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LPLV	Last Patient Last Visit
MBq	Mega-Becquerel
MCH	Mean Corpuscular Hemoglobin
mCi	Millicurie
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
MRI	Magnetic Resonance Imaging
mSV	millisievert
PA	Posteroanterior
PAS	Pharmacokinetic Analysis Set
PET	Positron Emission Tomography
PK	Pharmacokinetic(s)
PPV	Positive Predictive Value
PRO	Patient Reported Outcomes
PS&PV	Patient Safety and Pharmacovigilance
PSMA	Prostate-specific membrane antigen
PT	prothrombin time
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	standard deviation
SoA	Schedule of Activities

SoT	Standard of Truth
SPECT	Single-photon Emission Computerized Tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TNM	TNM Classification of Malignant Tumors
TP	True Positive
ULN	upper limit of normal
US	United States
WHO	World Health Organization

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Auxiliary Medicinal Product	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
CE marking	A marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in European Union legislation providing for its affixing. CE marking of medical devices is required prior to lawfully placing them on the European Union market.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study treatment (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.

Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (CRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Enrollment will take place at the time when all eligibility requirements are confirmed.
eSource Direct Data Capture (DDC)	eSource Direct Data Capture (DDC) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combine source documents and case report forms (CRFs) into one application, allowing for the real time collection of clinical trial information to Sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor

Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at a the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (e.g. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, the participant can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study device	Study device is a medical device (marketed or investigational) that is used in a circumstance that makes it part of the investigation.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes for example investigational drug(s, and controls)
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

The complete NCI CTCAE (version 5.0) can be found at the following site:

[https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.]

10.4 Appendix 4: Participant Engagement

Not Applicable

10.5 Appendix 5: Liver safety monitoring

Not Applicable

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Not Applicable

10.6 Appendix 6: Renal safety monitoring

Not Applicable

10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Not Applicable

11 References

References are available upon request

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