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Phase II/III study for evaluation of the diagnostic performance of [^{18}F]CTT1057 PET imaging for the detection of PSMA positive tumors using histopathology as a standard of truth (GuideView)

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List of abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
BCR	Biochemical recurrence
BUN	Blood Urea Nitrogen
C	Code of Federal Regulations
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CL	Clearance
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COVID-19	Coronavirus disease 2019
CPM	counts per minute
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CT	Computerized Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	Diastolic Blood Pressure
EANM	European Association of Nuclear Medicine
EAU	European Association of Urology
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	Study completion
ePLND	extended Pelvic Lymph Node Dissection
eSAE	Electronic Serious Adverse Event
EU	European Union
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FN	False Negative
FP	False Positive

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HPLC	High-Performance Liquid Chromatography
HR	Heart Rate
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
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LHRH	Luteinizing Hormone-Releasing Hormone
LLOQ	Lower Limit of Quantification
LN	Lymph Node(s)
MBq	Mega-Becquerel
MCH	Mean Corpuscular Hemoglobin
mCRPC	metastatic-Castration Resistant Prostate Cancer
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
PAS	Pharmacokinetic Analysis Set
PCa	Prostate Cancer
PD	Pharmacodynamic(s)
PET	Positron Emission Tomography
PK	Pharmacokinetic(s)
PLN	Pelvic Lymph Node
PPV	Positive Predictive Value
PS	Primary Staging
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
QC	Quality Control
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RDC	Remote Data Capture

RECIST	Response Evaluation Criteria In Solid Tumors
RP	Radical Prostatectomy
RR	Respiratory Rate
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
SD	standard deviation
SMQ	Standardized MedDRA Query
SoC	Standard of Care
SOP	Standard Operating Procedure
SoT	Standard of Truth
SUSAR	Suspected Unexpected Serious Adverse Reaction
[redacted]	
Tc	Calibration time
TEAE	Treatment Emergent Adverse Event
TN	True Negative
TP	True Positive
US	United States
USPI	US Prescribing Information
VAS	Visual Analog Scale
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

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
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
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.
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)
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 drug 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
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 (eCRFs) 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 or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
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 patients 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.
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 drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. 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). "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.
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.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
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
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 treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
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 study consent (WoC)/ Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not want agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Protocol Amendment 01 (20-Dec-2021)

Amendment Rationale

As of the date of release of this protocol amendment, 14 subjects have been enrolled in the study (9 dosed).

The main purpose of the amendment is to update the inclusion criterion on definition of high risk prostate cancer per D'Amico classification to also include patients with clinical stage T2c or higher at initial diagnosis (instead of T2c only) as those are considered high risk as well per D'Amico classification. Other clarifications and corrections of discrepancies or errors have been implemented across protocol. All changes implemented are detailed below with their justification.

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

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

The changes herein do not affect the Informed Consent.

Main changes implemented in the protocol amendment		
Section	**Change**	**Description and rationale**
Protocol summary Section 5.1 Section 2.1 Section 8.2	**Update of Inclusion criterion #1**	Modified inclusion criterion (numbered 1a) to include patients with clinical stages T2c and higher for prostate cancer as D'Amico classification is also considering such patients as high risk.
Protocol summary Section 5.2 Section 6.2.2	**Removal of exclusion criterion #6 and update of exclusion criterion #5 and clarification that LHRH analogues include LHRH agonists or antagonists**	Exclusion criterion #6 is removed as the targeted population for this study is subjects who are newly diagnosed with prostate cancer and did not receive any prior androgen-deprivation therapy (ADT). Exclusion criterion #5 was updated accordingly (numbered 5a) to exclude any prior ADT including LHRH analogues (agonists or antagonists). Section 6.2.2 was also updated to clarify that LHRH analogues include LHRH agonists or antagonists.
Protocol summary Section 2.1 Section 3 Section 8.3.2	**Update of Surgery timing**	Updated to mention that surgery will be performed up to 6 weeks after but not sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan. This change ensures all patients will go at least through a 2-day period to check their safety after PET scan without being confounded by the effects of surgery.
Section 5 Section 12.1 Section 12.8	**Update of definition for efficacy analysis set**	Update to take into account patients who will be evaluable for co-primary endpoints, i.e. patients who have both an evaluable PET/CT scan and histopathology assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CT and surgery.
Section 6.2.1	**Clarification of use of diuretics**	Clarification that the use of diuretics (e.g. furosemide) to help subject to void before

		PET/CT scan imaging acquisition is allowed in case of need, upon the criteria of the investigator.
Section 6.2.2	**Clarification of use of LHRH analogues and anti- androgens**	Clarification that use of any ADT including LHRH analogues (agonists or antagonists) as well as anti-androgens (both first and second generation compounds) and 5-alpha reductase inhibitors is prohibited prior to completing both PET imaging scans and surgery, to ensure that the same lesions are assessed on PET/CT scans and surgery without potential reduction in lesion size and therefore detectability due to administration of antineoplastic medications.
Table 8-1 (footnote#11) Section 8.4	**Update on safety follow-up visit assessments timing**	For participants undergoing surgery prior to planned safety visit, safety follow-up assessments will need to be performed before the surgery and not sooner than 48 hours after the PET scan. This change ensures all patients will go at least through a 2-day period to check their safety after PET scan without being confounded by the effects of surgery.
Section 10.1.3	**Reporting period for SAE**	Update to correct reporting period for any SAE to 14 days after the last dose of study treatment (instead of last study visit) for alignment with the definition of on-treatment period provided in Section 12.5.2.
Other changes implemented in the protocol amendment		
Section	**Change**	**Description and rationale,**
Table of Contents List of tables List of figures	**Updates**	Modified to reflect changes made in protocol body
Glossary of terms	**Updates and clarification**	Addition of definitions and clarifications of some definitions.
Table 2-1	**Alignment between Objectives and Endpoints wording**	Correction of discrepancies between name of the objectives and definition of the corresponding endpoints. For the patient-level primary and secondary objectives, “evaluated for all patients” was removed as efficacy endpoints will be evaluated in the efficacy set. For region level specificity and accuracy primary and secondary objectives, “evaluated for all regions” was removed as only pelvic lymph node (PLN) region will be evaluated for those endpoints considering that histopathology will be not be available as standard of truth for extra-PLN.
Table 2-1 Section 12.5.1	**Correction and Clarification in definition of distant metastases for the secondary objective**	Correction in definition of distant metastases for the secondary objective of detection of distant metastasis in PS patients was made as distant metastatic lesions for prostate cancer are defined in clinical practice as metastasis in extra-PLN or in any visceral or

		skeletal location. Lesions in PLN are considered local metastases. It was also clarified in the definition of this endpoint that it will be assessed in all patients with an evaluable [^{18}F]CTT1057 PET/CT scan.
Table 2-1	**Update of Incidence of AEs**	Update to remove that incidence of AEs will be described after each PET tracer injection, after each PET/CT scans and at 24-72 h after each PET/CT scan. Indeed, the incidence of AEs will be summarized for AEs occurring during each treatment period (i.e. within 14 days after each PET tracer administration) as described in Section 12.5.2.
Section 3	**Screening assessments update**	Update to remove imaging assessments from screening period paragraph as imaging procedures to be performed in the study do not belong to screening assessments.
Section 4.1	**Update in regions definition**	Update to mention the different regions considered for this study for the [^{18}F]CTT1057 PET/CT evaluation: prostate region (comprising prostate bed/prostate gland and any local invasion of the urinary bladder, rectum or seminal vesicles), PLN region, extra-PLN region, skeletal region and visceral region). The statement that all regions will be assessed for other endpoints is incorrect and was removed as some region-level endpoints are only evaluating the PLN region, while others consider all regions, as detailed in Section 12.
Section 6.3.2	**Update on timelines for ordering**	Update to remove timelines for ordering in the protocol and reference to pharmacy manual was added.
Section 8	**Clarification on assessment requirements for discontinuation from study**	Update to add that safety follow-up visit is to be performed in case of discontinuation from study.
Table 8-1 (footnote*)	**Addition of footnote***	Addition of footnote* to clarify that all screening assessments to confirm eligibility must be done prior enrollment.
Table 8-1	**Clarification of screening period timing**	The table is updated to clarify that enrollment in IRT can occur any time between Day -28 and Day -14 provided all results are available for assessment of subject's eligibility. Day 1 should occur maximum 14 days after enrollment.
Table 8-1	**Update of Day 1 visit window**	The table is updated to allow a visit window of 7 days since the enrollment could occur earlier than 14 days prior Day 1.
Table 8-1 (footnote #7)	**Update on ordering requirements**	Update to clarify that order is to be placed after enrollment and based on drug availability local timelines (refer to Pharmacy

		Manual) in order to perform PET imaging Day 1 no more than 14 days after enrollment.
Table 8-1	**Clarification of urinalysis requirements**	Update for urinalysis as urinalysis results will be documented in source and not captured in the eCRF. Any clinically significant finding for urinalysis testing should be reported in the eCRF as AE.
Section 8.3.1 Table 8-1 (Footnote #9)	**Terminology update for CT scan**	Update to remove the "low dose" terminology which is no longer used in clinical practice for the CT portion of PET/CT (transmission scan).
Section 8.3.1	**Addition of Cross-reference for PET positivity**	Update to add a cross-reference to Section 4.1 for the criteria to be applied for PET positivity for easier reference for local imaging readers.
Table 8-2	**Correction of misplaced information on collection of vital signs**	Update to remove vital signs from the physical examination and include all details in the part of the table already describing vital signs.
Section 8.4.1	**Clarification on lab test results at screening**	Updated to remove the statement that only central laboratory results will be used for assessment of participants' eligibility to the study as eligibility can be based on local laboratory results.
Table 8-4	**Clarification of lab tests**	Updated for clarification that phosphorus laboratory parameter is phosphate (inorganic phosphorus) and that glucose is non-fasting glucose.
Section 8.4.2.1	**Clarification on ECG assessments**	Clarified to confirm that the ECGs should be locally collected and evaluated
Section 8.4.2.2 Table 8-1 (footnote #2)	**Clarification in collection of blood/urine samples for PK**	Updated to clarify that the collection of blood and urine samples for PK subset applies for the patients who consent for the PK sample collection.
Section 9.1 Section 9.1.1	**Clarification in the discontinuation definition and wording**	Update to separate discontinuation from study treatment (not applicable for this study) and discontinuation from study.
Section 9.1.2	**Addition of section**	Update to separate discontinuation from study treatment (not applicable for this study) and discontinuation from study.
Section 9.1.3	**Addition of section**	Update to move the section "lost to follow-up" from "withdrawal of consent" section 9.2, added in the discontinuation study section.
Section 9.2	**Clarification and addition of new concept**	Update to add the concept of "opposition to use data/biological samples" which can occur on top of withdrawal of consent.
Section 9.3	**Clarification on definition and requirements**	Update to add specific actions to be performed prior early discontinuation of the study.
Section 10.1.3 Section 10.1.5	**Clarification on SAE reporting**	Update to emphasize reporting timelines requirements and all related documentation.
Section 10.1.5	**Update of study treatment error section**	Update to remove the concept of "abuse" of study treatment since not applicable to this

		study (only a single dose administered at clinical site).
Section 10.1.5 Table 10-1	**Clarification on study treatment errors/misuse**	Updated to clarify that all study treatment errors/misuse should be reported to the Sponsor. A reference to Table 10-1 was added for guidance on recording of study treatment errors or misuse on the relevant CRF and Table 10-1 was updated to clarify that cases of misuse must be recorded in AE eCRF even if not associated with an AE.
Section 10.1.5 Table 10-1	**Terminology "abuse" not relevant removed**	Updated to remove the terminology of abuse as this is not relevant for the PET imaging tracers used in this study, which are administered to patients on site by qualified site staff and not self-administered.
Section 12	**Clarification of cut-off for final analysis**	Updated to clarify that the cut-off for the final analysis will be the last visit for last subject in the study.
Section 12.5.2	**Update in stats presentation for some data.**	Updated to indicate that clinically notable values or changes in vital signs will be flagged in listings, the ECG result at screening will be summarized as number (%) of subjects with normal or abnormal (clinically significant) ECG and will be provided as listing. ECG timepoints for the patients in the PK subset have been added for reference.
Section 12.4.6	**Update the supplementary analysis description**	Updated to remove PPV from primary endpoint as it is part of secondary endpoint.
Section 12.5.1	**Update of sub-section title**	Updated as Pharmacodynamic is not applicable for the study.
Section 12.5.1	**Update and clarification of definitions**	Alignment with the updated Table 2-1 for endpoints wording.
Section 12.5.3	**Update Pharmacokinetics section**	Update to remove redundancy.
[redacted]		
Section 12.8	**Clarification on analysis set for co-primary endpoints**	Alignment with the updated EFF definition.
All sections	**Minor updates**	Minor typographical corrections, removal of duplicated wording and minor rewording were implemented across the document.

