NOVARTIS

Novartis Research and Development

AAA405

Clinical Trial Protocol CAAA405A12301/ NCT04838613

Phase III study for evaluation of the diagnostic performance of [^{18}F]CTT1057 PET imaging in patients with prostate cancer with rising PSA levels [biochemical recurrence (BCR)] (GuidePath)

Document type:	Amended Protocol Version
EUDRACT number:	2020-003959-16
Version number:	01 (Amended Protocol Clean)
Clinical Trial Phase:	III
Release date:	20-Dec-2021 (content final)

Clinical Trial Protocol Template Version 3.0 dated 31-Jan-2020

Table of contents

List of tables

List of figures

List of abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALT	Alanine Aminotransferase
ASCT2	Alanine, Serine, Cysteine Transporter 2
AST	Aspartate Aminotransferase
ASTRO	American Society for Radiation Oncology
ATC	Anatomical Therapeutic Chemical
AUA	American Urological Association
BCR	Biochemical recurrence
BUN	Blood Urea Nitrogen
CDR	Correct Detection Rate
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CLR	Correct localization rate
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COVID-19	Coronavirus disease 2019
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
cTNM	Clinical Stage
CTS	Composite Truth Standard
DBP	Diastolic Blood Pressure
EANM	European Association of Nuclear Medicine
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report/Record Form
ED	Effective Dose
EDC	Electronic Data Capture
EFF	Efficacy Analysis Set
EMA	European Medicines Agency
EOS	Study completion
EOT	End of Treatment
ePLND	extended Pelvic Lymph Node Dissection
eSAE	electronic Serious Adverse Event
EU	European Union
F-SAF	[^{18}F]CTT1057 Safety Set

FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FN	False Negative
FP	False Positive
Ga-SAF	[^{68}Ga]Ga-PSMA-11 Safety Set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
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
LAT-1	L-Type Amino Acid Transporter 1
LDH	lactate dehydrogenase
LHRH	Luteinizing Hormone-Releasing Hormone
MBq	Mega-Becquerel
MCH	Mean Corpuscular Hemoglobin
mCi	Millicurie
mCRPC	metastatic-Castration Resistant Prostate Cancer
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
min	minute(s)
mL	milliliter(s)
MRI	Magnetic Resonance Imaging
mSV	millisievert
NCI	National Cancer Institute
p.i.	post-injection
PCa	Prostate Cancer
PCWG3	Prostate Cancer Working Group 3
PET	Positron Emission Tomography
PLN	Pelvic Lymph Node
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen

pTNM	pathological stage
QC	Quality Control
QMS	Quality Management System
RECIST	Response Evaluation Criteria In Solid Tumors
RP	Radical Prostatectomy
RR	Respiratory Rate
RT	Radiation therapy
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
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 participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
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

Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
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
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
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, 20 subjects have been randomized in the study (12 dosed).

The main purpose of the amendment is to clarify the inclusion criterion on PSA level requirements for confirmation of biochemical recurrence (BCR) following radiation therapy and following Radical Prostatectomy (RP) to avoid misinterpretation and ensure full alignment with the published definitions for BCR per AUA and ASTRO-Phoenix guidelines and with the targeted study population (patients who have BCR following initial definitive therapy). The amendment also clarifies that subjects with prior salvage radiation therapy or salvage surgery are not eligible for the study to ensure alignment with the targeted patient population. Other clarifications and corrections of discrepancies or errors have been implemented across the 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 2.1 Section 3 Section 5	**Targeted population in the study** Additional information provided.	Clarification that targeted population for the study is prostate cancer patients diagnosed with biochemical recurrence (BCR) after initial definitive therapy (with either RP or curative intent RT)
Section 3	**Clarification of safety assessments follow-up timing**	Updated to ensure that safety assessments to be performed at the safety follow-up at 14 days (+ 3 day window) after each PET/CT scan day are also performed before any surgery/radiation therapy/initiation of antineoplastic medication, in the event where the patient would undergo surgery, radiation therapy or initiating any antineoplastic medication (provided all CTS procedures have been completed before this initiation) prior to planned safety visit.
Protocol summary Section 5.1	**Update of Inclusion criterion #3** For patients who had prior RP, BCR must be confirmed by an initial serum PSA of ≥0.2 ng/mL measured at least	Modified inclusion criterion (numbered 3a) to clarify the requirements for biochemical recurrence (BCR) following initial definitive therapy with either RP or curative-intent radiation therapy (RT) and fully align with the definitions of BCR from the publications referred to for AUA

	6 weeks after RP with a second confirmatory persistent PSA level of >0.2 ng/mL. For patients who had prior curative-intent radiation therapy (RT), BCR is defined as a rise of serum PSA measurement of 2 or more ng/mL above the nadir PSA observed post RT.	and ASTRO-Phoenix criteria and the targeted population.
Protocol summary Section 5.2 Section 6.2.2	**Removal of exclusion criterion #6 and update of exclusion criterion #7 and clarification that LHRH analogues include LRHR agonists or antagonists**	Exclusion criterion #6 is removed as this is not relevant for the purpose of this study to completely exclude prior treatment with LHRH analogues (agonists or antagonists) which are part of ADT. Many subjects receive ADT (including LHRH analogues) in combination with primary curative intent radiation therapy. The same washout period as for other ADTs (9 months) should apply for LHRH analogues. Exclusion criterion #7 was updated accordingly (numbered 7a) to exclude any prior ADT including LHRH analogues (agonists or antagonists) within 9 months before screening. Section 6.2.2 was also updated to clarify that LHRH analogues include LHRH agonists or antagonists.
Protocol summary Section 5.2	**Addition of a new exclusion criteria (#12)**	Clarification that patients who received prior salvage surgery or salvage RT are not eligible for the study as the targeted population is patients with BCR following initial definitive therapy.
Protocol summary Table 2-1Section 12.6	**Update of Secondary endpoint and** [redacted]	Clarification that the secondary endpoint (based on central imaging reads) and [redacted] for concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of PSMA-positive lesions (in terms of number of lesions detected and

		their location) will be assessed at lesion level, not patient level.
Protocol summary Section 3 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. patient who have both an evaluable [^{18}F]CTT1057 PET/CT scan imaging, and at least one evaluable CTS assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CTs and CTS procedures.
Section 3 Section 4.1 Section 8.3.1	**Clarification on [^{68}Ga]Ga-PSMA-11 PET/CT scan acquisition requirements**	Clarification that [^{68}Ga]Ga-PSMA-11 PET/CT scan is mandatory for all patients randomized.
Section 3 Section 4.1 Section 8.3.1	**Clarification on Standard of Care imaging part of CTS level 2 timing**	Clarification that the high resolution CT scan and any other imaging diagnostic procedure clinically indicated as per SoC part of CTS level 2 must be acquired within the 8 weeks either prior to or following the [^{18}F]CTT1057 PET/CT scan.
Section 8.3.1	**Addition of Table 8-2**	Addition to provide clarity to sites on the imaging procedures expected for this study and their timing. Subsequent tables in the document were re-numbered accordingly.
Section 8.3.1	[redacted]	[redacted]
Section 8.3.1	**Clarification on Characteristics of lesions**	Clarification that the characteristics of lesions should be documented for lesions that are visually positive on the [^{68}Ga]Ga-PSMA-11 PET but not considered as prostate cancer (i.e. non prostate cancer tumoral lesions, or benign non tumoral lesions).
Section 3 Section 12.5.1 Section 16.4 (Appendix 4)	**Addition of a new option in questionnaire #2**	Addition of a new option named "Radiation alone with change in radiation treatment plan", which will be applicable only for questionnaire 2, in order to capture any intended change in the radiation plan

		(e.g. change in the extent of the field of radiations).
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 discretion 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 CTS procedures, to ensure that the same lesions are assessed on PET/CT scans and CTS procedures without potential reduction in lesion size and therefore detectability due to administration of antineoplastic medications.
Section 8.5.1	**Clarification of patient management questionnaire #2** Timing for completion	Clarification that patient management questionnaire 2 should be completed before [^{68}Ga]Ga-PSMA-11 PET/CT is performed for subjects assigned to sequence 1.
Section 10.1.3 Section 10.1.5	**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 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	**Incidence of AEs wording clarification**	Updated 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.
Protocol summary Table 2-1 Section 12.4.6	**Subgroup of patients definition update**	The names for the 2 subgroups of patients defined for subgroup analyses are corrected to patients with prior RP and patients with prior curative intent radiation therapy
Section 3	**Screening assessments update**	Updated to remove imaging assessments from screening period paragraph as imaging procedures to be performed in the study do not belong to screening assessments.
Protocol summary Section 3 Section 4.1 Section 8.3.1 Section 12.4.1 Section 12.5.1	**Clarification of the different CTS levels**	Clarification that the different CTS levels will be applied hierarchically at lesion level for efficacy analyses. CTS level 2 will be used as SoT if histopathology is not available for a lesion, inconclusive (if biopsy/surgery tissue sample is not evaluable for histopathology assessment due to sample quality or inadequate quantity or any other technical causes) or negative (for biopsy only). CTS level 3 will be used as SoT if CTS level 2 imaging diagnostic procedures are not available or inconclusive (i.e. if images are not interpretable due to poor or inadequate image quality that precludes reliable assessment). Section 4.1 also clarified that for CTS level 3, the lesion on the [^{18}F]CTT1057 PET/CT scan that was irradiated will be classified as a true positive (TP) in case of ≥50% PSA decrease 3 months after RT, or as FP otherwise.
Section 4.1 Section 12.5.1 Section 12.8.1	**Regions definition for region-level efficacy endpoints analysis**	Updated to clearly mention the different regions considered for this study as used for the region-level efficacy endpoints analyses: prostate region (comprising prostate bed/prostate gland and any local invasion of the urinary bladder, rectum or seminal vesicles), pelvic lymph nodes (PLN) region, extra-PLN region, skeletal region and visceral region).