Protocol summary

Protocol number	CAAA405A12302
Full Title	Phase II/III study for evaluation of the diagnostic performance of [^{18}F]CTT1057 PET imaging for the detection of PSMA positive tumors using histopathology as a standard of truth (GuideView)
Brief title	Study of diagnostic performance of [^{18}F]CTT1057 for PSMA-positive tumors detection
Sponsor and Clinical Phase	Novartis Phase II/III
Investigation type	Radiopharmaceutical
Study type	Interventional
Purpose and rationale	[^{18}F]CTT1057 is a promising novel Prostate Specific Membrane Antigen (PSMA)-targeting [^{18}F]-labeled Positron Emission Tomography (PET) imaging agent. Unlike other PSMA agents which share a urea backbone, [^{18}F]CTT1057 is based on a phosphoramidate scaffold that [redacted] binds to PSMA with high nanomolar affinity, which may account for a higher and prolonged tumor uptake. Together with the higher resolution of PET/Computerized Tomography (CT) images when using a [^{18}F]-labelled PET agent, it would therefore favor the identification of smaller lesions, and consequently, also at earlier stages of the disease. A [^{18}F]CTT1057 Phase-I study has shown an acceptable safety profile without any radiotracer-related adverse reactions, and has provided preliminary evidence of diagnostic performance of [^{18}F]CTT1057 PET in detecting and localizing PSMA-positive tumors using pathology as standard of truth (SoT). The purpose of this study is to evaluate the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positive tumors using histopathology as SoT. Tissue specimens from both the primary tumor and PLN dissected during surgery from patients with newly-diagnosed high-risk prostate cancer (PCa) will be used for the histopathology assessments.
Primary Objective(s)	The co-primary objectives of this study are • to evaluate the patient-level sensitivity of [^{18}F]CTT1057 • to evaluate the region-level specificity of [^{18}F]CTT1057 The primary clinical question of interest is: Does [^{18}F]CTT1057 target PSMA expressing PCa cells, allowing to obtain adequate [^{18}F]CTT1057 PET/CT images to detect and localize PSMA positivity using histopathology as SoT?
Secondary Objectives	• To evaluate the patient-level specificity of [^{18}F]CTT1057 • To evaluate the patient-level positive predictive value of [^{18}F]CTT1057 • To evaluate the patient-level negative predictive value of [^{18}F]CTT1057 • To evaluate the patient-level accuracy of [^{18}F]CTT1057 • To evaluate the region-level sensitivity of [^{18}F]CTT1057 for patients excluding micro-metastasis • To evaluate the region-level sensitivity of [^{18}F]CTT1057 • To evaluate the region-level positive predictive value of [^{18}F]CTT1057 • To evaluate the region-level negative predictive value of [^{18}F]CTT1057 • To evaluate the region-level accuracy of [^{18}F]CTT1057 • Detection of distant metastasis in PS patients

	• To characterize the safety and tolerability of [^{18}F]CTT1057 • [^{18}F]CTT1057 scan inter-reader variability • [^{18}F]CTT1057 scan intra-reader variability • To further assess [^{18}F]CTT1057 pharmacokinetics in humans in subset of approximately 10 patients
Study design	This is a multi-center, single-arm, open-label prospective study to evaluate the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positive tumors, using histopathology as SoT. Tissue specimens from both the primary tumor and PLN dissected during surgery from patients with newly-diagnosed high-risk PCa will be used for the histopathology assessments. All participants will receive [^{18}F]CTT1057 for PET/CT scan imaging, and surgery will be performed up to 6 weeks after but not sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan [^{18}F]CTT1057 PET/CT for pathology assessment of the tissue specimens. The co-primary endpoints of patient-level sensitivity and region-level specificity will be assessed by comparing the central reading results of the [^{18}F]CTT1057 PET scan to the histopathology results in the dissected tissue specimens, i.e. both the primary tumor and the dissected PLN. Pathology will be assessed by the local pathologists as per Standard of Care (SoC), who will be blinded to the PET data.
Study population	Male participants ≥ 18 years of age, with newly diagnosed high-risk PCa who are candidates for radical prostatectomy (RP) and extended lymph node resection as per SoC. Approximately 195 participants will be enrolled to ensure that at least 156 participants are evaluable (i.e. have both an evaluable PET/CT scan and histopathology assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CT and surgery), which will be required for the calculation of the co-primary endpoints.
Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • Untreated high risk biopsy-proven PCa patients according to D'Amico classification (Stage ≥ T2c or Prostate Specific Antigen (PSA) level >20ng/ml or Gleason score ≥8) • Scheduled or planned radical prostatectomy and extended pelvic lymph node resection up to 6 weeks after the investigational PET/CT scan followed by histopathology assessment • Eastern Cooperative Oncology Group (ECOG) performance status 0-2 • Participants must be adults ≥ 18 years of age
Exclusion criteria	• Inability to complete the needed investigational and standard-of-care imaging examinations due to any reasons (severe claustrophobia, inability to lie still for the entire imaging time, etc.) • 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, including, but not limited to, current severe urinary incontinence, hydronephrosis, severe voiding dysfunction, need of indwelling/condom catheters, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome,

	uncontrolled infection, active hepatitis B or C, and Coronavirus Disease 2019 (COVID-19) • Known allergy, hypersensitivity, or intolerance to [^{18}F]CTT1057 • Prior and current use of PSMA targeted therapies • Prior and current treatment with any Androgen Deprivation Therapy (ADT) (first or second generation), including Luteinizing Hormone-Releasing Hormone (LHRH) analogues (agonists or antagonists) • Any 5-alpha reductase inhibitors within 30 days before screening • Patients with small cell or neuroendocrine PCa in more than 50% of biopsy tissue • Patients with incidental PCa after transurethral resection • Use of other investigational drugs within 30 days before screening
Study treatment	The term "Study Treatment" indicates the administration of [^{18}F]CTT1057 whether the PET/CT scan was acquired or not.
Treatment of interest	In this study, the investigational imaging agent of interest [^{18}F]CTT1057, injected as a single intravenous dose of approximately 370 Mega-Becquerel (MBq) and subsequent PET/CT scan.
Efficacy assessments	Efficacy assessments in this study include local histopathology assessments (primary tumor and PLN) and central reads of PET/CT images using a [^{18}F]CTT1057 agent.
Pharmacokinetic assessments	Summary statistics of [^{18}F]CTT1057 pharmacokinetic parameters (i.e. Cmax, Tmax, Area under the plasma concentration-time curve (AUC)last, AUCinf, T1/2, Vz and clearance (CL) from blood radioactivity data Quantification of urinary excretion of [^{18}F]CTT1057 from urine data
Key safety assessments	• Adverse Events (AEs) • Serious Adverse Events (SAEs) • Vital signs, physical examinations • Electrocardiograms (ECGs) • Laboratory parameters including hematology, clinical chemistry, urinalysis • Concomitant medications and/or therapies
[redacted]	

Data analysis	The following data analyses are planned for the study:
	The co-primary endpoints of the study are patient-level sensitivity and region-level specificity.
	• Patient-level sensitivity is defined as the proportion of PSMA true positive (TP) patients among PSMA TP patients and PSMA false negative (FN) patients.
	  • PSMA TP patients are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLN with anatomically localized correspondence with the SoT.
	  • PSMA FN patients are those who do not show any pathological [^{18}F]CTT1057 uptake either in the primary tumor or metastatic PLN but will be confirmed having primary tumor or metastatic PLN with the SoT.

	Patient-level sensitivity and its 95% confidence interval (CI) will be calculated based on the binomial distribution. The lower bound of the 95% CI for patient-level sensitivity should be greater than 0.5 to attain the first co-primary endpoint.
	• Region-level specificity is defined as the proportion of PSMA true negative (TN) regions among PSMA TN regions and PSMA false positive (FP) regions.
	  • PSMA TN regions are regions that test negative for PLN on [^{18}F]CTT1057 and confirmed negative on the SoT.
	  • PSMA FP regions are regions that test positive for PLN on [^{18}F]CTT1057 but verified negative on the SoT.
	Region-level specificity and its 95% CI will be calculated based on the binomial distribution.
	The lower bound of the 95% CI for specificity should be greater than 0.70 for the study to attain the second co-primary endpoint.
	Analyses for co-primary endpoints will be based on the efficacy analysis set. Other secondary endpoints including patient-level specificity of [^{18}F]CTT1057, patient-level positive predictive value, patient-level negative predictive value, patient-level accuracy, region-level sensitivity excluding micro-metastasis, region-level sensitivity including micro-metastasis, region-level positive predictive value, region-level negative predictive value, region-level accuracy, incidence of AEs, inter-reader agreement, Intra-reader agreement, Pharmacokinetic (PK) parameters will also be analyzed. Detailed statistical methodology for these analyses will be provided in the statistical analysis plan.

Key words	[^{18}F]CTT1057, PET/CT, Radioligand, Imaging, Primary Staging (PS), SoT, PCa

1 Introduction

1.1 Background

Prostate-specific membrane antigen (PSMA) and prostate cancer

Prostate-specific membrane antigen (PSMA) is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed in the tumor cells of prostate adenocarcinomas (Mannweiler et al 2009, Hupe et al 2018, Bravaccini et al 2018) and has also been reported to be overexpressed in tumor cells and tumor-vasculature of endometrial and ovarian cancer (Wernicke et al 2017), and mainly in tumor-vasculature of a variety of other cancer types such are breast (Tolkach et al 2018), colorectal, gastric (Haffner et al 2009), glioblastoma (Wernicke et al 2011, Tanjore Ramanathan et al 2020), kidney (Spatz et al 2018), liver (Tolkach et al 2019), lung (Wang et al 2015, Schmidt et al 2017) and pancreatic cancer (Stock et al 2017). PSMA has restricted and several hundred-fold lower expression than PCa cells in some normal tissues such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al 1998, Ghosh and Heston 2004).

From all the above named PSMA-overexpressing tumors, PCa is the one in which the role of PSMA has been more extensively studied. PCa remains the cancer with the second highest mortality in the United States (US), and the third leading cause of cancer-related death in Europe in men (Siegel et al 2017, Malvezzi et al 2019). It also remains the most diagnosed cancer with an estimated increase of 9,960 new cases with a total of 164,690 in 2018 (Siegel et al 2018) to174,650 in 2019 (Siegel et al 2019). Most of the diagnosed cases are in more developed regions due to the use of PSA testing, but there is only modest variation in mortality rates globally which is driven by metastatic, and often castration-resistant disease (Bray et al 2013). Subsequent treatment is multifaceted and may involve observation, surgery (prostatectomy), radiation therapy (external beam or brachytherapy), hormonal therapy, chemotherapy, and in the near future, radioligand therapy (Roscigno et al 2005, Jani 2006). PSMA overexpression correlates with advanced, high-grade, metastatic, androgen-independent disease (Ross et al 2003). The differential expression of PSMA from tumor to non-tumor tissue has resulted in numerous targeted strategies involving both disease localization using PSMA-PET imaging as well as therapeutic intervention. Correct identification of disease location and extent determines treatment decisions for patients with PCa. Identification of distant metastatic disease at the initial diagnosis of PCa is important in planning PCa management. There is increasing evidence that primary landing sites for PCa lie outside the template of an extended pelvic lymph node dissection (ePLND). Primary lymph node landing sites outside an ePLND have been reported in 47.7% of men with suspected node-positive disease on [^{68}Ga]Ga-PSMA PET/CT (Yaxley et al 2019a). This is very important, as the morbidity of an ePLND could be avoided, given the change in expectation of management from one of curative intent, to management that will require a multimodality approach after treatment of the prostate primary (Yaxley et al 2018, Yaxley et al 2019b). It is relevant, therefore, to detect smaller lesions as early as possible. With the emergence of PSMA-targeted radioligand therapy, in addition to early diagnosis accurate PSMA-positivity detection is needed to determine the future use of radioligand therapy.