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 assessments 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	**Clarification on PSA levels requirement in CTS level 3**	Clarification that PSA levels should be tested prior RT and 90 days post RT as part of additional follow-up if CTS level 3 is applicable for the patient, as described in Section 8.3.3.
Table 8-1 (footnote*)	**Addition of footnote***	Addition of footnote* to clarify that all screening assessments to confirm eligibility must be done prior randomization.
Table 8-1	**Clarification of timing of enrolment and Day 1**	The table is updated to clarify that enrolment 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 (first dosing visit) should occur maximum 14 days after enrolment.
Table 8-1 (footnote 7)	**Update on ordering requirements**	Updated to mention that ordering should be done after randomization and based on the radiopharmaceutical that requires the longest period from order to delivery
Table 8-1	**Update of Day 1 visit window**	The table is updated to allow a visit window of 7 days since the enrolment/randomization could occur earlier than 14 days prior Day 1
Table 8-1	**Clarification of urinalysis requirements**	Updated 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 8.2 was also updated to reflect that urinalysis test results (that are part of baseline characterictics data) will be assessed but not captured in eCRF.

Section 8.3.2 Table 8-1 (Footnote #2)	**Additional information and update on histopathology assessment**	Information updated (footnote #10 removed) to separate histopathology (biopsy/salvage surgery) assessment (CTS level 1) in the table from the SoC diagnostic procedures performed as part of CTS level 2 and also clarify the specific timing for each assessment. If indicated for the subject, biopsy/salvage surgery should be performed within 8 weeks after the [^{18}F]CTT1057 PET/CT scan AND after [^{68}Ga]Ga-PSMA-11 PET/CT scan. SoC diagnostic procedures, which include at least a high resolution CT scan with intravenous and oral contrast (or MRI if CT scan with contrast is medically contraindicated), and any other SoC imaging diagnostic procedure as clinically indicated per SoC (CT/MRI, Bone Scan, etc.), should be performed within 8 weeks before or after [^{18}F]CTT1057 scan.
Section 8.3.1 Table 8-1 (Footnote #9)	**Terminology update for CT scan**	Updated to remove the “low dose” terminology which is no longer used in clinical practice for the CT portion of PET/CT (transmission scan).
Section 8.2	**Diagnostic criteria redundancy removed**	Updated to remove that diagnostic criteria is to be reported in the eCRF as this is redundant with the already mentioned collection of Gleason grade, PSA and clinical stage at diagnosis in the eCRF.
Section 8.4 Table 8-3	**Correction of misplaced information on collection of vital signs**	Updated 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 any clinically significant finding from local laboratory results available for the patient should also be considered for eligibility assessment, notably for exclusion criterion #2.
Section 8.4.1 Table 8-5	**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	**Clarification on ECG review requirements**	Update to add that ECG will be locally collected and evaluated.
Section 9.1	**Clarification in the discontinuation definition and wording**	Update to separate discontinuation from study treatment and discontinuation from study.
Section 9.1.2	**Addition of section**	Update to separate discontinuation from study treatment 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 discontinuation of 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	**Clarification on SAE reporting**	Update to emphasize reporting timelines requirements and all related documentation.
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	**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	**Clarification on lab values listing**	Updated to indicate that clinically notable values or changes in vital signs will be flagged in listings.
All sections	**Minor updates**	Minor typographical corrections, removal of duplicated wording and minor rewording were implemented across the document.

Protocol Summary

Protocol number	CAAA405A12301
Full Title	Phase III study for evaluation of the diagnostic performance of [^{18}F]CTT1057 PET imaging in patients with prostate cancer with rising PSA levels [biochemical recurrence (BCR)] (GuidePath)
Brief title	Study of diagnostic performance of [^{18}F]CTT1057 in BCR
Sponsor and Clinical Phase	Novartis Phase 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 tumour 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 current study aims at evaluating the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positivity in patients diagnosed of biochemical recurrence of prostate cancer (PCa), using a composite truth standard.
Primary Objective(s)	The co-primary objectives of this study are • to evaluate the **region-level correct localization rate** (CLR) of [^{18}F]CTT1057 • to evaluate the **patient-level positive predictive value** (with anatomical localization) of [^{18}F]CTT1057 The primary clinical question of interest is: What is the probability that a positive [^{18}F]CTT1057 PET/CT scan truly detects and localizes (PSMA-expressing) tumor recurrence in BCR PCa patients?
Secondary Objectives	• To evaluate the patient-level sensitivity of [^{18}F]CTT1057 • To evaluate the patient-level specificity 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 • To evaluate the region level specificity 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 • To evaluate correct detection rate (CDR) • To evaluate detection rate • To evaluate the patient-level positive predictive value related to PSA levels • To characterize the safety and tolerability of [^{18}F]CTT1057 • [^{18}F]CTT1057 scan inter-reader variability • [^{18}F]CTT1057 scan intra-reader variability • Concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of lesions at lesion level using central reads • To evaluate the change in patient management plans attributed to the PET/CT scan • Assess all the above primary and secondary objectives independently in the subgroup of patients with prior radical prostatectomy (RP) and the subgroup of patients with prior curative intent radiation therapy (RT).
Study design	This is a prospective, open-label, multi center, single-arm Phase III study to evaluate the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positive tumors in PCa patients diagnosed with biochemical recurrence (BCR) after initial definitive therapy with either radical prostatectomy (RP) or curative intent radiation therapy (RT), using a CTS as reference. The CTS to be used as reference will be hierarchical in nature, with 3 levels of Standard of Truth (SoT) procedures, that will be applied as follows: **CTS Level 1: Histopathology** if available for the lesion (from prospective biopsy or salvage surgery performed within 8 weeks after the [^{18}F]CTT1057 PET/CT scan); OR in case that histopathology is not available for a lesion, inconclusive or negative (for biopsy only): **CTS Level 2: Imaging** diagnostic procedures performed on each patient as clinically indicated per SoC, which must include at least a high resolution CT scan with contrast and a [^{68}Ga]Ga-PSMA-11 PET/CT) performed within 8 weeks (either before or after) the [^{18}F]CTT1057 PET/CT scan. Three-month follow-up imaging (from baseline) will also be used as part of the CTS level 2 in cases where it is clinically required for the diagnosis of particular lesion(s); OR if neither of the two above are feasible or deemed appropriate or they are inconclusive: **CTS Level 3:** 50% or greater decline in **PSA following radiation therapy** (as long as no concomitant androgen deprivation therapy (ADT) is given) as per Prostate Cancer Working Group 3 (PCWG3) criteria. All participants will undergo 2 PET/CT scans: one with the investigational agent [^{18}F]CTT1057 and another with [^{68}Ga]Ga-PSMA-11 (as a component of the CTS Level 2 and for a secondary endpoint of assessment of concordance between the 2 PET/CT scans for detection of lesions). The 2 PET imaging procedures will be performed at least 14 days apart, and the PET/CT scan sequence for each participant will be assigned at random in a 1:1 ratio.

Study population	Male participants ≥ 18 years of age, with biopsy proven prostate adenocarcinoma and rising PSA after definitive therapy with RP or curative intent radiation therapy (external beam or brachytherapy), diagnosed of biochemically recurrent PCa. Approximately 190 participants will be enrolled to ensure at least 152 participants are evaluable (i.e. have both an evaluable [^{18}F]CTT1057 PET/CT scan imaging, and at least one evaluable CTS assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CTs and CTS procedures) , 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 • Biopsy proven prostate adenocarcinoma. • Biochemical recurrence following initial definitive therapy (with either radical prostatectomy or curative-intent radiation therapy) as defined: ○ by American Urological Association (AUA) criteria for patients who have undergone RP: Initial serum PSA of ≥0.2 ng/mL measured at least 6 weeks after RP with a second confirmatory persistent PSA level of >0.2 ng/mL, or ○ by American Society for Radiation Oncology (ASTRO)-Phoenix criteria for patients who have undergone curative-intent RT: Rise of serum PSA measurement of 2 or more ng/mL above the nadir PSA observed post RT. • 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) • Prior major surgery undergone less than 12 weeks prior to screening (with the exception of any surgery related to prostatic cancer) • Known allergy, hypersensitivity, or intolerance to [^{18}F]CTT1057, [^{68}Ga]Ga-PSMA-11, or to CT contrast • Prior and current use of PSMA targeted therapies • Prior ADT (first or second generation), including Luteinizing Hormone-Releasing Hormone (LHRH) analogues (agonists or antagonists) within 9 months before screening • Any 5-alpha reductase inhibitors within 30 days before screening • Use of other investigational drugs within 30 days before screening • Castration-resistant patients • Patients with small cell or neuroendocrine PCa in more than 50% of biopsy tissue • Prior salvage surgery or salvage radiation therapy

Study treatment	The term "Study Treatment" indicates the administration of at least one of the two PET imaging agents: [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 independently of whether the PET/CT scans were acquired or not
Treatment of interest	In this study, the investigational imaging agent of interest is [^{18}F]CTT1057, injected as a single intravenous dose of approximately 370 Mega-Becquerel (MBq) and subsequent PET/CT scan.
Efficacy assessments	Hierarchical CTS with 3 levels: • Level 1: Histopathology assessments • Level 2: Imaging diagnostic assessments: at least a high-resolution CT with contrast and a [^{68}Ga]Ga-PSMA-11 PET/CT. Other SoC imaging modalities if clinically indicated. Imaging data will be read centrally • Level 3: PSA assessments [^{18}F]CTT1057 PET/CT assessments, read centrally
Key safety assessments	• Adverse Events (AEs) • Serious Adverse Events (SAEs) • Vital signs, physical examinations • Electrocardiograms (ECGs) • Laboratory parameters including hematology, clinical chemistry • Concomitant medications and/or therapies
Other assessments	• Patient management questionnaire for secondary endpoint to evaluate the change in patient management plans attributed to the PET/CT scan
Data analysis	The following data analyses are planned for the study: The co-primary endpoints of the study are region-level CLR and patient-level Positive Predictive Value (PPV) • Region-level CLR is defined as the proportion of regions containing at least one true positive (TP) lesion (exactly localized correspondence between PET imaging and the reference standard), regardless of any co-existent false positive (FP) findings within the same region, out of all regions containing at least one PET-positive finding. Region-level CLR and its 95% confidence interval (CI) will be calculated using logistic random-effects models taking into account the correlation among regions within one patient. The lower bound of the 95% CI for CLR should be greater than 0.5 to attain the first co-primary endpoint. • Patient-level PPV is defined as the proportion of patients who have at least one TP lesion (exactly localized correspondence between PET imaging and the reference standard), regardless of any co-existent FP findings, out of all patients who are PET/CT scan positive. Patient-level PPV and its 95% CI will be calculated based on the binomial distribution. The lower bound of the 95% CI for patient-level PPV should be greater than 0.2 to attain the second co-primary endpoint. Analyses for co-primary endpoints will be based on the efficacy analysis set (EFF). Centralized imaging assessments (CTS Level 2) will be used as reference standard if pathology (CTS Level 1) is not available for a lesion, inconclusive or negative (for biopsy only).