Positron Emission Tomography (PET) imaging in PCa

The usual diagnostic tools for PCa include PSA testing, digital rectal palpation, transrectal ultrasound, prostate biopsy, and histopathologic examination (Schwarzenböck et al 2012, Smith et al 2016, Prasad et al 2016). Additionally, further imaging techniques such as Magnetic Resonance Imaging (MRI), bone scintigraphy, CT, and [^{18}F]Fluorodeoxyglucose (FDG), [^{18}F]Choline, [^{11}C]Choline and the most recently approved [^{18}F]-fluciclovine (Nanni et al 2016, Odewole et al 2016) PET/CT are used for staging primary PCa and restaging biochemical recurrences (Schwarzenböck et al 2012). CT and MRI are the standard of care imaging procedures for measuring tumors at baseline and lesions selected for response assessment as per Response Evaluation Criteria In Solid Tumors (RECIST) criteria 1.1(Eisenhauer et al 2009). However, these imaging modalities have shown limited yielding in the staging of PLN in patients with PCa. A meta-analysis showed pooled sensitivities of 0.42 (95% CI 0.26-0.56) for CT, and of 0.39 (95% CI 0.22-0.56) for MRI (Hövels et al 2008). Therefore, more sensitive and accurate imaging tests than the currently available Standard of Care (SoC) examinations are needed (Hricak et al 1987, Shinohara et al 1989, Scheidleret al 1999, Blomqvist et al 2014). Novel PET radiotracers promise to overcome this limitation. PET imaging is an enticing choice as it offers the potential to both stage patients and provide insight into tumor biology. Among the various PET probes available, ^{68}Ga-labeled ligands of the PSMA were associated with unprecedented accuracy and effect on treatment in several meta-analyses of retrospective studies (Perera et al 2016, Han et al 2018, Von Eyben et al 2018). Recent studies reported that ^{68}Ga-labeled PSMA PET/CT has excellent detection rates for lymph node metastases, skeletal metastases, local relapses, and soft-tissue metastases compared with other PET tracers such as ^{18}F- and ^{11}C-labeled choline derivatives (Afshar-Oromieh et al 2013, Afshar-Oromieh et al 2014, Ceci et al 2015, Eiber et al 2015, Budäus et al 2016). Since its introduction in 2012, [^{68}Ga]Ga-PSMA-11 is the most studied PSMA PET agent to date. It has been widely used in clinical practice on a compassionate use basis and reported in prospective studies and numerous retrospective case series (Afshar-Oromieh et al 2015, Eiber et al 2015, Morigi et al 2015, Meredith et al 2016, Sachpekidis et al 2016, Afshar-Oromieh et al 2017, Berliner et al 2017, Gupta et al 2017, Hope et al 2017, Sanli et al 2017, Schmuck et al 2017, Derlin et al 2018, Grubmüller et al 2018, Kranzbühler et al 2018, Lengana et al 2018, Rauscher et al 2018, Fendler et al 2019), and it has been recently approved in the USA (December 2020) as a radioactive diagnostic PET imaging agent in men with PCa with suspected metastasis who are candidates for initial definitive therapy, or with suspected recurrence based on elevated serum PSA level ([15Ga]Ga-PSMA-11 USPI). However, despite the diagnostic accuracy of [^{68}Ga]Ga-PSMA-11, its practical use at scale is limited by the short half-life of ^{68}Ga, which requires radiolabeling in close proximity to the point of care. Moreover, the yield of currently available ^{68}Ga generators limits the manufacturing of the number of doses required to address the growing population of PCa patients. This gap between the unmet need and availability is expected to widen as radio-ligand therapy options are available for treatment. While solid targetry using cyclotrons (currently unapproved for clinical use) can generate greater quantities of ^{68}Ga, and thereby more doses, the geographical reach of the few cyclotrons coupled with the short half-life of ^{68}Ga would still leave this need unaddressed.

[^{18}F]CTT1057: A promising investigational PSMA-PET radiotracer

Most experts in the field agree, the future of PSMA-based PET imaging will be with ^{18}F-labeled tracers because of the practical advances: ^{18}F has a longer half-life than ^{68}Ga, which enables the tracers to be distributed to PET centers without a cyclotron and to be easily handled in clinical routine. In addition, the higher positron decay branching of ^{18}F (96.9%) versus ^{68}Ga (87.7%), together with the shorter positron range of ^{18}F, account to the higher PET imaging resolution achieved with ^{18}F-labeled radiopharmaceuticals (Conti and Eriksson 2016). [^{18}F]CTT1057 is a promising novel PSMA-targeting ^{18}F-labeled PET imaging agent. Unlike most other PSMA agents labelled with either ^{68}Ga or ^{18}F (e.g. [^{68}Ga]Ga-PSMA-11, [^{18}F]PSMA1007, [^{18}F]DCFPyL) which share a urea backbone, [^{18}F]CTT1057 is based on a phosphoramidate scaffold that [redacted] binds to PSMA with high nanomolar affinity, which may account for a higher and prolonged tumor uptake (Behr et al 2019). Together with the higher resolution of PET/CT images when using a ^{18}F-labelled PSMA agent, it would therefore favor the identification of smaller lesions, and consequently, also at earlier stages of the disease.

A Phase-I study in 20 PCa patients (n=5 primary staging, n=15 metastatic-castration resistant prostate cancer (mCRPC)) (Behr et al 2019) has shown an acceptable safety profile, without any radiotracer-related adverse reactions. The biodistribution of [^{18}F]CTT1057 in humans is similar to that of other PSMA-targeted agents, and exposure rates of [^{18}F]CTT1057 are also similar to those of the urea-based PET compounds, with the advantageous exception of lower exposure to kidneys and salivary glands. Preliminary evidence of diagnostic performance of [^{18}F]CTT1057 PET in detecting and localizing PSMA-positive tumors was provided from the n=5 primary staging patients using pathology as SoT. Abnormal [^{18}F]CTT1057 PET uptake corresponding to the pathology-proven cancer was shown in 4 of the 5 subjects. The only subject who did not show PET uptake in the primary tumor had the lowest PSA in the cohort. The Phase-I study also demonstrated that metastatic lesions are detected with higher sensitivity on [^{18}F]CTT1057 imaging than on conventional imaging (Behr et al 2019). Another smaller study showed that the image quality on [^{18}F]CTT1057 PET imaging was qualitatively similar to that obtained on [^{68}Ga]Ga-PSMA-11 PET (Behr et al 2017*)*.

Further details on [^{18}F]CTT1057 can be found in the Investigator's Brochure (IB).

1.2 Purpose

The purpose of this study is to evaluate the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positive tumors using histopathology as SoT. Tissue specimens from both the primary tumor and PLN dissected during surgery from patients with newly-diagnosed high-risk PCa will be used for the histopathology assessments.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Evaluate the patient-level sensitivity of [^{18}F]CTT1057	• Sensitivity of [^{18}F]CTT1057 PET imaging, considering PSMA positive patients as those who show at least one pathological

Objective(s)	Endpoint(s)
	[^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLN regions, with anatomically localized correspondence with the SoT. See Section 2.1 for Primary Estimand.
• Evaluate the region-level specificity of [^{18}F]CTT1057	• Specificity of [^{18}F]CTT1057 PET imaging, defined as proportion of PLN regions that test negative for lymph nodes on [^{18}F]CTT1057 among those that are lymph node negative on the SoT. See Section 2.1 for Primary Estimand.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Evaluate the patient-level specificity of [^{18}F]CTT1057	• Specificity of [^{18}F]CTT1057 PET imaging, considering PSMA negative patients as those who do not show any pathological [^{18}F]CTT1057 uptake either in the primary tumor or PLNs and will be confirmed not having primary tumor or metastatic PLNs with the SoT
• Evaluate the patient-level positive predictive value of [^{18}F]CTT1057	• Proportion of patients who are both [^{18}F]CTT1057 and SoT positive (true positives (TP) among those who test positive on [^{18}F]CTT1057 (TP+ false positives(FP))
• Evaluate the patient-level negative predictive value of [^{18}F]CTT1057	• Proportion of patients who are both [^{18}F]CTT1057 and SoT negative (true negatives (TN)) among those who test negative on [^{18}F]CTT1057 (TN+ false negatives (FN))
• Evaluate the patient-level accuracy of [^{18}F]CTT1057	• Proportion of patients that are SoT and [^{18}F]CTT1057 positive (TP) and negative (TN) among all patients in EFF (TP+TN+FP+FN)
• Evaluate the region-level sensitivity of [^{18}F]CTT1057 for patients excluding micro-metastasis	• Sensitivity of [^{18}F]CTT1057 PET imaging in the PLN region, excluding from the analysis those lymph nodes showing metastasis <2mm (micro-metastasis)
• Evaluate the region-level sensitivity of [^{18}F]CTT1057	• Proportion of PLN regions that test positive on both [^{18}F]CTT1057 and SoT (TP) among those that are SoT positive (TP+FN)
• Evaluate the region-level positive predictive value of [^{18}F]CTT1057	• Proportion of PLN regions that are SoT and [^{18}F]CTT1057 positive (TP) among those regions that test positive on [^{18}F]CTT1057 (TP+FP)
• Evaluate the region-level negative predictive value of [^{18}F]CTT1057	• Proportion of PLN regions that are SoT and [^{18}F]CTT1057 negative (TN) among those regions that test negative on [^{18}F]CTT1057 (TN+FN)
• Evaluate the region-level accuracy of [^{18}F]CTT1057	• Proportion of PLN regions that are SoT and [^{18}F]CTT1057 positive (TP) and negative (TN) among all PLN regions assessed [^{18}F]CTT1057 (TP+TN+FP+FN)
• Detection of distant metastasis in PS patients	• Number of distant metastasis (extra-PLN, visceral or skeletal) identified at PET/CT scan per patient, and percentage of patients with at least one distant metastatic lesion identified by PET/CT scan
• Characterize the safety and tolerability of [^{18}F]CTT1057	• Incidence of AEs. Treatment emergent adverse event (TEAE) rate within 14 days of administration
• [^{18}F]CTT1057 scan inter-reader variability	• Inter-reader agreement of [^{18}F]CTT1057 images

Objective(s)	Endpoint(s)
• [^{18}F]CTT1057 scan intra-reader variability	• Intra-reader agreement of [^{18}F]CTT1057 images
• To further assess [^{18}F]CTT1057 pharmacokinetics in humans in subset of approximately 10 patients	• Summary statistics of [^{18}F]CTT1057 pharmacokinetic parameters (i.e. Cmax, Tmax, AUClast, AUCinf, T1/2, Vz and CL from blood radioactivity data; quantification of urinary excretion of [^{18}F]CTT1057 from urine data)
[redacted]	

2.1 Primary estimands

The primary clinical question of interest is: Does [^{18}F]CTT1057 target PSMA expressing PCa cells, allowing to obtain adequate [^{18}F]CTT1057 PET/CT images to detect and localize PSMA positivity using histopathology as SoT?

The justification for the primary estimand is that we wish to assess the diagnostic performance of [^{18}F]CTT1057 PET in detecting and localizing PSMA positivity. For this reason, newly-diagnosed high risk PCa patients will undergo a [^{18}F]CTT1057 PET/CT scan within 6 weeks before surgery (but not sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan), and results of the [^{18}F]CTT1057 PET/CT scans will be compared against the histopathology results (SoT) in the dissected tissue specimens (primary tumor and PLN), both at a patient and region level.