	Other secondary endpoints including patient-level sensitivity, patient-level specificity, patient-level negative predictive value, patient-level accuracy, patient-level correct detection rate, patient-level detection rate, [^{18}F]CTT1057 scan inter-reader agreement, [^{18}F]CTT1057 scan intra-reader agreement, change in patient management plans, region-level sensitivity, region-level specificity, region-level negative predictive value, region-level accuracy, concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 will also be analyzed. Detailed statistical methodology for these analyses will be provided in the statistical analysis plan (SAP).
Key words	[^{18}F]CTT1057, [^{68}Ga]Ga-PSMA-11, PET/CT, Radioligand, Imaging, BCR, CTS, PCa

1 Introduction

1.1 Background

Prostate-specific membrane antigen (PSMA) and prostate cancer

Prostate-specific membrane antigen is a transmembrane protein, also known as folate hydrolase or glutamate carboxypeptidase II. PSMA is highly overexpressed on the tumor cells of prostate adenocarcinomas (Hupe et al 2018, Bravaccini et al 2018), and has also been reported to be overexpressed on tumor cells and tumor-vasculature of endometrial and ovarian cancer (Wernicke et al 2017), and mainly on 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 most 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 174,650 in 2019 (Siegel et al 2018, 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 future, radioligand therapy (Oh and Kantoff 1999, Roscigno et al 2005, Jani 2006). Prostate-specific membrane antigen 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 early stages 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-PSMA PET/CT (Yaxley et al 2019a). This is very important, as the morbidity of a surgery could be avoided, given the change in management from one of curative intent, to management that will require a multimodality approach after treatment of the prostate primary tumor (Yaxley et al 2018, Yaxley et al 2019b).

Up to 40% of the patients with PCa develop biochemical recurrence (BCR) within 10 years after initial treatment (Isbarn et al 2010). Usually an increase of the PSA-level precedes a clinically detectable recurrence by months to years (Van Poppel et al 2006**)**. However, it cannot differentiate between local, regional or systemic disease with the necessary precision that is essential for further disease management (Bott 2004).

It is relevant, therefore, to detect smaller and distant lesions as early as possible. With the emergence of PSMA-targeted radioligand therapy, in addition to early diagnosis, it is useful to diagnose PSMA-positivity to determine the future use of radioligand therapy. This is now becoming a reality since the recent approval of [^{68}Ga]Ga-PSMA-11 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 ([^{68}Ga]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 radioligand therapy options are available for treatment. While solid target 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.

Positron Emission Tomography (PET) imaging in prostate cancer

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 more 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) 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 examinations are needed (Hricak et al 1987, Shinohara et al 1989, Scheidler et 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).

Several head to head comparison studies have been performed on the uptake of [^{18}F]Fluciclovine *vs* [^{68}Ga]Ga-PSMA-11 for localization of PCa BCR. Detection rates were superior for [^{68}Ga]Ga-PSMA-11 *vs* [^{18}F]Fluciclovine after RP in patients with PSA < 2.0 ng/ml on per-patient and per-region basis (Calais et al 2018). However, a larger prospective head-to-head comparison study on [^{18}F]Fluciclovine *vs* [^{68}Ga]Ga-PSMA-11 in patients with BCR of PCa found no statistical differences in the overall detection rate for PCa recurrence between the two different radioligands (Pernthaler et al 2019). The differences between these studies may be attributed to various factors, including but not limited to sample size differences, differences in PSA levels of median values of < 2.0 ng/ml *vs* 14.9 ng/mL, time between scanning sessions, and standardization of the imaging study protocols.

Fluciclovine is a synthetic amino acid, which is transported across cell membranes by amino acid transporters known to be upregulated in cancer tumors, such as L-Type Amino Acid Transporter 1 (LAT-1) and Alanine Serine Cysteine Transporter 2 (ASCT2). [^{18}F]Fluciclovine uptake is not specific for PCa and may occur in other cancer types. In addition, the lack of selectivity for PCa may contribute to false-positive cases, which may be associated with inflammatory responses to therapeutic interventions. Contrarily, radioligands selective for the PSMA, such as [^{68}Ga]Ga-PSMA-11, provide greater sensitivity and specificity for imaging patients with PCa.

[^{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 advantages: ^{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 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 [^{18}F]CTT1057 Phase-I study in 20 PCa patients (n = 5 primary staging and 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 standard of truth (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 current study aims at evaluating the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positivity in patients diagnosed of biochemical recurrence of PCa , using a composite truth standard.

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 **region-level correct localization rate** (CLR) of [^{18}F]CTT1057	• Proportion of regions containing at least one TP lesion (anatomically localized correspondence between PET imaging and the reference standard), regardless of any co-existent FP findings within the same region, out of all regions containing at least one PET-positive finding by central assessments. See Section 2.1 for Primary Estimand
• Evaluate the **patient-level positive predictive value** (with anatomical localization) of [^{18}F]CTT1057	• Proportion of patients who have at least one TP lesion (anatomically localized correspondence between PET imaging and the reference standard), regardless of any co-existent FP findings, out of all patients who are PET/CT scan positive by central assessments. See Section 2.1 for Primary Estimand
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**

Objective(s)	Endpoint(s)
• Evaluate the patient-level **sensitivity** of [^{18}F]CTT1057	• Proportion of patients that test positive on [^{18}F]CTT1057 and CTS (TP) among those that are CTS positive (TP or FN)
• Evaluate the patient-level **specificity** of [^{18}F]CTT1057	• Proportion of patients that test negative on [^{18}F]CTT1057and CTS (TN) among those that are CTS negative (TN or FP)
• Evaluate the patient-level **negative predictive value** of [^{18}F]CTT1057	• Proportion of patients who are both [^{18}F]CTT1057 and CTS negative (TN) among those who test negative on [^{18}F]CTT1057 (TN or FN)
• Evaluate the patient-level **accuracy** of [^{18}F]CTT1057	• Proportion of patients that are CTS and [^{18}F]CTT1057 positive (TP) and negative (TN) among those patients that identified on [^{18}F]CTT1057 (TP, TN, FP or FN)
• Evaluate correct detection rate (CDR)	• Proportion of patients who have at least one TP lesion (exactly localized correspondence between PET imaging and the reference standard), regardless of any co-existent FP findings, out of all patients who are scanned
• Evaluate detection rate	• Proportion of patients who have at least one PET positive lesion, regardless of TP or FP findings, out of all patients who are scanned
• Evaluate the region level **sensitivity** of [^{18}F]CTT1057	• Proportion of regions that test positive on both [^{18}F]CTT1057 and CTS (TP) among those regions that are CTS positive (TP or FN)
• Evaluate the region level **specificity** of [^{18}F]CTT1057	• Proportion of regions that test negative on both [^{18}F]CTT1057 and CTS (TN) among those regions that are CTS negative (FP, or TN)
• Evaluate the region level **negative predictive value** of [^{18}F]CTT1057	• Proportion of regions that are CTS and [^{18}F]CTT1057 negative (TN) among those regions that test negative on [^{18}F]CTT1057 (TN or FN)
• Evaluate the region level **accuracy** of [^{18}F]CTT1057	• Proportion of regions that are CTS and [^{18}F]CTT1057 positive (TP) and negative (TN) among those regions that identified on [^{18}F]CTT1057 (TP, TN, FP and FN)
• Evaluate the patient-level positive predictive value related to PSA levels	• Percentage of patients who have at least one TP lesion (exactly anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the reference standard), regardless of any co-existent FP findings, out of all patients who are [^{18}F]CTT1057 positive, stratified by PSA levels
• Characterize the safety and tolerability of [^{18}F]CTT1057	• Incidence of AEs Treatment emergent adverse event (TEAE) rate within 14 days after each PET tracer administration

Objective(s)	Endpoint(s)
• [^{18}F]CTT1057 scan inter-reader variability	• Inter-reader agreement of [^{18}F]CTT1057 images
• [^{18}F]CTT1057 scan intra-reader variability	• Intra-reader agreement of [18F]CTT1057 images
• Concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of lesions at lesion level using central reads	• Concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of PSMA-positive lesions (location and number) using central reads
• Evaluate the change in patient management plans attributed to the PET/CT scan	• Percentage of patients who underwent a change in intended treatment plan attributed to the PET/CT scan as assessed by pre and post imaging questionnaires
• Assess all the above primary and secondary objectives independently in the subgroup of patients with prior radical prostatectomy and the subgroup of patients with prior curative intent radiation therapy	• All the above primary and secondary endpoints independently in the subgroup of patients with prior RP and the subgroup of patients with prior curative intent radiation therapy

[redacted]

2.1 Primary estimands

The primary clinical question of interest is: What is the probability that a positive [^{18}F]CTT1057 PET/CT scan truly detects and localizes (PSMA-expressing) tumor recurrence in BCR PCa patients?