The primary estimands are described by the following attributes:

Primary estimand 1:

1. Population: Untreated high risk PCa patients according to D'Amico classification (Stage ≥ T2c or PSA level >20ng/ml or Gleason score ≥8) (D'Amico et al 1998), who are scheduled or planned RP and lymph node resection. Further details about the population are provided in Section 5.
2. Variables: Proportion of patients that test positive on both [^{18}F]CTT1057 and SoT (TP) among those that are SoT positive (TP + FN), considering PSMA positive patients are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLN, with anatomically localized correspondence with the SoT.

3. Treatment (investigational imaging agent) of interest: [^{18}F]CTT1057 injected as a single intravenous dose of approximately 370 MBq and subsequent PET/CT scan. Further details about the investigational imaging agent are provided in Section 6.
4. Handling of remaining intercurrent events:
   - Patients who received the investigational imaging agent [^{18}F]CTT1057 but did not undergo/complete the PET/CT scan for any reasons (e.g. consent withdrawal, PET camera failures, etc.), will be excluded from the primary analysis. Details on how to handle intercurrent events are provided in Section 12.4.3.
5. Summary measure: Estimate of proportion of patients that test positive on both [^{18}F]CTT1057 and SoT (TP) among those that are SoT positive (TP + FN), considering PSMA positive patients are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLN, with anatomically localized correspondence with the SoT, along with its 95% CI Further details on how the summary measure will be tested are provided in Section 12.4.2.

Primary estimand 2:

1. Population: the same as the primary estimand 1
2. Variables: Proportion of PLN regions that test negative on both [^{18}F]CTT1057 and SoT (TN) among those PLN region that test negative on the SoT (TN + FP), considering PSMA negative PLN regions those that do not show any pathological [^{18}F]CTT1057 uptake within the region.
3. Treatment (investigational imaging agent) of interest: the same as the primary estimand 1
4. Handling of remaining of intercurrent events: the same as the primary estimand 1
5. Summary measure: Estimate of the proportion of PLN regions that test negative on both [^{18}F]CTT1057 and SoT (TN) among those PLN region that test negative on the SoT (TN + FP), considering PSMA PLN negative regions those that do not show any pathological [^{18}F]CTT1057 uptake within the region, along with its 95% CI. Further details on how the summary measure will be tested are provided in Section 12.4.2.

2.2 Secondary estimands

Not applicable

3 Study design

This is a multi-center, single-arm, open-label prospective study to evaluate the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positive tumors, using histopathology as SoT. Tissue specimens from both the primary tumor and PLN dissected during surgery from patients with newly-diagnosed high-risk PCa will be used for the histopathology assessments.

Approximately 195 participants will be enrolled to ensure that at least 156 participants are evaluable for co-primary endpoints. Surgery will be performed up to 6 weeks after [^{18}F]CTT1057 PET/CT but not sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan (in order to limit the potential confounding factors related to the effects of surgery

for the assessment of [^{18}F]CTT1057 PET/CT safety) for pathology assessment of the tissue specimens.

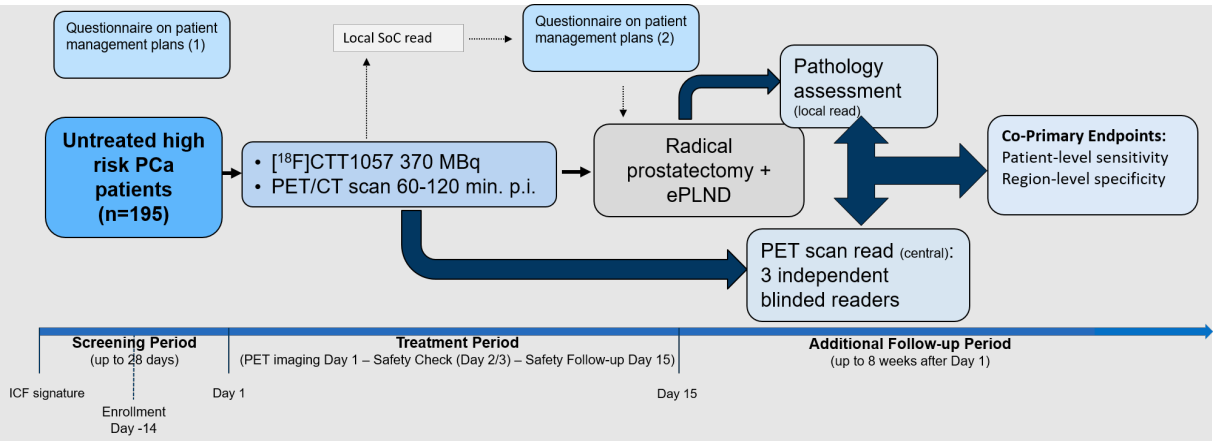
The co-primary endpoints of patient-level sensitivity and region-level specificity will be assessed by comparing the central reading results of the [^{18}F]CTT1057 PET/CT scan (see Section 4.1 and Section 8.3.1 for central read details and Section 6.4 for blinding details) to the histopathology results in the dissected tissue specimens, i.e. both the primary tumor and the dissected PLN (Maurer et al 2016, Woythal et al 2018, Kuten et al 2020).

Pathology will be assessed by the local pathologists as per SoC. Pathologists will be blinded to the PET data. For anatomical localization, a sextant anatomic template for the prostate and a left/right template for the PLN will be used (see appendix Section 16.2). Pathology results should be available within 2 weeks after surgery.

[redacted]

See Figure 3-1 for study design schema.

Figure 3-1 Study Design



Screening Period

Written informed consent form (ICF) must be obtained prior to any screening procedures. The participant must be registered in the Interactive Response Technology (IRT) for screening and [^{18}F]CTT1057 requested. All procedures described in the Assessment Schedule as per Table 8-1 must be carried out, prioritizing laboratory assessments to allow time to obtain the results at least 14 days prior the planned PET imaging day (Day 1). The participants will be

assessed for eligibility before they will undergo a [^{18}F]CTT1057 PET/CT scan. Eligibility must then be confirmed at the latest on Day -14. The screening period should last up to 28 days.

[^{18}F]CTT1057 PET imaging day:

[^{18}F]CTT1057 PET imaging will be performed using a standard integrated PET/CT system. The following steps to take place during this day are described in Section 8.3.1.

In the PK subset of approximately 10 participants at the same site, several blood and urine samples as well as additional ECG assessments for safety will be done at the pre-specified time points on PET imaging day.

Safety Check

All treated participants will be contacted by phone within 24 to 72 hours following the scan in order to capture potential occurring Adverse Events.

Safety Follow-up

Participants will come back to the hospital 14 days after the PET/CT scan day, for a safety visit including vital signs, lab and urine analysis. For participants undergoing surgery prior to planned safety visit, these safety follow-up assessments will need to be performed before the surgery but not sooner than 48 hours after the PET/CT scan.

Additional Follow-up

Surgery (RP/ePLND) will be scheduled for all participants as planned per SoC on a date that must not be sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan, and no later than 6 weeks after completion of the [^{18}F]CTT1057 PET/CT scan. Final histopathology results have to be obtained within 2 weeks after surgery.

4 Rationale

4.1 Rationale for study design

In this study, a single-dose of the investigational PET imaging radiopharmaceutical [^{18}F]CTT1057 will be administered intravenously, in an open-label single-arm design.

The most commonly used measures for evaluating the diagnostic performance of a new imaging modality are sensitivity and specificity. Histopathology of the tumor samples is considered as the SoT to assess the diagnostic performance of PET tracers targeting PSMA (Maurer et al 2016, Woythal et al 2018, Kuten et al 2020). In PS patients, both the primary tumor and the metastatic lymph nodes (LN) are expressing PSMA, which is the target for [^{18}F]CTT1057 binding. Within a period of up to 6 weeks after completion of the [^{18}F]CTT1057 PET/CT scan, patients will undergo surgery as per their standard of care treatment plan, consisting of RP and ePLND, as per the European Association of Urology (EAU) guidelines for Prostate Cancer 2020 (refer to Section 16.1).

In addition to the prostate dissection, a minimum of 12 PLN per patient will be dissected in order to have enough numbers of PLN in total for the calculation of the co-primary endpoints and the diagnostic performance yielding secondary endpoints.

Local pathologists with experience in PCa who will be blinded to the [^{18}F]CTT1057 PET/CT results will then assess the tissue specimens as per SoC. For the anatomical correspondence with PET/CT images, a sextant template will be used for the prostate (Kuten et al 2020). For the PLN, an anatomical side approach left/right will be used, since the borders of dissection are not usually very clear neither for the surgeon nor for the pathologist.

A central read of the PET/CT scan will be performed at a Contract Research Organization (CRO) by a total of three independent nuclear medicine physicians or radiologists experienced in reading oncology PET, who will be blinded to patient data, including the clinical condition of the patient, results of histopathology/biopsy, and results of conventional imaging. Patients and regions will be graded on a two-point scale by each reader (0 = negative; 1 = positive). The results from each of the 3 readers will be individually compared to the SoT to generate per-reader performance. An individual PET reader will be considered successful if he/she meets predefined thresholds for both co-primary endpoints, and at least two of three readers should be successful for overall study positive. PET results will be compared to histopathology results, and anatomically localized positive lesions in both PET and histopathology will be considered "TP" for sensitivity and specificity calculations as the primary endpoints of the study.

Regions defined for this study are prostate region (comprising prostate bed/prostate gland and any local invasion of the urinary bladder, rectum or seminal vesicles), PLN region, extra-PLN region, skeletal region and visceral region.

The criteria to be applied for PET positivity is the following:

- A patient will be judged as positive if at least one lesion in any region is visually positive.
- A region will be judged as positive if at least one lesion in the region is visually positive.
- Visually PET positive lymph nodes will be considered greater than blood pool (adjacent or mediastinal blood pool).
- PET positive bone lesions will be considered greater than physiologic bone marrow.
- PET positive prostate, prostate bed and visceral lesions will be considered greater than physiologic background activity of the involvement organ or anatomic site, as previously described (Ceci et al 2015, Eiber et al 2015, Fendler et al 2019).

Only prostate region and PLN will be used as regions for comparison to the SoT and co-primary endpoint calculations.

Consistency of the PET/CT scan interpretation both between different readers and within readers is an important issue in medical imaging, as it affects portability of results between institutions and may affect patient care. The degree of inter- and intra-reader variability in the qualitative assessment of [^{18}F]CTT1057 PET/CT images will be assessed as a secondary endpoint to ensure consistency of interpretation and hence reliable diagnosis, which has pivotal role in the patient management.

[redacted]

[redacted]. Further details on the questionnaire and procedure are provided in Section 3.

In order to reproduce as much as possible the real clinical context, this [^{18}F]CTT1057 PET/CT scan will be read by a local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans who will not be blinded to patient data. See also Section 6.4 and Section 8.3 for blinding and reading details.

The co-primary endpoints will not be assessed in those patients who, as a consequence of a change in treatment will not be considered suitable for surgery. These patients will remain in the study for the assessment of some secondary [redacted]

4.2 Rationale for dose/regimen and duration of treatment

For PET diagnostic radiopharmaceuticals, only a single administration is required, usually intravenously. The investigational PET radiopharmaceutical [^{18}F]CTT1057 will be administered accordingly, as a single intravenous (i.v.) dose of approximately 370 MBq (266 – 407 MBq). This dose was shown to be safe and well tolerated in the Phase I study (Behr et al 2019), and it is in line with the recommended dose of the commercial product [^{18}F]FDG according to both the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine guidelines (Delbeke et al 2006, Boellaard et al 2015). Human dosimetry was studied in the Phase I study. The effective dose (ED) was estimated at 0.023±0.007 mSv/MBq, which is in line as well with the ED of the commercial product [^{18}F]FDG (0.019 mSv/MBq) according to the EANM guideline (Boellaard et al 2015) and in other publications (0.020-0.025 mSv/MBq) (Kaushik et al 2015), as well as the ED of other PSMA PET agents (Behr et al 2019). The radiation dose estimated from an i.v. administration of 370 MBq of [^{18}F]CTT1057 is 8.51 mSV. Moreover, this dose allowed to obtain the optimal image quality, which was rated 76 ± 5.4 on a Visual Analog Scale (VAS) of 1 to 100 (1 = nondiagnostic, 100 = perfect study), by 2 experienced Nuclear Medicine physicians (Behr et al 2019). Further details on [^{18}F]CTT1057 can be found in the IB.

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

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable

4.5 Risks and benefits

The use of PSMA-PET scanning of PCa participants has been ongoing since 2011, mostly with [^{68}Ga]Ga-PSMA-11, to assess disease burden in the setting of both biochemical recurrence (BCR) and advanced/metastatic disease. Publications that report clinical use have demonstrated better sensitivity and specificity than choline-based PET imaging for PCa, with a very low rate of adverse events. [^{68}Ga]Ga-PSMA-11 has been shown to be well tolerated with no adverse events following infusion in a retrospective analysis of 1007 participants (Afshar-Oromieh et al 2017). Recently, [^{68}Ga]Ga-PSMA-11 has been approved in the USA (December 2020) as a

radioactive diagnostic PET imaging agent in men with PCa with suspected metastasis who are candidates for initial definitive therapy, or with suspected recurrence based on elevated serum PSA level ([15Ga]Ga-PSMA-11 USPI). Subsequently, other PSMA-PET agents have been investigated and are under clinical development, all of them showing a good safety and tolerability profile. PCa patients diagnosed of localized disease, at primary staging, have been enrolled in studies requiring histopathology comparisons to determine diagnostic yield of the technique. A Phase-I study of [^{18}F]CTT1057 in 20 PCa patients (n=5 primary staging, n=15 mCRPC (NCT02916537) has shown an acceptable safety profile, without any radiotracer-related adverse reactions. The biodistribution of [^{18}F]CTT1057 in humans is similar to that of other PSMA-targeted agents, and exposure rates of [^{18}F]CTT1057 are also similar to those of the urea-based PET compounds, with the advantageous exception of lower exposure to kidneys and salivary glands. Preclinical work, dosimetry studies, and clinical experience with [^{18}F]CTT1057 suggest good imaging quality properties and a favorable safety profile (Behr et al 2019).

As this is a study on the diagnostic performance of an investigational PET agent, patients enrolled are not expected to derive direct benefit. It is expected that distant disease will be identified in some patients as a consequence of this study and these patients may benefit from a more appropriated management plan, which will not be based on the investigational procedure alone, but confirmed by SoC diagnostic procedures. The risk-benefit ratio is expected to be favorable to the [^{18}F]CTT1057 imaging agent.

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

Additional details of the nonclinical and clinical experience with [^{18}F]CTT1057 are provided in the Investigator's Brochure.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

In this study, the participant population will consist of males ≥ 18 years of age, with newly diagnosed high-risk PCa who are candidates for RP and extended lymph node resection as per SoC.

Approximately 195 participants will be enrolled to ensure that at least 156 participants are evaluable (i.e. have both an evaluable PET/CT scan and histopathology assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CT and surgery), which will be required for the calculation of the co-primary endpoints. Refer to Section 12.8.1 for sample size calculation.

5.1 Inclusion criteria

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

1a. Untreated high risk biopsy-proven PCa patients according to D'Amico classification (Stage ≥ T2c or PSA level >20ng/ml or Gleason score ≥8) (D'Amico et al 1998)

2. Scheduled or planned radical prostatectomy and extended pelvic lymph node resection up to 6 weeks after the investigational PET/CT scan followed by histopathology assessment
3. ECOG performance status 0-2
4. Signed informed consent must be obtained prior to participation in the study
5. Participants must be adults ≥ 18 years of age

5.2 Exclusion criteria

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

1. Inability to complete the needed investigational and standard-of-care imaging examinations 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, including, but not limited to, current severe urinary incontinence, hydronephrosis, severe voiding dysfunction, need of indwelling/condom catheters, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, uncontrolled infection, active hepatitis B or C, and COVID-19.
3. Known allergy, hypersensitivity, or intolerance to [^{18}F]CTT1057
4. Prior and current use of PSMA targeted therapies

5a. Prior and current treatment with any ADT (first or second generation), including LHRH analogues (agonists or antagonists)

7. Any 5-alpha reductase inhibitors within 30 days before screening
8. Patients with small cell or neuroendocrine PCa in more than 50% of biopsy tissue
9. Patients with incidental PCa after transurethral resection
10. Use of other investigational drugs within 30 days before screening

6 Treatment

6.1 Study treatment

In this study, the investigational imaging agent is the radioligand imaging compound [^{18}F]CTT1057. Participants will be administered [^{18}F]CTT1057 as an intravenous injection, single dose (Refer to Section 6.7 for study drug preparation and dispensation).

All study participants will receive [^{18}F]CTT1057 and the dose is listed in Table 6-1. [^{18}F]CTT1057 will be provided by Novartis.

6.1.1 Investigational and control drugs

Administration of [^{18}F]CTT1057

Study participants will be injected intravenously with approximately 370 MBq (range 266 – 407 MBq) of [^{18}F]CTT1057 (Refer to Section 6.7 for study drug preparation and dispensation).

Table 6-1 Investigational drug

Investigational name	Pharmaceutical Dosage Form	Route of Administration	Frequency	Supply Type	Sponsor (global or local)
[^{18}F]CTT1057 (370 MBq/mL at calibration time (Tc))	Radiopharmaceutical solution for injection	Intravenous use	Single administration	Open label, vial/Syringe	Sponsor (Global)

6.1.2 Additional study treatments

No other treatment beyond investigational imaging agent is included in this trial.

6.1.3 Supply of study treatment

[^{18}F]CTT1057 will be provided as a single mono-dose in syringe (for US) or a single multidose vial (for European Union (EU)) ready to use radiopharmaceutical solution for injection, with a volumetric activity of 370 (±10%) MBq/mL at the reference date and time (calibration time (Tc)). The natural decay of the radionuclide leads to a continuous decrease of the specific activity, the total radioactivity and the radioactive concentration (volumetric activity) over the time. Therefore, the volume of the solution injected varies in order to provide the required amount of radioactivity at the date and time of injection. The exact expiry time based on shelf life of the product and the production activities is reported on the [^{18}F]CTT1057 certificate of release as described in the Pharmacy Manual.

6.1.4 Treatment duration

Participants will receive a single injection intravenously of approximately 370 MBq (range 266 – 407 MBq) of [^{18}F]CTT1057 during the single imaging day.

6.2 Other treatment(s)

6.2.1 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 Case Report Forms.

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

Use of diuretics (e.g. furosemide) to help subject to void before PET/CT scan imaging acquisition is allowed in case of need, upon the discretion of the investigator.

6.2.2 Prohibited medication

Any medication that may interfere with PSMA PET imaging is not allowed. Prior to completing [^{18}F]CTT1057 PET/CT imaging and surgery, any ADT including LHRH analogues (agonists or antagonists) as well as anti-androgens (both first and second generation compounds) and 5-alpha reductase inhibitors are prohibited. Any therapy/procedure that could interfere with PET PSMA imaging is not allowed.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is entered for screening and is retained for the participant throughout his participation in the trial. A new Participant No. will be assigned at every subsequent study participation if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

All eligible participants will be enrolled via IRT. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria.

The investigator or his/her delegate will order the [^{18}F]CTT1057 dose prior to the scheduled dosing date (refer to Pharmacy Manual). The administration will be tracked by the investigator or his/her delegate via IRT. Detailed instructions of Investigational Medicinal Product (IMP) ordering and IRT use will be provided in the Pharmacy Manual.

6.4 Treatment blinding

Treatment will be open to participants, investigator staff, persons performing the assessments, and the study team. The following blinding is applicable in this study:

- [^{18}F]CTT1057 PET/CT images will be submitted to a CRO for independent centralized review by 3 independent reviewers blinded to patient data collected in clinical database (such as medical history details or diagnostic test results).
- Pathology assessments by the local pathologists will be performed as per SoC. Pathologists will be blinded to the [^{18}F]CTT1057 PET/CT data, but not to other relevant patient data.
- [^{18}F]CTT1057 PET/CT images will be reviewed by a local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans, who will not be blinded to

patient data and the results will be provided to the treating physician / Clinical Study [redacted]

6.5 Dose escalation and dose modification

Investigational dose adjustments and/or interruptions are not applicable in this study in which the imaging agent is administered only once.

6.5.1 Follow-up for toxicities

Participants whose treatment is discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. All participants must be followed up for adverse events as described in Table 8-1.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

All participants will have the study treatments administered during site visits as per schedule of events in Table 8-1. All study treatments must be recorded in the Drug Accountability Log and in the corresponding electronic case report form (eCRF) pages.

6.7 Preparation and dispensation

Each study site will be supplied with the study drug packaged as described under Section 6.1.1.

[^{18}F]CTT1057 is a ready to use solution for injection therefore no preparation is needed. Please refer to procedure and instructions contained in the Pharmacy Manual.

Immediately after administration to the participant, site personnel will complete the study treatments accountability logs for traceability purpose. For more detailed instructions, please refer to the Pharmacy Manual.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 IB.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

The investigator must maintain an accurate record of the shipment and dispensing of study treatments in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

[^{18}F]CTT1057

The packaging [^{18}F]CTT1057 consists of a white glass multidose vial (For EU) or a mono-dose syringe (US) containing the sterile radioactive solution.

[^{18}F]CTT1057 solution should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

Since [^{18}F]CTT1057 is a ready-to-use solution, no manipulation of the investigational product is intended at the clinical site, except the:

- dispensation into mono-dose syringes, or the use of automatic dispenser and infusion system, according to local procedure, when applicable.
- disposal which must be documented appropriately and a copy of the completed drug accountability log should be sent on a regular basis to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

The radioactive [^{18}F]CTT1057 will be locally discarded according to all disposal requirements and local regulations for radioactive materials.

For [^{18}F]CTT1057 solution storage conditions, quality control (QC), administration and disposal, clinical sites must follow instruction as describe in the [^{18}F]CTT1057 Pharmacy Manual.

These different steps in [^{18}F]CTT1057 product management have to be documented as described in the Pharmacy Manual using forms/log provided in the investigator folder at each site in order to ensure traceability of the product at any time.

[^{18}F]CTT1057 labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions, batch number, expiry date.

6.7.2 Instruction for preparing and administering study treatment

[^{18}F]CTT1057

Preparation

[^{18}F]CTT1057 is a ready-to-use multi-dose vial (EU) or a mono-dose syringe (US).

The instruction for cautionary notes, analytical controls and stability of the radiolabeled product will be provided to each site (please refer to the Pharmacy Manual).

Administration

Injection of [^{18}F]CTT1057 must be performed in accordance with national and/or local radiation and safety requirements.

Approximately 370 MBq (range 266 – 407 MBq) of [^{18}F]CTT1057 will be injected intravenously then flushed by 10 mL of saline.

The radioactive [^{18}F]CTT1057 will be locally discarded according to all disposal requirements and local regulations for radioactive materials.

The total activity administered must be recorded (mCi or MBq) by measuring the residual radioactivity in the vial or in the syringe before and after administration with the dose calibrator (or activimeter).

For clinical sites equipped with an automatic infusion system, apply the local procedure to register the exact amount of radioactivity injected.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (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 understanding. If the participant is capable of doing so, he must indicate agreement by personally signing and dating the written informed consent document.

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.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference), if allowable by a local Heath Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc).

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug 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 informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - a subsection that requires a separate signature for the Optional Consent for the PK analyses. The study includes optional additional assessments for PK analyses that

requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to patients, as permitted by local governing regulations. Declining to participate in these optional assessments for PK analyses will in no way affect the patient's ability to participate in the main research study.

- a subsection that requires a separate signature for the Optional Consent for Additional Research to allow future research on data/samples collected during this study.

A copy of the approved version of all consent forms must be provided to Novartis/Sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants whodiscontinue from the study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule. Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples 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, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the case report form (CRF).