The justification for the primary estimand is that we wish to assess the diagnostic performance of [^{18}F]CTT1057 PET/CT in detecting and localizing PSMA positivity in PCa patients diagnosed of biochemical recurrence (BCR), which represents a stage of PCa where there is an increase in PSA levels after initial treatment. Correct identification of disease location and extent guides treatment decisions. It is relevant, therefore, to detect smaller lesions as early as possible. Sensitivity and specificity of [^{18}F]CTT1057 PET/CT in detecting and localizing PSMA positivity using histopathology as SoT will be assessed in an independent study in newly diagnosed high-risk PCa patients candidate to surgery. However, in this primary staging population a low prevalence and high variability of metastatic lymph nodes has been reported (from 4-58%) (Petersen and Zacho 2020). Therefore, an additional study in the BCR setting is needed, since this is a relevant patient population which is expected to have an adequate representation of metastasis-positive and metastasis-negative patients by any available reference standard. In this population, a CTS is needed for reference (for CTS details see Section 3 and Section 4.1**)**. Pathology is available in only a limited number of cases, and morphological imaging is negative in a substantial number of cases. This makes the identification of true and false negative results a challenge, thus complicating the evaluation of sensitivity and specificity. Therefore, the region-level **correct localization rate (CLR)** defined as the region-level PPV with anatomical localization and the patient-level PPV with anatomical localization are more appropriate co-primary endpoints than sensitivity and specificity in the BCR setting. The patient-level PPV with anatomical localization, as the conditional probability of positivity given the result of the PET/CT scan is more meaningful than the correct detection rate (CDR) defined as the percentage of true-positive patients in the whole population

(unconditional probability of positivity). Moreover, the CDR has reported to be dependent of the PSA levels in the BCR population using another [^{18}F]-PSMA labeled PET agent (Chantadisai et al 2020).

The primary estimands are described by the following attributes:

Primary estimand 1:

1. Population: Patients with biopsy proven prostate adenocarcinoma and rising PSA after definitive therapy with RP or curative-intent radiation therapy (external beam or brachytherapy), diagnosed of biochemically recurrent PCa. Further details about the population are provided in Section 5.
2. Variable: Proportion of regions containing at least one TP lesion (anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the reference standard), regardless of any co-existent FP findings within the same region, out of all regions containing at least one [^{18}F]CTT1057 PET-positive finding, using central readings
3. Treatment 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 treatment is 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 scan for any reasons (e.g. consent withdrawal, PET camera failures, etc.) Details on how to handle intercurrent events are provided in Section 12.4.3.
5. Summary measure: Estimate of proportion of regions containing at least one TP lesion (anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the reference standard), regardless of any co-existent FP findings within the same region, out of all regions containing at least one [^{18}F]CTT1057 PET-positive finding (CLR) and CLR along with 95% CI estimated using logistic random-effects models taking into account the correlation among regions within one patient.

Primary estimand 2:

1. Population: the same as primary estimand 1
2. Variable: Proportion of patients who have at least one TP lesion (anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the reference standard), regardless of any co-existent FP findings, out of all PET positive patients, using central readings.
3. Treatment of interest: the same as primary estimand 1
4. Handling of remaining of intercurrent events: the same as primary estimand 1
5. Summary measure: Estimate of proportion of patients who have at least one TP lesion (anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the reference standard), regardless of any co-existent FP findings, out of all patients who are PET/CT scan positive (PPV) and PPV along with 95% CI estimated using binomial distribution.

2.2 Secondary estimands

Not applicable

3 Study design

This is a prospective, open-label, multi center, single-arm Phase III study to evaluate the diagnostic performance of [^{18}F]CTT1057 as a PET imaging agent for detection and localization of PSMA positive tumors in PCa patients diagnosed with biochemical recurrence (BCR) after initial definitive therapy with either RP or curative-intent RT, using a CTS as reference.

Approximately 190 participants will be enrolled to ensure at least 152 participants are evaluable for the co-primary endpoints. [^{18}F]CTT1057 PET/CT scan imaging will be read in a central Contract Research Organization (CRO) by 3 independent nuclear medicine physicians who will be blinded to any other patient data. See Section 4.1 and Section 8.3.1 for central read details.

The CTS to be used as reference will be hierarchical in nature, with 3 levels of SoT procedures that will be applied as follows:

Level 1)

- **Histopathology** if available for a lesion (from prospective biopsy or salvage surgery performed within 8 weeks after the [^{18}F]CTT1057 PET/CT scan); OR in case that histopathology is not available for a lesion, inconclusive (i.e. if biopsy/surgery tissue sample is not evaluable for histopathology assessment due to sample quality or inadequate quantity or any other technical causes) or negative (for biopsy only):

Level 2)

- **Imaging** diagnostic procedures performed on each patient as clinically indicated per SoC, which must include the [^{68}Ga]Ga-PSMA-11 PET/CT scan that is mandatory for all subjects randomized in the study and at least a high resolution CT scan (covering at least chest, abdomen, and pelvis and any other region as clinically indicated) with intravenous and oral contrast (or MRI if CT scan with contrast is medically contraindicated). The high resolution CT scan and any other imaging diagnostic procedure clinically indicated as per SoC must be acquired within the 8 weeks either prior to or following the [^{18}F]CTT1057 PET/CT scan. Three-month follow-up imaging (from baseline) will also be used as part of the CTS level 2 in cases where it is clinically required for the diagnosis of particular lesion(s); OR if neither of the two above are feasible or deemed appropriate or they are inconclusive (i.e. images are not interpretable due to poor or inadequate image quality that precludes reliable assessment):

Level 3)

- 50% or greater decline in **PSA following radiation therapy** (as long as no concomitant androgen deprivation therapy (ADT) is given) as per PCWG3 criteria (Scher et al 2016).

In the cases where pathology will be available, assessments by the local pathologists will be performed as per SoC, and results should be available within 2 weeks after surgery. Pathologists will be blinded to any PSMA-PET data (i.e. both PET/CT scans). In this case, only pathology will be used as SoT for the concerned lesion(s).

In the cases where pathology will not be available for a lesion, the central read results of the [^{68}Ga]Ga-PSMA-11 PET/CT scan (performed for all subjects randomized) and other imaging diagnostic procedures to be performed on each participant for the CTS level 2 will be used as SoT for the co-primary endpoint calculations. See Section 4.1 for central read details.

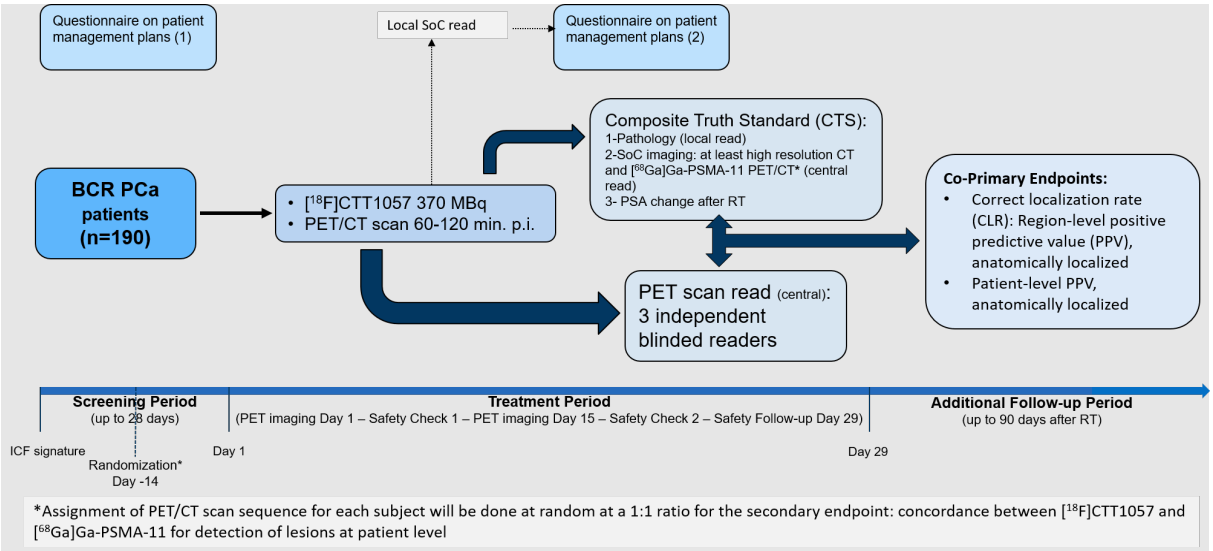
All patients will undergo a [^{68}Ga]Ga-PSMA-11 PET/CT as part of the study, for both the CTS Level 2 (in case it is required as SoT) and the secondary endpoint of assessment of concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of lesions (as detailed in Section 2).

In addition to central review, local review of SoC images (including [^{68}Ga]Ga-PSMA-11) will be performed to be used by the treating physician/Clinical Study Investigator for patient management decisions and overall assessment.

See Section 8.3.1 for assessment details and Section 6.4 for blinding requirements.

A questionnaire on the planned patient management will be filled-in by the treating physician/Clinical Study Investigator before (questionnaire 1) and within 14 days after (questionnaire 2) knowing the results of the [^{18}F]CTT1057 PET/CT scan. A local review of [^{18}F]CTT1057 PET/CT images will also be performed by a local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans and the results will be provided to the treating physician/Clinical Study Investigator for completion of questionnaire 2. Options will be given in the questionnaire to capture possible management plan, such as Surgery, Radiation alone, Radiation alone with change in radiation treatment plan (only applicable for questionnaire 2), Radiation plus ADT, ADT alone, Observation/surveillance, Other (free text box). Any change in patient management plan between the questionnaire 1 and questionnaire 2 should not be based only on [^{18}F]CTT1057 PET/CT scan results since this is an investigational diagnostic imaging product. Other diagnostic procedures should be performed as per SoC in order to confirm and implement the changed management plan. 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. 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 first PET imaging day (Day 1). Eligibility must then be confirmed at the latest on Day -14. The screening period should last up to 28 days.

Once eligibility is confirmed, the participants will be randomized in IRT to be assigned to one of the following two PET/CT scan sequences at random in a 1:1 ratio:

- Sequence 1: [^{18}F]CTT1057 on Day 1 (investigational imaging agent of interest) followed by [^{68}Ga]Ga-PSMA-11 at least 14 days apart (as part of CTS if required, and for secondary endpoint)
- Sequence 2: [^{68}Ga]Ga-PSMA-11 (as part of CTS if required, and for secondary endpoint) on Day 1 followed by [^{18}F]CTT1057 (investigational imaging agent of interest) at least 14 days apart

PET Imaging days

The 2 PET imaging procedures will be done at least 14 days apart. The day of the first PET imaging agent injection will be considered study Day 1. Please refer to Section 8.3.1 for the steps that will take place on each PET imaging day.

Both visits will also be considered as the End of Treatment (EOT) visits.

Safety Checks

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

Safety Follow-up

Participants will come back to the hospital 14 days (+ 3 day window) after each PET/CT scan day, for a safety visit including vital signs, lab and urine analysis. For participants undergoing surgery, radiation therapy or initiating any antineoplastic medication (provided all CTS procedures have been completed before this initiation) prior to planned safety visit, these safety follow-up assessments will need to be performed before the surgery/radiation therapy/initiation of antineoplastic medication.

Additional Follow-up

Additional follow up period will be applicable where additional diagnostic procedures are to be performed. These may include SoC pathology, imaging or other modality disease assessments (CTS Levels 1 or 2) up to 8 weeks after [^{18}F]CTT1057 PET/CT scan or three-month follow-up imaging (from baseline) where it is clinically required for the diagnosis of particular lesion(s).

In addition, in cases where the CTS Level 2 is not feasible/appropriate or inconclusive, and the CTS Level 3 will apply and will include the assessment of PSA levels prior to starting RT (which should commence within 8 weeks of completing [^{18}F]CTT1057 PET/CT scan) and at approximately 90 days from last day of radiation.

4 Rationale

4.1 Rationale for study design

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

[^{18}F]CTT1057 PET/CT results will be compared to the applicable SoT from the corresponding level of the CTS (as described in Section 3) for calculation of the co-primary endpoints and the diagnostic performance yielding secondary endpoints.

Novel imaging agents are routinely evaluated comparing imaging results with histopathological findings. In the BCR setting, pathology is expected to be available only in approximately 35-40% of the patients, and in a subset of the lesions (Fendler et al 2019). Therefore, a combination of conventional diagnosis procedures, relying on a combination of biopsy (when possible), imaging procedures, and clinical follow up or changes in biomarkers such as PSA levels, collectively known as the composite truth standard (CTS), has been used to evaluate the diagnostic accuracy of new diagnostic agents in BCR patients. This methodology has limitations as the ascertainment of CTS may be subject to non-homogeneous evaluation between subjects as biopsy may not be feasible in all patients with metastatic lesions. Therefore, diagnosis based on CTS in the majority of the patients relies on conventional imaging, mainly morphological imaging procedures which are based on the detection of changes in lesion's size and has limitations, including the inability to detect smaller lesions accurately. Accordingly, for lesions that cannot be subjectively characterized on a single CT/MRI scan, serial follow up scans are obtained in order to observe changes in the morphology over time. Serial CT/MRI scans may, therefore, increase the accuracy of diagnosis of smaller, doubtful lesions observed on a single scan at the expense of time. However, in the proposed BCR population, conventional imaging will be negative in a substantial proportion of cases (Hövels et al 2008). 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 (AfsharOromieh et al 2015, AfsharOromieh et al 2017, Fendler et al 2019). It has also demonstrated high sensitivity in detecting PSMA positivity when comparing its diagnostic accuracy with histopathologic findings in these patients (Fendler et al 2019). Based on this body of evidence, and given the recent approval of [^{68}Ga]Ga-PSMA-11 in the USA ([^{68}Ga]GaPSMA11 USPI), it can be used to significantly enhance and address the limitations of routinely used CTS for the evaluation of new diagnostics. Given the acknowledged lack of optimal reference standard in patients with biochemical recurrence (BCR) in cases where pathology is not available, [^{68}Ga]Ga-PSMA-11 PET/CT will provide a validated approximation to the truth, for new, upcoming PSMA-PET imaging agents that overcome the ^{68}Ga production and delivery hurdles. In this study, the CTS imaging component (CTS Level 2) must include at least a high resolution CT scan with i.v. and oral contrast (or MRI if CT scan with contrast is medically contraindicated) and a [^{68}Ga] Ga-PSMA-11 PET/CT scan. Given that in the proposed BCR population, morphological imaging has been reported to be negative in a substantial proportion of cases (Hövels et al 2008), the recently approved [^{68}Ga]Ga-PSMA-11 PET imaging agent is considered a surrogate standard of truth. In addition, any other imaging diagnostic procedures clinically indicated for each patient as per

SoC will be included in the CTS Level 2). An 8-week time window before and after the investigational PET/CT scan is proposed for the performance of the imaging diagnostic component of the CTS Level 2, since no major changes in the disease are expected within this timeframe.

Anatomically localized positive lesions in [^{18}F]CTT1057 PET/CT and the applicable SoT from the hierarchical CTS will be considered true positives for the region-level correct localization rate (CLR, i.e. region-level PPV) and patient-level PPV calculations as the co-primary endpoints of the study.

In the cases where pathology will be available, it will be used as SoT (CTS Level 1). Pathology may be available in case of identified lesions that can be either biopsied or suitable for salvage surgery (in case of solitary or few localized lymph nodes). Local pathologists who will be blinded to any PSMA-PET data (i.e. both PET/CT scan results) will assess the tissue specimens as per SoC (see Section 6.4 for blinding details)

If pathology is not available for a lesion, inconclusive or negative (for biopsy only), CTS Level 2 (imaging diagnostic procedures) will be used as SoT. These must include at least a high-resolution CT scan with i.v. and oral contrast (or MRI if CT scan with contrast is medically contraindicated) and a[^{68}Ga]Ga-PSMA-11 PET/CT scan, but will include also any other imaging diagnostic procedures clinically indicated for each patient as per SoC. In order to reduce variability of image readings across multiple study sites, a centralized reading of these imaging diagnostic procedures will be performed in a CRO by 3 readers who will be blinded to [^{18}F]CTT1057 PET/CT scan results, but not to other patient data. The majority rule (2/3 readers) will be used as a final outcome of the reads. Further details will be provided in the imaging charter. See also Section 6.4 and Section 8.3 for blinding and reading details.

If neither of the two first CTS components (i.e. pathology or imaging) are feasible, conclusive or deemed appropriate, then CTS Level 3 (50% or greater decline in PSA following radiation therapy (as long as no concomitant androgen deprivation therapy (ADT) is given) as per PCWG3 criteria) will be used as SoT. The lesion on the [^{18}F]CTT1057 PET/CT scan that was irradiated will be classified as a TP in case of ≥50% PSA decrease 3 months after RT, or as FP otherwise.

A central read of the [^{18}F]CTT1057 PET/CT scans will be performed at a CRO by three independent nuclear medicine physicians or radiologists experienced in reading PET, who will be blinded to patient data, including the clinical condition of the patient, results of histopathology/biopsy, results of conventional imaging and PSA levels. Patients and regions will be graded on a two-point scale by each reader (0 = negative; 1 = positive). The 3 PET readers' results will be individually compared to the SoT to generate per-reader performance. An individual PET reader will be considered successful if he/she meets the predefined thresholds for both co-primary endpoints, and at least two of three readers should be successful for overall study positivity.

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 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 (Eiber et al 2015, Ceci et al 2015, Fendler et al 2019).

Consistency of the PET 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.

All patients will undergo 2 PET/CT scans: a [^{18}F]CTT1057 PET/CT scan (investigational imaging agent) and a [^{68}Ga]Ga-PSMA-11 PET/CT scan (as part of the CTS level 2 if required, and for the secondary endpoint of assessment of concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of lesions) (see Section 3). The two scans will be performed at least 2 weeks apart for each participant in order to ensure a clean safety profile assessment for each PET imaging radiopharmaceutical. Moreover, in order to counter-balance any potential change in lesions between the 2 PET/CT scans, the PET/CT scan sequence for each patient will be assigned at random, in a 1:1 ratio after enrolment (see Section 6.1.4 for the definition of PET/CT scan sequence).

There is preliminary evidence that PSMA PET imaging allows detection and localization of metastases in some BCR patients leading to significant changes in therapeutic approaches (Afshar-Oromieh et al 2017). Therefore, assessment of the clinical impact of [^{18}F]CTT1057 PET/CT in patient management by means of 2 questionnaires has been included as a secondary endpoint. Further details on the questionnaire are provided in Section 3. In order to reproduce as much as possible the real clinical context, the treating physician / Clinical Study Investigator will receive the [^{18}F]CTT1057 PET/CT scan report from a local nuclear medicine physician who will be blinded to the results of the [^{68}Ga]Ga-PSMA-11 PET/CT scan, but will not be blinded to other patient data.