As per Section 4.6, 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 allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	**Screening**		**Treatment**							**Additional Follow-up**	**Study Completion**
Visit Name	**Screening**	**Enrolment**	**PET Imaging**					**Safety Check**	**Safety Follow-up**	**Additional Follow-up**	**EOS**[1]
Days	**Day -28 to Day -14**	**Day -28 to Day -14**	**Day 1 (+ 7)**					**Day 2 to 3**	**Day 15 (+3)**[11]	**Up to 8 weeks after Day 1**	**Day 15 to Follow-up end**
Time (post-dose)	**-**	**-**	**Pre-Injection**	**Injection**	**Post-Injection/ Pre-imaging**	**Imaging**	**Post-Imaging/ EOT**	**-**	**-**	**-**	**-**
Informed consent	X										
IRT participant registration	X										
Inclusion / Exclusion criteria	X										
Medical History & Demographics	X										
Electrocardiogram (ECG)	X		X[2]		X[2]		X[2]		X[2]		
ECOG Performance Status	X										
Physical Examination	S (short)		S (short)						S (short)		

Period	**Screening**		**Treatment**							**Additional Follow-up**	**Study Completion**
Visit Name	**Screening**	**Enrolment**	**PET Imaging**					**Safety Check**	**Safety Follow-up**	**Additional Follow-up**	**EOS**[1]
Days	**Day -28 to Day -14**	**Day -28 to Day -14**	**Day 1 (+ 7)**					**Day 2 to 3**	**Day 15 (+3)**[11]	**Up to 8 weeks after Day 1**	**Day 15 to Follow-up end**
Time (post-dose)	**-**	**-**	**Pre-Injection**	**Injection**	**Post-Injection/ Pre-imaging**	**Imaging**	**Post-Imaging/ EOT**	**-**	**-**	**-**	**-**
Body Weight	X		X								
Body Height	X										
Vital Signs[3]	X		X		X		X		X		
Hematology[4]	X		X						X		
Clinical Chemistry[4]	X		X						X		
PSA level	X										
Urinalysis[5]	S		S						S		
PK Sample Collection[6]			For approximately 10 participants from the same clinical site only								
Adverse Events	AEs to be collected throughout this period										
Concomitant medications	Concomitant Medications to be collected throughout this period										
IRT enrollment		X									

Period	Screening		Treatment							Additional Follow-up	Study Completion
Visit Name	Screening	Enrolment	PET Imaging					Safety Check	Safety Follow-up	Additional Follow-up	EOS[1]
Days	Day -28 to Day -14	Day -28 to Day -14	Day 1 (+ 7)					Day 2 to 3	Day 15 (+3)[11]	Up to 8 weeks after Day 1	Day 15 to Follow-up end
Time (post-dose)	-	-	Pre-Injection	Injection	Post-Injection/ Pre-imaging	Imaging	Post-Imaging/ EOT	-	-	-	-
[^{18}F]CTT1057 ordering[7]		X									
[^{18}F]CTT1057 Administration[8]				X							
[^{18}F]CTT1057 PET/CT Imaging[9]						X					
[redacted]											
Safety Follow-up Call								X			X
Histopathology Assessment[10]										Up to 8 weeks after imaging Day1	
End of Phase Disposition	X						X				X

Period	Screening		Treatment							Additional Follow-up	Study Completion
Visit Name	Screening	Enrolment	PET Imaging					Safety Check	Safety Follow-up	Additional Follow-up	EOS[1]
Days	Day -28 to Day -14	Day -28 to Day -14	Day 1 (+ 7)					Day 2 to 3	Day 15 (+3)[11]	Up to 8 weeks after Day 1	Day 15 to Follow-up end
Time (post-dose)	-	-	Pre-Injection	Injection	Post-Injection/ Pre-imaging	Imaging	Post-Imaging/ EOT	-	-	-	-

[*] All Screening assessments to confirm eligibility into the study must be performed prior enrollment

[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] Phone call will be performed when histopathology results are available and recorded in CRF
[2] For a subset of approximately 10 participants from the same clinical site consenting for the PK sample collection
[3] Vital signs will be performed at screening, at PET imaging day (pre and post-injection and prior to discharge) and at Safety Follow-up visit
[4] Peripheral venous blood samples will be collected at screening and PET imaging day pre-injection and at Safety follow-up (Day 15)
[5] Urine samples will be collected at screening, at PET imaging day and Safety Follow-up and analyzed at the clinical site if dipstick results are abnormal
[6] For 10 participants from the same clinical site, blood and urine samples will be collected for PK analysis, refer to Section 8.5.1 of the protocol
[7] Order to be placed after enrollment and based on drug availability local timelines (refer to Pharmacy Manual) in order to perform PET imaging Day 1 no more than 14 days after enrollment.
[8] Participant will be injected intravenously approximately 370 MBq (range 266–407 MBq) of [^{18}F]CTT1057, flushed with 10 mL saline
[9] [redacted] after [^{18}F]CTT1057 imaging agent injection, a CT will be obtained from vertex to mid-thighs, followed by static PET emission scan over same area starting from mid-thighs
[10] Histopathology results must be obtained within up to 2 weeks following RP with ePLND, which must be planned within up to 6 weeks after but not sooner than 48 hours after PET Imaging Day
[11] For participants undergoing surgery prior to planned safety visit, these safety follow-up assessments will need to be performed before the surgery and not sooner than 48 hours after the PET scan and in that case safety assessments are not to be repeated on Day15

8.1 Screening

Written informed consent must be obtained prior to any screening procedures. Please refer to Section 7 for the Informed Consent procedures. After informed consent is collected, the participant must be registered in IRT.

Laboratory assessments should be carried out as priority to allow the necessary time to obtain the results and to confirm participant eligibility prior to placing the [^{18}F]CTT1057 order. All Screening assessments to confirm eligibility into the study should be performed between Day-28 and Day-14 as per Visit Assessment Schedule Table 8-1.

It is permissible to re-screen (only once) a participant if he 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 medical records.

8.1.1 Eligibility screening

Following registration in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system at IRT enrollment. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to enrollment will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion 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 phase (see SAE section for reporting details Section 10.1.3). If the participant fails to be enrolled, the IRT must be notified, within 2 days of the screen fail, that the participant was not enrolled.

Participants who are enrolled and fail to start treatment, e.g. participants enrolled in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

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

Participant demographic and baseline characteristic data are to be collected on all participants. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Subject demographic and baseline characteristic data to be assessed on all subjects include:

- Demographic information: age, gender, self-identified ethnicity and race
- Vital signs: body temperature, blood pressure, heart rate (HR), respiratory rate (RR),
- Weight, and height
- ECOG Performance status scale
- Laboratory evaluations: hematology, chemistry, urinalysis test and PSA (see Section 8.4.1)

Medical history:

- Date of diagnosis of PCa (diagnostic criteria is to be reported also in the eCRF) ((Stage ≥ T2c or PSA level >20ng/ml or Gleason score ≥8)
- Results of digital rectal examination (cT1c, cT2a, cT2b, cT2c, cT3)
- 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 enrollment (dose, dates)
- Other important medical, surgical, and allergic conditions that could have an impact on the participant's evaluation) / current medical conditions (e.g. all relevant current medical conditions which are present at the time of signing informed consent).

Other data:

- Date of planned RP and extended ePLND (up to 6 weeks after PET/CT scan)

8.3 Efficacy

Efficacy assessments in this study include histopathology assessments (primary tumor and PLN) and assessments of PET/CT images using a [^{18}F]CTT1057 agent. Please refer to the schedule of assessments provided in Table 8-1.

8.3.1 Imaging for tumor assessment

Post-baseline [^{18}F]CTT1057 PET imaging assessments

[^{18}F]CTT1057 PET imaging assessments as described in Table 8-1 should be performed at Day 1. The following steps will take place on PET imaging day:

1. Participant will be asked to drink 1-2 glasses of water before arrival at the clinic.
2. Participant will be weighed and vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be recorded prior injection.
3. Participant will be injected i.v. with approximately 370 MBq (range 266 – 407 MBq) of [^{18}F]CTT1057, flushed by 10 ml of saline.
4. Vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be recorded after the injection.

5. Participant will void immediately prior to the scan. If it is not possible for the participant to void, a urethral catheterization will be considered.
6. [^{18}F]CTT1057 PET/CT scan acquisition will preferably, [redacted] A CT (transmission scan) will be obtained from vertex to midthighs for anatomical reference and attenuation correction purposes. This will be followed by a static PET emission scan over the same area, starting from mid thighs. Refer to imaging charter and/or site imaging manual for details.
7. If intense activity in the urinary bladder is seen in the PET/CT images that precludes appropriate assessment of the prostate bed and/or PLN regions, then the patient will be allowed to void again, and urethral catheterization and a new (1 bed) PET/CT image of the pelvis will be considered in case of need. This additional pelvic image can then be acquired within [redacted]
8. Vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be recorded again at the completion of the study (prior to patient discharge).
9. Participant will be discharged with the reminder of the safety follow-up as described in the ICF.

[^{18}F]CTT1057 PET/CT images will be submitted to the designated imaging CRO for independent central read. All reviewers have to be blinded to patient data (including clinical condition, histopathology and imaging results). Central read results will not be provided to site/Study Investigator.

[^{18}F]CTT1057 PET/CT images will also be read by an independent local nuclear medical physician or radiologist with expertise in reading oncology PET/CT scans, who will not be participating in the central read of images. The report from this local reader will be provided to the treating physician/ Clinical Study Investigator to complete [redacted] before the participant undergoes surgery. The criteria to be applied for PET positivity are detailed in Section 4.1.

[^{18}F]CTT1057 PET/CT imaging data to be documented in eCRF will include the outcome of the assessment, i.e. if negative or positive for PCa tumor or metastases, region(s) and location of the lesions as well as their characteristics.

8.3.2 Histopathology assessments

Within a period of not sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan and not later than the 6 weeks after the [^{18}F]CTT1057 PET/CT scan, patients will undergo surgery as per their standard of care treatment plan, consisting of RP and ePLND, as per the EAU guidelines of Prostate Cancer 2020. (uroweb.org/guideline/prostate-cancer/)

A minimum of 12 PLN per patient will be dissected in order to have enough number of positive (i.e. metastatic) and negative (i.e. normal) PLN in total. Refer to Section 16.2.

The histopathology results are the only efficacy assessment as SoT, and will be compared to the [^{18}F]CTT1057 PET/CT scan central read results for the calculation of the co-primary endpoints.

Pathology data to be documented in eCRF will include the outcome of the assessment, i.e. if negative or positive for adenocarcinoma, if other tumor histological types are present, size of the tumor or metastatic lesions within the tissue specimens, and location according to the anatomical templates described in Section 16.2.

8.3.3 Appropriateness of efficacy assessments

Histopathology of the tumor samples is considered as the SoT to assess the diagnostic performance of [^{18}F]CTT1057 PET agent. After surgery, pathology of the primary tumor and the dissected PLN will be used as SoT.

The assessment will be performed by the local pathologists with experience in PCa at each site, as per SoC, in order to mimic as much as possible the clinical situation. Pathologists will be blinded to the PET/CT scan results.

8.4 Safety

Safety assessments are specified below (Table 8-2) with the assessment schedule detailing when each assessment is to be performed. For participants undergoing surgery prior to planned safety visit, these safety follow-up assessments will need to be performed before the surgery and not sooner than 48 hours after the PET scan and in that case safety assessments are not to be repeated on Day15.

As per Section 4.6, 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 will occur (as close as possible to the visits as per schedule) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again. If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

For details on AE collection and reporting, refer to the AE section.

Table 8-2 Assessments and Specifications

Assessment	Specification
Physical examination	A short physical exam will include the examination of general appearance. A short physical exam will be at all visits starting from screening visit. 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 CRF 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.
Vital signs	Vital signs include Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) (supine position preferred when ECG is collected), HR, RR and body temperature.
Weight and height	Body weight (in indoor clothing, but without shoes) and height will be measured as specified in Table 8-1.