In addition, the imaging diagnostic procedures included in CTS Level 2 will be read by local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans as per SoC, who will be blinded to the [^{18}F]CTT1057 PET/CT scan results, but not to other patient data. [redacted].

See also Section 6.4 and Section 8.3 for blinding and reading details.

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 (range 266– 407 MBq). This dose was shown to be safe and well tolerated in the Phase I study (NCT02916537), and it is in line with the recommended dose of the commercial product [^{18}F]-FDG according to the European Association of Nuclear Medicine (EANM) (Boellaard et al 2015). Human dosimetry was studied in the Phase I study. The effective dose (ED) was estimated at 0.023±0.007 millisievert (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. injection of 370 MBq of [^{18}F]CTT1057 is 8.51 mSV. Moreover, this dose allowed to obtain an optimal image quality, which was rated 76 ± 5.4 on a Visual Analog Scale (VAS) of 1 to 100 (1 = non diagnostic, 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.

The [^{68}Ga]Ga-PSMA-11 radiopharmaceutical will be administered as a single intravenous (i.v.) dose of approximately 150 MBq. Administered doses must not be lower than 111 MBq or higher than 185 MBq in case. [^{68}Ga]Ga-PSMA-11 PET/CT scans will be used as part of the imaging component of the CTS. Refer to the [^{68}Ga]Ga-PSMA-11 USPI for an overview of [^{68}Ga]Ga-PSMA-11 recommendations. Refer to Section 6.7 for study drug preparation and dispensation. Further details on [^{68}Ga]Ga-PSMA-11 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 [^{68}Ga]Ga-PSMA-11 for PET scanning of PCa patients has been ongoing since 2011 to assess disease burden in the setting of primary staging (localized disease), biochemical recurrence (BCR; rising PSA) and advanced/metastatic disease. There are now numerous centers around the world that have clinical experience with [^{68}Ga]Ga-PSMA-11, which has been approved by the FDA for clinical use in the US ([^{68}Ga]Ga-PSMA-11 USPI).

The published data consistently demonstrates that imaging with [^{68}Ga]Ga-PSMA-11 is well tolerated. Four publications report on a total of 7047 PCa patients that have received [^{68}Ga]Ga-PSMA-11 (N=1007 (Afshar-Oromieh et al 2017), N=1256 (Von Eyben et al 2018), N=635 (Fendler et al 2019), N=4149 (Hope et al 2019)). These four studies have further reinforced the ability of [^{68}Ga]Ga-PSMA-11 to identify PSMA-expressing PCa and demonstrate it is well tolerated. 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 ([^{68}Ga]Ga-PSMA-11 USPI). The risk-benefit ratio is expected to be favorable to the [^{68}Ga]Ga-PSMA-11 imaging agent. Further details of [^{68}Ga]Ga-PSMA-11 can be found in the IB.

Subsequently, other PSMA-PET agents have been investigated and are under clinical development, all of them showing a good safety and tolerability profile. (Kuten et al 2020, Szabo et al 2015). The [^{18}F]CTT1057 PET Phase-I study in 20 PCa patients (n=5 primary staging, n=15 mCRPC (NCT02916537) has shown an acceptable safety profile, without any radiotracer-related adverse reactions (Behr et al 2019). The bio distribution 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 and human dosimetry studies, and clinical experience with [^{18}F]CTT1057 suggest good imaging quality properties and a favorable safety profile.

As this is a diagnostic study patients enrolled are not expected to derive direct benefit even though 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 appropriate management plan, which will not be based on the investigational procedure alone, but confirmed by SoC diagnostic procedures.

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

The risk-benefit ratio is expected to be favorable to the [^{18}F]CTT1057 imaging agent. Additional details of the nonclinical and clinical experience with [^{18}F]CTT1057 are provided in the IB.

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 male participant ≥ 18 years of age, with biopsy proven prostate adenocarcinoma and rising PSA after definitive therapy with RP or curative-intent radiation therapy (external beam or brachytherapy), diagnosed of biochemically recurrent PCa.

Approximately 190 participants will be enrolled to ensure at least 152 participants are evaluable (i.e. have both an evaluable [^{18}F]CTT1057 PET/CT scan imaging, and at least one evaluable

CTS assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CTs and CTS procedures), 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:

1. Signed informed consent must be obtained prior to participation in the study
2. Biopsy proven prostate adenocarcinoma.

3a. Biochemical recurrence following initial definitive therapy (with either RP or curative intent radiation therapy) as defined:

- by AUA criteria (Cookson et al 2007) for patients who have undergone RP: Initial serum PSA of ≥0.2 ng/ml measured at least 6 weeks after RP with a second confirmatory persistent PSA level of >0.2 ng/ml, or
- by ASTRO-Phoenix criteria (Roach et al 2006) for patients who have undergone curative-intent radiation therapy (RT): Rise of serum PSA measurement of 2 or more ng/mL above the nadir PSA observed post RT.

4. ECOG performance status 0-2
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. Prior major surgery undergone less than 12 weeks prior to screening (with the exception of any surgery related to prostatic cancer)
4. Known allergy, hypersensitivity, or intolerance to [^{18}F]CTT1057, [^{68}Ga]Ga-PSMA-11, or to CT contrast
5. Prior and current use of PSMA targeted therapies

7a. Prior ADT (first or second generation), including LHRH analogues (agonists or antagonists), within 9 months before screening

8. Any 5-alpha reductase inhibitors within 30 days before screening
9. Use of other investigational drugs within 30 days before screening
10. Castration-resistant patients

11. Patient with small cell or neuroendocrine PCa in more than 50% of biopsy tissue
12. Prior salvage surgery or salvage radiation therapy

6 Treatment

6.1 Study treatment

The term "Study Treatment" indicates the administration of at least one of the two PET imaging agents: [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 independently of whether the PET/CT scans were acquired or not. In this study, the investigational imaging agent of interest is the radioligand imaging compound [^{18}F]CTT1057. [^{68}Ga]Ga-PSMA-11 will be used as a component of the CTS Level 2 if required, and in all participants for the secondary endpoint of assessment of concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of lesions (as detailed in Section 2).

Participants will be administered both agents at least 2 weeks (14 days) apart as an intravenous injection (Refer to Section 6.7 for study drug preparation and dispensation) according to the randomly assigned PET/CT scan sequence after enrolment.

Participants will be administered [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 as an intravenous injection, single dose (Refer to Section 6.7 for study drug preparation and dispensation). Both agents will be provided by Novartis.

The general doses of the study treatment are listed in Section 6.1.

6.1.1 Investigational and control drugs

Table 6-1 Investigational PET imaging agents

Investigational PET imaging agents (Name and Strength)	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply Type**	**Sponsor (global or local)**
[^{18}F]CTT1057 370 MBq/mL at Calibration time (Tc)	Radiopharmaceutical solution for injection	Intravenous use	Open label, vial or syringe	Sponsor (global)

Investigational PET imaging agents (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
[^{68}Ga]Ga-PSMA-11 (150 MBq)	Either provided as Kit for the radiopharmaceutical preparation of [^{68}Ga]Ga-PSMA-11 or as ready to use radiopharmaceutical solution for injection	Intravenous use	Open label, vial or syringe	Sponsor (global)

For background and additional details on [^{18}F]CTT1057, refer to Section 6.7 for study drug preparation and dispensation and to the [^{18}F]CTT1057 IB. The [^{18}F]CTT1057 radiopharmaceutical will be administered intravenously at a dose of approximately 370 MBq (range 266 – 407 MBq). The exact dose that will have been administered to each patient will be recorded in the case report form (CRF) after measurement of the syringe both before and after administration in a dose calibrator.

For background and additional details on [^{68}Ga]Ga-PSMA-11, refer to Section 6.7 for study drug preparation and dispensation and to the [^{68}Ga]Ga-PSMA-11 IB. The [^{68}Ga]Ga-PSMA-11 radiopharmaceutical will be administered as a single intravenous (i.v.) dose of approximately 150 MBq. Administered doses must not be lower than 111 MBq or higher than 185 MBq in any case. The exact dose that will have been administered to each patient will be recorded in the CRF after measurement of the syringe both before and after administration in a dose calibrator.

6.1.2 Additional study treatments

No other treatment beyond investigational imaging agent and the component of CTS imaging agent are included in this trial.

6.1.3 Supply of study treatment

The investigational imaging agent [^{18}F]CTT1057 will be provided:

- as a single mono-dose 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. .

The component of CTS imaging agent [^{68}Ga]Ga-PSMA-11 will be provided:

- as a kit for radiopharmaceutical preparation: single vial with a white lyophilized powder to be locally reconstituted with a solution of gallium-68 chloride ($^{68}GaCl_3$) in HCl eluted from an approved $^{68}Ge/^{68}Ga$ generator (for the clinical sites equipped with an approved $^{68}Ge/^{68}Ga$ generator).
- as a single dose ready to use radiopharmaceutical solution: vial or syringe with the radiopharmaceutical solution supplied by the partner radiopharmacy (for the clinical sites not equipped with an approved $^{68}Ge/^{68}Ga$ generator).

The volume of [^{68}Ga]Ga-PSMA-11 solution for injection, corresponding to the radioactive dose to be administered, is calculated according to the estimated time of injection, on the basis of the current activity provided by the generator and of physical decay of the radionuclide (half-life = 68 min). After reconstitution, the [^{68}Ga]Ga-PSMA-11 solution must be used according to instructions provided in the Pharmacy Manual.

The process of ordering and delivery, as well as the procedure for any solution preparations is described in the Pharmacy Manual.

Both products must be handled and administered by qualified/authorized personnel only and must be prepared in accordance with pharmaceutical quality requirements and radiation safety regulations.