Performance status:

ECOG Performance status scale will be used as described in Table 8-3.

Table 8-3 ECOG Performance status

Score	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, light housework, 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

8.4.1 Laboratory evaluations

Central laboratory will be used for analysis of hematology, chemistry and PSA testing according to the schedule of assessments as described in Table 8-1. The samples need to be taken prior the administration of the Investigational Product. Details on the collections, shipment of the samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

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.

Unscheduled local laboratory assessments may be performed if medically indicated to assess a (potential) adverse event or when the treating physician cannot wait for central laboratory results for decision making (e.g. therapeutic intervention, interruption of study treatment). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis. The results of the local laboratory will be recorded in the eCRF if any of the following criteria are met:

- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event severity is worse than the one reported by the central lab, or
- There are no concomitant central results available

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 (Section 16.1). 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, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
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 Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If needed, Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells)
PSA	PSA

8.4.2 Electrocardiogram (ECG)

8.4.2.1 All participants

A standard 12 lead ECGs will be performed at screening and should be recorded after 10 minutes rest in the supine position to ensure a stable baseline. 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. ECGs will be locally collected and evaluated.

Clinically significant ECG abnormalities present at screening should be reported on the appropriate eCRF. Clinically significant findings must be discussed with Novartis prior to 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.

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF. Each 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.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate.

8.4.2.2 PK subset of participants

For a subset of approximately 10 participants from the same site consenting for PK sample collection, additional ECGs will be done to collect cardiac safety data in a representative sample of patients at timepoints at which PK characteristics are known. ECGs will be recorded as below.

Standard triplicate 12 lead ECG recording will be performed at Day 1 as described in the Table 8-5. The individual ECGs should be recorded approximately 2 minutes apart. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate eCRF together with specified parameters (PR, QRS, QT, QT interval corrected by Fridericia's formula (QTcF), and RR intervals).The mean value of each parameter for each time point will be calculated from the triplicate ECGs for each participant.

A standard 12 lead ECGs will be performed at Safety follow-up Day 15.

Table 8-5 ECG collection plan

Treatment Period or Cycle	Day	Scheduled Time Point	ECG type
	Screening		12 Lead
1	1	Pre-Injection	12 Lead, triplicate
1	1	30 min- 1h Post-injection	12 Lead, triplicate
1	1	3h - 5h Post- injection	12 Lead, triplicate
	15		12 Lead

8.4.3 Pregnancy and contraception

Contraception measures are not required. However, due to potential radiation exposure/contamination to partners, it is recommended that study patients refrain from sexual activity/intercourse for 12 hours following the administration of [^{18}F]CTT1057.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Pharmacokinetics

Pharmacokinetic (PK) samples (blood / urine) will be collected at the visits defined in the assessment schedule (Table 8-6 and Table 8-7) from a subset of approximately 10 participants from the same, singular site.

The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Blood and urine samples will be counted at the investigational site in an accurately calibrated gamma-counter (e.g. NaI spectrometer) with a suitable reference source of ^{18}F of known activity counted in the same geometry as that of the biological samples (e.g. 1 mL in a vial).

Information related to the administration of [^{18}F]CTT1057, including but not limited to the activity of the dose at the time administration, date and time of dosing, date and time of dose preparation and specific activity at time of dose preparation, must be recorded in the appropriate eCRF page. All samples will be counted locally at the site and the counts per minute (CPM) value will be recorded in the appropriate blood or urine eCRF pages. Well/gamma counter calibration records will be collected from the participating site prior to patient enrollment. Calibrations related information such as date of calibration, calibration factor and background count must be recorded in a dedicated eCRF.

[redacted]

8.5.1.1 Pharmacokinetic Blood collection and handling

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 8-6, 1-1.2 mL blood draws will be collected into tubes containing an anticoagulant and gently inverted several times to thoroughly mix the anticoagulant. 1 mL of blood will be transferred into a vial for radioactivity measurement in the well/gamma-counter.

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

Table 8-6 Pharmacokinetic blood collection log (PK patient subset only)

Dose Reference ID	Treatment Period or Cycle	Day	Scheduled Time (post-dose/injection)	PK Sample No
1	1	1	Pre-dose (before injection)	101

Dose Reference ID	Treatment Period or Cycle	Day	Scheduled Time (post-dose/injection)	PK Sample No
1	1	1	0-5 min	102
1	1	1	15 min (± 5 min)	103
1	1	1	30 min (± 5 min)	104
1	1	1	1 h (± 15 min)	105
1	1	1	2 h (± 30 min)	106
1	1	1	3-4 h	107
1	1	1	5 h (± 30 min)*	108

* This sample is optional but clinical logistics permitting effort should be taken to collect this sample

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation from study treatment and study

9.1.1 Discontinuation from Study treatment

This is a single injection study of an investigational imaging agent and therefore treatment discontinuation is not applicable.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment (e.g. declines to receive the single injection or cannot receive it for any reason), 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 the assessment table (refer to Section 8).

Discontinuation from study is required under the following circumstances:

- Unacceptable patient condition as assessed by Investigator
- Participant non-compliance or voluntary withdrawal from study
- Required use of a prohibited treatment for participant safety reasons
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- At the sponsor's or investigator's discretion

The investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation of study and record this information in the source and corresponding eCRF pages. The investigator must also contact the IRT to register the participant's end of treatment.

Participants who discontinue from the study can agree to return for the end of treatment and follow-up visits and any efficacy assessments as indicated in the assessment schedule (Table 8-1).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study discontinuation, at a minimum, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples) and
  - No longer wishes to receive study treatment (e.g. declines to receive the single injection)

  and
  - Does not want any further visits or assessments

  and
  - Does not want any further study related contacts

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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 his consent and/or for his opposition to use data/biological samples and record this information.

Where consent to the use of personal and coded data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their personal data.

Study treatment must not be administered and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

All efforts should be made to complete the assessments prior to study discontinuation. If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition to use data/biological samples.

9.3 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination

- 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 drug development

In taking the decision to terminate, Novartis 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: that the safety follow-up period must be completed if applicable and which 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 sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes the last visit for the study or, in the event of an early study termination decision, the date of that decision.

All treated participants should have a safety follow-up conducted approximately 14 days (+3 days) after the imaging visit, followed by an additional follow-up prior the final call Study completion (EOS). Please refer to Table 8-1 for the required assessments at these visits.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation 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 a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events 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.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC) AE grade version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event. (Section 16.1) Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form.
2. Its relationship to the study investigational imaging agent [^{18}F]CTT1057. If the event is due to progression of underlying illness (i.e. exacerbation of pre-existing conditions) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding the study treatment.
6. Its outcome.

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 14 days following the last dose of [^{18}F]CTT1057.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute adverse events 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 which are considered to be non-typical in participant with the underlying disease.

10.1.2 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 reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH E2D (2004) Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/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 or abuse (please refer to the ICH E2D (2004) Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 14 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. 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 eSAE eCRFs (with paper Serious Adverse Event Report Form back-up); all applicable sections of the eCRFs/form must be completed in order to provide a clinically thorough report.

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 within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 14-day period after the last dose of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Not applicable

10.1.5 Reporting of study treatment errors including misuse

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 (European Medicines Agency (EMA) definition).

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

Study product injection errors and uses outside of what is foreseen in the protocol will be reported irrespective of whether or not associated with an AE/SAE (please refer to Table 10-1 for guidance on recording on the appropriate CRF) and reported to Safety only if associated with an SAE. Misuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE immediately, without undue delay, under no circumstances later than within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse	Yes	Yes, even if not associated with an AE	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.3 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial and other experts.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

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

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. 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.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. 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 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.

Dates of screenings, imaging, screen failures and study completion, and data about all study drug dispensed to the participant will be tracked using an Interactive Response Technology (IRT). The system will be supplied by Novartis, who will also manage the database.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after the lock, can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Primary efficacy and safety analyses will be conducted at the time of final analysis on the final locked clinical database, for the efficacy analysis set (EFF) and safety set (SAF) respectively. Cut-off for the final analysis will be the last visit for last subject in the study.

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

12.1 Analysis sets

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

The **Efficacy Analysis Set (EFF)** includes all enrolled participants who receive study drug, and have both an evaluable PET/CT scan and histopathology assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CT and surgery.

The **Pharmacokinetic analysis set (PAS)** includes all patients who provide at least one evaluable PK concentration. A profile is considered evaluable if all of the following conditions are satisfied: patient receives the investigational treatment (i.e. [^{18}F]CTT1057) and provides at least on primary PK parameter. The PAS will be used for all PK analyses.

Note: Patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. Specific time points might be removed from the analysis set if technical issues with sample are reported (e.g. sampling issues, missing information) or if Lower Limit of Quantification (LLOQ) sample is observed between measurable concentrations. These patients and concentration data points will be identified at the time of analysis.

The **Safety Set (SAF)** includes all participants who received the investigational treatment (i.e. [^{18}F]CTT1057).

12.2 Participant demographics and other baseline characteristics

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

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.

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

12.3 Treatments

Actual received [^{18}F]CTT1057 dose and time interval from injection to [^{18}F]CTT1057 PET/CT scan acquisition start will be summarized by means of descriptive statistics using the SAF.

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

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

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary objective of the study is described in Table 2-1. Efficacy analysis will use the EFF.

12.4.1 Definition of primary endpoint(s)/estimand(s)

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

- Patient-level sensitivity is defined as the proportion of PSMA TP patients among PSMA TP patients and PSMA FN patients.
  - PSMA TP patients are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLNs with anatomically localized correspondence with the SoT.
  - PSMA FN patients are those who do not show any pathological [^{18}F]CTT1057 uptake either in the primary tumor or metastatic PLNs but will be confirmed having primary tumor or metastatic PLNs with the SoT.
- Region-level specificity is defined as the proportion of PSMA TN PLN regions among PSMA TN PLN regions and PSMA FP PLN regions.
  - PSMA TN PLN regions are regions that test negative for PLN on [^{18}F]CTT1057 and confirmed negative on the SoT.
  - PSMA FP PLN regions are regions that test positive for PLN on [^{18}F]CTT1057 but verified negative on the SoT.

12.4.2 Statistical model, hypothesis, and method of analysis

To address the co-primary efficacy objectives:

Patient-level sensitivity and its 95% CI will be calculated based on the binomial distribution. The lower bound of the 95% CI for patient-level sensitivity should be greater than 0.5 to attain the first co-primary endpoint.
Region-level specificity and its 95% CI will be calculated based on the binomial distribution. The lower bound of the 95% CI for specificity should be greater than 0.70 for the study to attain the second co-primary endpoint.

12.4.3 Handling of remaining intercurrent events of primary estimand

The primary analysis will account for intercurrent events as explained in the following:

- Patients receive the investigational imaging agent [^{18}F]CTT1057 but do not undergo/complete the [^{18}F]CTT1057 PET/CT scan for any reasons (e.g. drop out, PET camera failures, etc): they will not be used for the primary endpoint analysis, but safety data will be collected after the administration of the investigational imaging agent.

12.4.4 Handling of missing values not related to intercurrent event

This is a diagnostic study, primary endpoint is calculated on the basis of one-time imaging assessment, missing data not related to intercurrent events will not be imputed.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Not applicable

12.4.6 Supplementary analysis

As supplementary analyses performed in the EFF, the 95% CI for patient-level sensitivity and region-level specificity will be obtained from covariate adjusted logistic regression model. Important covariates will be specified in the Statistical Analysis Plan (SAP).

If the primary endpoints of patient-level sensitivity and region-level specificity are met, other subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed. Other subgroups will be specified in the SAP. Further supplementary analyses will be specified in the SAP.

12.5 Analysis of secondary endpoints/estimands

The secondary objectives are described in Table 2-1.

12.5.1 Efficacy endpoint(s)

Patient-level specificity is defined as the proportion of TN patients among those who are TN or FP.

Patient-level positive predictive value is defined as the proportion of TP patients among those who are TP or FP.

Patient-level negative predictive value is defined as the proportion of TN patients among those who are TN or FN.