6.1.4 Treatment arms/group

This is a single-arm study. However, the PET/CT scan sequences for each participant will be assigned at random in a 1:1 ratio after enrolment:

- Sequence 1: [^{18}F]CTT1057 (investigational imaging agent of interest) followed by [^{68}Ga]Ga-PSMA-11 (as part of CTS [if required] and for secondary endpoint).
- Sequence 2: [^{68}Ga]Ga-PSMA-11 (as part of CTS [if required] and for secondary endpoint) followed by [^{18}F]CTT1057 (investigational imaging agent of interest).

Please refer to Section 6.3.2 for assignment details.

6.1.5 Treatment duration

The planned duration of treatment period (i.e. single-dose administration of the 2 PET imaging agents) is at least 2 weeks, with single i.v. injection performed at Day 1 and approximately at Day 15. Participants may be discontinued from treatment due to unacceptable toxicity following the first administered imaging agent or at the discretion of the investigator or the participant. Upon end of treatment and the study, participants may be treated with any other medications per discretion of the treating physician.

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 randomizing 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, therapy or procedure (other than the study treatment) that may interfere with PSMA PET imaging is not allowed. Prior to completing both PET imaging scans and CTS procedures, 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 enrolled for screening and is retained for the participant throughout his participation in the trial. A new Participant No. will be assigned at every subsequent enrollment 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

The IRT will be used to assign the PET/CT scan sequence to each eligible participants at random (1:1 ratio), and the randomization numbers will be stored in 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 [^{18}F]CTT1057 or [^{68}Ga]Ga-PSMA-11 dose prior to the scheduled dosing date (refer to Pharmacy Manual). Each 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 and PET/CT scan sequence assignment 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 read by 3 independent readers blinded to patient data collected in clinical database (such as medical history details or diagnostic test results).
- In addition, [^{18}F]CTT1057 PET/CT images will be read by local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans at each site, who will be blinded to [^{68}Ga]Ga-PSMA-11 PET/CT imaging results, but not to other patient data. The results will be shared with the treating physician / Clinical Study Investigator to support the completion of the patient management questionnaire 2.
- Images from diagnostic procedures included in the CTS Level 2 will be submitted to a CRO for independent centralized read by independent readers, blinded to [^{18}F]CTT1057 PET/CT images, but not to other patient data collected in clinical database.
- In addition, these CTS images will be read by a local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans at each site as per SoC, who will be blinded to [^{18}F]CTT1057 PET/CT imaging results, but not to other patient data. [redacted]
- In the cases where pathology will be available, assessments by the local pathologists will be performed as per SoC. Pathologists will be blinded to any PSMA-PET data (i.e. both PET/CT scans).

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not applicable in this study in which each 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 study investigational imaging agent in packaging as described under investigational and control drugs Section 6.1.1.

For [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 preparation and administration, please refer to procedure and instructions contained in the Pharmacy Manual.

Investigator staff will know the study treatments to dispense to the participant by accessing the IRT during the screening period (between Day -28 and Day -14). For [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 ordering, please refer to procedure and instructions contained in the Pharmacy Manual.

Following administration of the study treatments to the participant, the site personnel will capture this information in the source document and will complete the accountability logs for traceability purposes. For more detailed instructions please refer to the Pharmacy Manual.

6.7.1 Handling of study treatment and additional treatment

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 in a white glass multidose vial (For EU) or a monodose 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 imaging agent is intended at the clinical site, except the:

- dispensation into monodose 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 Phamacy 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 no, expiry date.

[^{68}Ga]Ga-PSMA-11

The packaging of PSMA-11 kit consists of a box (secondary packaging) and one 10 mL glass vials (primary packaging).

[^{68}Ga]Ga-PSMA-11 will be supplied by Sponsor as a sterile, one-vial kit for reconstitution with ^{68}Ga solution eluted from approved commercial Good Manufacturing Practice (GMP) ^{68}Ge/^{68}Ga generator to:

1. the clinical site, in case of the kit's reconstitution and radiolabelling will be performed at hospital's radiopharmacy,
2. the radiopharmacy appointed by the sponsor, in case of an external radiopharmacy will be in charge of the kit's reconstitution and radiolabeling.

In the second case, the clinical site will order the [^{68}Ga]Ga-PSMA-11 single dose ready to use solution for injection following the instructions described in the Pharmacy manual.

[^{68}Ga]Ga-PSMA-11 must be prepared and administered at the investigational site by appropriately trained personnel. The instruction for radiolabeling procedure and dispensing [^{68}Ga]Ga-PSMA-11, cautionary notes, analytical controls and stability of the radiolabeled product will be provided to each site (please refer to the Pharmacy Manual).

After reconstitution with ^{68}Ga solution eluted from GMP ^{68}Ge/^{68}Ga generator, the imaging agent is a radioactive substance which must be stored, handled and administered by qualified/authorized personnel only as described in the Pharmacy Manual and must be prepared in accordance with pharmaceutical quality requirements and radiation safety regulations.

The kit for the preparation of [^{68}Ga]Ga-PSMA-11 should be stored upon receipt according to storage conditions as described in the medication label.

The imaging agent [^{68}Ga]Ga-PSMA-11 will be locally discarded according to all disposal requirements and local regulations for radioactive materials. The disposal of all study treatment will 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.

Kits 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.

[^{68}Ga]Ga-PSMA-11 ready to use radioactive solution labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions, batch no and 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.

[^{18}F]CTT1057 will be injected intravenously at approximately 370 MBq (range 266 – 407 MBq), then flushed by 10 mL of saline during the imaging day.

The investigational product is a radioactive substance which must be used, handled and administered by qualified/authorized personnel only and must be prepared in accordance with the Pharmacy Manual, pharmaceutical quality requirements and radiation safety regulations.

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.

[^{68}Ga]Ga-PSMA-11

Preparation

In case of the kit's reconstitution and radiolabelling will be performed at hospital's radiopharmacy.

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

In case of an external radiopharmacy will be in charge of the kit's reconstitution and radiolabeling, the clinical site will receive the [^{68}Ga]Ga-PSMA-11 single dose ready to use solution for injection.

Administration

[^{68}Ga]Ga-PSMA-11 must be administered at the dose as presented in Section 6.1.1 investigational site by appropriately trained personnel. The instruction for radiolabeling procedure and dispensing [^{68}Ga]Ga-PSMA-11, cautionary notes, analytical controls and

stability of the radiolabeled product will be provided to each site (please refer to the Pharmacy Manual).

After reconstitution with ^{68}Ga solution eluted from GMP ^{68}Ge/^{68}Ga generator, the investigational product is a radioactive substance which must be used, handled and administered by qualified/authorized personnel only and must be prepared in accordance with the Pharmacy Manual, pharmaceutical quality requirements and radiation safety regulations. The total activity administered must be recorded (GBq, Millicurie (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).

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/she 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 Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) 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 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 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 who discontinue 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 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 administered imaging agents should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the 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	Randomization	PET Imaging 1[1]					Safety Check 1	PET Imaging 2[1]					Safety Check 2	Safety Follow-up	Additional Follow-up[2]	EOS
Days	Day -28 to Day -14	Day –28 to Day -14	Day 1 (+7)					Day 2 to 3	Day 15 (+7)					Day 16 to 17	Day 29 (+ 3)	up to 90 days after RT	Day 29 to Follow-up end
Time (post-dose)	-	-	Pre-Injection	Injection	Post-Injection/ Pre-Imaging	Imaging	Post-Imaging / EOT 1	-	Pre-Injection[3]	Injection	Post-Injection/ Pre-Imaging	Imaging	Post-Imaging / EOT 2	-	-	-	-
Informed Consent	X																
IRT Participant Registration	X																
Inclusion / Exclusion Criteria	X																
Medical History & Demographics	X																

Period	Screening*		Treatment													Additional Follow-up	Study Completion
Visit Name	Screening	Randomization	PET Imaging 1[1]					Safety Check 1	PET Imaging 2[1]					Safety Check 2	Safety Follow-up	Additional Follow-up[2]	EOS
Days	Day -28 to Day -14	Day –28 to Day -14	Day 1 (+7)					Day 2 to 3	Day 15 (+7)					Day 16 to 17	Day 29 (+ 3)	up to 90 days after RT	Day 29 to Follow-up end
Time (post-dose)	-	-	Pre-Injection	Injection	Post-Injection/ Pre-Imaging	Imaging	Post-Imaging / EOT 1	-	Pre-Injection[3]	Injection	Post-Injection/ Pre-Imaging	Imaging	Post-Imaging / EOT 2	-	-	-	-
Electrocardiogram (ECG)	X																
ECOG Performance Status	X																
Physical Examination	S (short)		S (short)						S (short)						S (short)		
Body Weight	X		X						X								
Body Height	X																
Vital Signs[4]	X		X		X		X		X		X		X		X		
Hematology[5]	X		X						X						X		
Clinical Chemistry	X		X						X						X		

Period	**Screening***		**Treatment**												**Additional Follow-up**	**Study Completion**
Visit Name	**Screening**	**Randomization**	**PET Imaging 1[1]**					**Safety Check 1**	**PET Imaging 2[1]**					**Safety Check 2**	**Safety Follow-up**	**Additional Follow-up[2]**	**EOS**
Days	**Day -28 to Day -14**	**Day –28 to Day -14**	**Day 1 (+7)**					**Day 2 to 3**	**Day 15 (+7)**					**Day 16 to 17**	**Day 29 (+3)**	**up to 90 days after RT**	**Day 29 to Follow-up end**
Time (post-dose)	**-**	**-**	**Pre-Injection**	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 1**	**-**	**Pre-Injection[3]**	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 2**	**-**	**-**	**-**	**-**
PSA level	X															X (Prior RT and 90 days post RT)	
Urinalysis[6]	S		S						S						S		
IRT Randomization		X															
[^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 Ordering[7]		X															
Adverse Events	AEs to be collected throughout this period																