Patient-level accuracy is defined as the proportion of TP and TN patients among all patients in EFF (regardless of TP, TN, FP, FN)

where TP, TN, FP, FN patients are defined as follows:

- PSMA TP patients are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLNs with anatomically localized correspondence with the SoT.
- PSMA TN patients are those who do not show any pathological [^{18}F]CTT1057 uptake neither in the primary tumor nor metastatic PLNs and will be confirmed NOT having primary tumor nor metastatic PLNs with the SoT.
- PSMA FP patients are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLNs but will be verified NOT having primary tumor nor metastatic PLNs with the SoT or none of the lesions is correctly localized in anatomical location by the SoT.
- PSMA FN patients are those who do not show any pathological [^{18}F]CTT1057 uptake neither in the primary tumor nor metastatic PLNs but will be confirmed having primary tumor or metastatic PLNs with the SoT.

Number of TP, TN, FP, FN patients will be presented and used to calculate the diagnostic performance parameters.

95% CI for diagnostic performance parameters will be calculated based on the binomial distribution.

[^{18}F]CTT1057 scan inter-reader variability is defined as agreement rate among reader determinations and will be assessed by Fleiss' Kappa statistic. Further details will be specified in the SAP.

[^{18}F]CTT1057 scan intra-reader variability is defined as within-reader agreement rate and will be assessed by Cohen's Kappa statistic. Further details will be specified in the SAP.

Detection number of distant metastasis is defined as number of distant metastasis (extra-PLN, visceral or skeletal) identified at PET scan for each patient in all patients with an evaluable [^{18}F]CTT1057 PET/CT scan.

Detection rate of distant metastasis is defined as percentage of patients with at least one distant metastatic lesion (extra-PLN, visceral or skeletal)identified by PET scan in all patients with an evaluable [^{18}F]CTT1057 PET/CT scan.

Region-level sensitivity is defined as the proportion of TP PLN regions among those that are TP or FN.

Region-level-sensitivity excluding from the analysis those PLN showing metastasis <2mm (micro-metastasis).

Region-level positive predictive value is defined as the proportion of TP PLN regions among those that are TP or FP.

Region-level negative predictive value is defined as the proportion of TN PLN regions among those that are TN or FN.

Region-level accuracy is defined as the proportion of TP and TN PLN regions among those that are identified on [^{18}F]CTT1057 (regardless of TP, TN, FP, FN)

where TP, TN, FP, FN PLN regions are defined as follows:

- PSMA TP regions are regions that test positive for PLN on [^{18}F]CTT1057 and confirmed positive on the SoT
- PSMA TN regions are regions that test negative for PLN on [^{18}F]CTT1057 and confirmed negative on the SoT
- PSMA FP regions are regions that test positive for PLN on [^{18}F]CTT1057 but verified negative on the SoT
- PSMA FN regions are regions that test negative for PLN on [^{18}F]CTT1057 but verified positive on the SoT

Number of TP, TN, FP, FN regions will be presented and used to calculate the diagnostic performance parameters.

95% CI for diagnostic performance parameters will be calculated based on the binomial distribution.

12.5.2 Safety endpoints

For all safety analyses, the SAF will be used.

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 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 and time before dosing of study medication.
2. On-treatment period: from day of dosing of study medication to 14 days after dosing of study medication.
3. Post-treatment period: starting 15 days after dosing of study medication.

Adverse events

All information obtained on adverse events will be displayed by participant.

The number (and percentage) of participants with TEAE (events started after the first dose of study medication or events present prior to start of study treatment but increased in severity based on preferred term) will be summarized in the following ways:

- primary system organ class and preferred term.
- primary system organ class, preferred term and maximum severity.
- Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Summary tables for AEs will include only AEs that started or worsened during the on-treatment period, i.e. the **treatment-emergent** AEs.

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 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

All vital signs data will be listed by participant, and visit/time and clinically notable values or changes in vital signs will be flagged. Summary statistics will be provided by visit/time.

12-lead ECG

For all participants:

The ECG result at screening will be summarized as number (%) of subjects with normal or abnormal (clinically significant) ECG and will be provided as listing.

In addition for the 10 PK subset participants:

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study on treatment day (Day 1) at pre-injection, post-injection/pre-imaging, and post-imaging and at Safety follow-up Day 15. ECG data will be read and interpreted (locally).
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these participants will be produced.

Clinical laboratory evaluations

All laboratory data will be listed by participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (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 listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades if applicable and the classifications relative to the laboratory normal ranges

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.

In addition to the above mentioned tables and listings, other [redacted], for example, figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

12.5.3 Pharmacokinetics

For all PK analyses, the PAS will be used.

The [^{18}F]CTT1057 pharmacokinetic analysis will be performed based on decay-corrected blood radioactivity concentration data converted to mass unit, obtained by measuring the blood samples drawn at pre-defined time points (Table 8-6) using a calibrated gamma-counting device.

Blood radioactivity concentration and blood mass concentration data will be listed by patient and visit/sampling time point. Pharmacokinetic parameters will be listed by patient. Descriptive summary statistics will be provided by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where only median, minimum, and maximum will be presented.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin® (Version 8 or higher): Cmax, Tmax, AUClast, AUCinf, T1/2, Vz and CL (Table 12-1).

Table 12-1 Non-compartmental pharmacokinetic parameters

AUC%Extrap[1]	Area under the plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC (%)
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})
Clast[2]	Last measurable concentration (mass 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)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time)
Tlast[2]	Last measurable concentration sampling (time)
Rsqadj[1]	Square of the correlation coefficient associated with lambda_z
CL	The total body clearance (CL) of drug from plasma, blood serum, or other body fluid drug concentration (volume x time^{-1})
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)

[1] AUC%Extrap and Rsqadj will be used in the interpretation of the primary PK parameters and therefore will be included in the listings only.
[2] Clast and Tlast will only be listed but not summarized

The elimination of the compound in urine will be evaluated based on decay-corrected urine radioactivity concentration data obtained by measuring the blood samples drawn a pre-defined

time points (Table 8-7) using a calibrated gamma-counting device. Urine elimination data will be expressed as percentage of injected activity (%ID) in each specified time interval and also as cumulative %ID excreted up to the end of each time interval. Urine elimination data will be listed by patients. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

The sample size calculation is based on the co-primary endpoints patient-level sensibility and region-level specificity.

Overall, a total study sample size of approximately 195 participants will be enrolled in order to get at least 156 evaluable participants for co-primary endpoints (i.e. have both an evaluable PET/CT scan and histopathology assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CT and surgery). These calculations were made using the software PASS 11 and R 3.6.1.

12.8.1 Primary endpoint(s)

This study is planned to recruit approximately 195 patients. The primary objective is to evaluate the patient-level sensitivity of [^{18}F]CTT1057 (evaluated for all patients including primary tumors and PLN) and the region-level specificity of [^{18}F]CTT1057 (evaluated only for PLN regions). The sample size calculation is based on the co-primary endpoints of patient-level sensitivity and region-level specificity of [^{18}F]CTT1057.

The rationale for the choice of the co-primary endpoints is provided below:

In PS patients before surgery, both the primary tumor and the metastatic PLN are expressing PSMA, which is the target for [^{18}F]CTT1057 binding. After surgery, pathology of both the primary tumor and the dissected pelvic LN will be used as a SoT. A patient-level analysis would allow to identify positive lesions in both regions. A region-level analysis for sensitivity is not considered appropriate for the primary endpoint as 156 positive PLN would be needed in order to determine sensitivity with a power of 90% on a regional level. Given the low prevalence and high variability of metastatic lymph nodes in the PS population (from 4-58%) (Petersen and Zacho 2020), approximately 520 patients would have to be injected with the radioactive investigational PET tracer to yield the 156 positive PLN. In order to limit the number of participants exposed to radiation for this purpose and given that both the primary tumor and affected PLN are [^{18}F]CTT1057 targets, sensitivity is proposed to be analyzed on patient level. Region-level sensitivity is included as a secondary endpoint. On the other hand, specificity can be assessed on the regional level (at the PLN region) since enough number of negative PLN are expected to be obtained at pathology.

The assumptions for sample size calculations are based on estimates available from prior studies as described below.

A large variability in sensitivity of PSMA-PET in the primary staging setting has been reported. Two recent systematic reviews of [^{68}Ga]PSMA PET /CT diagnostic accuracy focused on the PS population using pathology as SoT, sensitivity of 33–99% across studies has been reported (Corfield et al 2018), as well as pooled sensitivity and specificity ranges of 23-100% and 67-100% respectively (Petersen and Zacho 2020). Recent preliminary data on the diagnostic efficacy of F-18-rhPSMA-7.3 PET imaging in PS patients compared to histopathology (n=56) reported a 95% CI low bound patient level sensitivity of 54.4% (81.3 (95% CI-54.4-96.0) (Maurer et al 2020). CT and MRI are the standard of care imaging procedures for measuring tumors at baseline and lesions selected for response assessment as per RECIST criteria 1.1 (Eisenhauer et al 2009). A meta-analysis on the diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with PCa reported a pooled sensitivity of 0.42 (95% CI 0.26-0.56) for CT, and of 0.39 (95% CI 0.22-0.56) for MRI (Hövels et al 2008). A study evaluating the diagnostic value of [^{68}Ga]PSMA PET versus CT and MRI for lymph node staging in 130 consecutive patients who got RP and PLN dissection after PET/Magnetic Resonance (MR) (n=95) and PET/CT (n=35) and who had tumor specimens available for reanalysis to correlate with PET reported a sensitivity of 43.9% (95% CI 28.5-60.3) and 85.4% specificity (95% CI 76.3-92.0) for morphological imaging alone (CT and MRI) (Maurer et al 2016).

Taking all the above into consideration, an overall patient-level sensitivity of 50% and a region level specificity of 70% will be considered as unacceptably low. Hence, the sample size calculation will be performed based on the null and alternative hypotheses as follows.

- Patient-level sensitivity

For patient-level sensitivity, the null hypothesis H0: patient-level sensitivity p0 = 0.50 will be tested against the alternative hypothesis H1: p1>0.50, assuming a sensitivity of 0.63 under the alternative hypothesis, approximately 156 patients with primary tumor and/or metastatic lymph nodes would achieve 90% statistical power to detect a change in sensitivity of 0.13 using a one-sided binomial test at a target significance level of 2.5%. Taking into account 20% dropout rate, 195 patients can ensure the 90% statistical power.

- Region-level specificity

For region-level specificity, the null hypothesis H0: region-level specificity p0 = 0.70 will be tested against the alternative hypothesis H1: p1 > 0.70. Assuming a specificity of 0.85 under the alternative hypothesis, approximately 123 patients (which includes 37 patients with PLN based on 30% prevalence) would achieve 90% statistical power to detect a change in specificity of 0.15 using a one-sided binomial test at a target significance level of 2.5 %. Taking into account 20% dropout rate, 154 patients can ensure the 90% statistical power. The lower bounds of the 95% CI for specificity should be greater than 0.70 to be considered success.

The lower bound of the 95% CI for sensitivity should be greater than 0.50 and the lower bound of the 95% CI for specificity should be greater than 0.70 for the study to be considered a success.

A total sample size of 195 patients can ensure 90% statistical power for patient-level sensitivity and 99% statistical power for region-level specificity resulting in an overall study statistical power of at least 89.1% (0.9 x 0.99).

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign 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 monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. 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 clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

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

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

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 interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis 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 approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, 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 should

be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Common Terminology Criteria for Adverse Events

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

[ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf]

16.2 Appendix 2: European Association of Urology Guidelines of Prostate cancer

The latest EAU Guidelines for Prostate cancer can be found at the following site:

uroweb.org/guideline/prostate-cancer/

Refer to Section 6.1.2.3.2 for the pelvic lymph node dissection guidelines.

16.3 Appendix 3: Anatomic template specification for histopathology assessment

For the anatomical localization for prostate, a **sextant anatomic** template will be used (Kuten et al 2020).

For the PLN, an anatomical **side approach left/right** will be used, since the borders of dissection are not usually very clear neither for the surgeon nor for the pathologist.

[redacted]