Period	**Screening***		**Treatment**												**Additional Follow-up**	**Study Completion**
Visit Name	**Screening**	**Randomization**	**PET Imaging 1[1]**					**Safety Check 1**	**PET Imaging 2[1]**					**Safety Check 2**	**Safety Follow-up**	**Additional Follow-up[2]**	**EOS**
Days	**Day -28 to Day -14**	**Day –28 to Day -14**	**Day 1 (+7)**					**Day 2 to 3**	**Day 15 (+7)**					**Day 16 to 17**	**Day 29 (+ 3)**	**up to 90 days after RT**	**Day 29 to Follow-up end**
Time (post-dose)	-	-	**Pre-Injection**	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 1**	-	**Pre-Injection[3]**	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 2**	-	-	-	-
[^{18}F]CTT 1057 / [^{68}Ga]Ga-PSMA-11 or [^{68}Ga]Ga-PSMA-11 / [^{18}F]CTT 1057 Administration[8]				X						X							
Concomitant Medications	Concomitant Medications to be collected throughout this period																

Period	**Screening***		**Treatment**												**Additional Follow-up**	**Study Completion**
Visit Name	**Screening**	**Randomization**	**PET Imaging 1**[1]					**Safety Check 1**	**PET Imaging 2**[1]					**Safety Check 2**	**Safety Follow-up**	**Additional Follow-up**[2]	**EOS**
Days	**Day -28 to Day -14**	**Day –28 to Day -14**	**Day 1 (+7)**					**Day 2 to 3**	**Day 15 (+7)**					**Day 16 to 17**	**Day 29 (+ 3)**	**up to 90 days after RT**	**Day 29 to Follow-up end**
Time (post-dose)	-	-	**Pre-Injection**	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 1**	-	**Pre-Injection**[3]	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 2**	-	-	-	-
[^{18}F]CTT1057 /[^{68}Ga]Ga-PSMA-11 PET/CT Imaging[9]						X						X					
Patient Management Questionnaire	Before and within 14 days after [^{18}F]CTT1057 PET/CT scan results																
Histopathology, if applicable															If indicated, biopsy/salvage surgery should be performed within 8 weeks after completion of the [^{18}F]CTT1057 PET/CT scan AND after completion of the [^{68}Ga]Ga-PSMA-11 PET/CT scan		

Period	**Screening***		**Treatment**													**Additional Follow-up**	**Study Completion**
Visit Name	**Screening**	**Randomization**	**PET Imaging 1[1]**					**Safety Check 1**	**PET Imaging 2[1]**					**Safety Check 2**	**Safety Follow-up**	**Additional Follow-up[2]**	**EOS**
Days	**Day -28 to Day -14**	**Day –28 to Day -14**	**Day 1 (+7)**					**Day 2 to 3**	**Day 15 (+7)**					**Day 16 to 17**	**Day 29 (+ 3)**	**up to 90 days after RT**	**Day 29 to Follow-up end**
Time (post-dose)	**-**	**-**	**Pre-Injection**	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 1**	**-**	**Pre-Injection[3]**	**Injection**	**Post-Injection/ Pre-Imaging**	**Imaging**	**Post-Imaging / EOT 2**	**-**	**-**	**-**	**-**
SoC diagnostic imaging procedures assessment	At least a high resolution CT scan with intravenous and oral contrast (or MRI if CT scan with contrast is medically contraindicated), and any other SoC imaging diagnostic procedure as clinically indicated per SoC (CT/MRI, Bone Scan, etc.), performed within 8 weeks before or after [^{18}F]CTT1057 scan																
Safety Follow up Call								X						X			X
End of Phase Disposition	X						X						X				X

* All Screening assessments to confirm eligibility into the study must be performed prior randomization.

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 Participants will undergo either [^{68}Ga]Ga-PSMA-11 PET/CT followed by [^{18}F]CTT1057 PET/CT at least 14 days apart, or [^{18}F]CTT1057 PET/CT followed by [^{68}Ga]Ga-PSMA-11 PET/CT at least 14 days apart

2 Additional follow-up includes any SoC pathology assessment (of a biopsy/salvage surgery performed up to 8 weeks from [^{18}F]CTT1057 PET/CT scan, CTS level 1) and/or any SoC imaging diagnostic procedures assessments (at least a high-resolution CT with contrast) performed up to 8 weeks from [^{18}F]CTT1057 PET/CT scan for CTS level 2; If CTS level 3 is applicable for the participant (in case Levels 1 or 2 are not feasible, inconclusive or negative), the PSA levels will be assessed prior to RT,

Period	Screening*		Treatment												Additional Follow-up	Study Completion
Visit Name	Screening	Randomization	PET Imaging 1[1]					Safety Check 1	PET Imaging 2[1]					Safety Check 2	Safety Follow-up	Additional Follow-up[2]	EOS
Days	Day -28 to Day -14	Day –28 to Day -14	Day 1 (+7)					Day 2 to 3	Day 15 (+7)					Day 16 to 17	Day 29 (+3)	up to 90 days after RT	Day 29 to Follow-up end
Time (post-dose)	-	-	Pre-Injection	Injection	Post-Injection/ Pre-Imaging	Imaging	Post-Imaging / EOT 1	-	Pre-Injection[3]	Injection	Post-Injection/ Pre-Imaging	Imaging	Post-Imaging / EOT 2	-	-	-	-

which should commence within 8 weeks after [^{18}F]CTT1057 PET/CT scan and after both PET/CTs are completed, and at approx. 90 days from the last day of radiation

[3] Assessments done prior to starting 2nd injection will be also considered as safety follow-up 14 days after the first PET Imaging Day

[4] Vital signs will be performed at screening, at Imaging days (pre and post-injection and then before patient discharge) and at Safety follow-up visit (Day29)

[5] Peripheral venous blood samples will be collected at screening, PET Imaging Days pre-injection and at Safety follow-up (Day 29)

[6] Urine sample will be collected at screening and imaging days and analyzed at the clinical site if dipstick results are abnormal

[7] Order to be placed after randomization and based on the radiopharmaceutical that requires the longest period from order to delivery

[8] Participant will be injected intravenously either approximately 370 MBq (range 266–407 MBq) of [^{18}F]CTT1057 or approximately 150 MBq (range 111-185MBq) of [^{68}Ga]Ga-PSMA-11, 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. 50-100 min after [^{68}Ga]Ga-PSMA-11 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.

8.1 Screening

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, eligibility reviewed and, once eligible, study treatment ordered.

Laboratory assessments should be carried out as priority to allow the necessary time to obtain the results and to confirm participant eligibility prior to randomization and study treatment ordering in IRT. All Screening assessments to confirm eligibility into the study should be performed between Day -28 and Day -14 as per Visit Assessment Schedule in 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 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 registering 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. 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 randomization 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). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized 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-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.

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

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

Participant medical history to be documented in eCRF include:

- Date of diagnosis of PCa
- Gleason grade at diagnosis, PSA at diagnosis, Clinical stage (cTNM) at diagnosis
- In patients with RP or patients with RT: PSA at diagnosis, gleason score of the RP specimen, pathological stage (pTNM) at diagnosis, information on additional salvage RT (prostate bed, lymphatic drainage), PSA nadir, first PSA >2ng/ml.
- PSA nadir after RT (if applicable)
- 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).

8.3 Efficacy

Efficacy assessments in this study include disease assessment per SoC at baseline (and if clinically indicated, post-baseline) as well as assessments of PET/CT images using the two PET agents. Please refer to the schedule of assessments provided in Table 8-1 and Section 8.3.1.

8.3.1 Imaging for tumor assessment

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

Table 8-2 Imaging Assessment Collection Plan

Imaging procedures	Mandatory or Optional	Image Acquisition Timing
[^{18}F]CTT1057 PET/CT	Mandatory - all participants	Day 1 or Day 15*
[^{68}Ga]Ga-PSMA-11 PET/CT	Mandatory - all participants	Day 1 or Day 15*
High Resolution CT with i.v. and Oral Contrast (or MRI if CT scan with contrast is medically contraindicated) of at least Chest Abdomen and Pelvis (and any additional region as clinically indicated)	Mandatory - all participants	+/- 8 weeks from [^{18}F]CTT1057 PET/CT Acquisition
Other Standard of Care Imaging diagnostic procedures (MRI, Bone Scan, PET with other imaging agents, etc.)	As clinically indicated per SoC	+/- 8 weeks from [^{18}F]CTT1057 PET/CT Acquisition
Follow-up Standard of Care Imaging diagnostic procedures (CT, MRI, Bone Scan, PET with other imaging agents, etc.)	If clinically required per SoC for the diagnosis of particular lesion(s)	3 months after the initial imaging procedure performed

*Day 1 or 15 determined by participant's randomization into sequence 1 or 2.

Imaging diagnostic procedures (CT/MRI, bone scan, or other modalities) should be performed as clinically indicated for each patient per SoC within 8 weeks (either before or after) the [^{18}F]CTT1057 PET/CT scan. Any imaging assessments already completed during the regular work-up of the participant within 8 weeks prior to [^{18}F]CTT1057 PET/CT scan, including before signing the main study ICF, can be considered as part of imaging component of the CTS Level 2.

CTS Level 2 will be used as reference for co-primary endpoints if pathology is not available for a lesion, inconclusive or biopsy is negative.

The CTS level 2 imaging diagnostic procedures must include at least a high-resolution CT scan with i.v. and oral contrast (or MRI if CT scan with contrast is medically contraindicated) and the [^{68}Ga]Ga-PSMA-11 PET/CT scan. It may include also any other imaging diagnostic procedures clinically indicated for each participant as per SoC (including three-month follow-up imaging where it is clinically required for the diagnosis of particular lesion(s)). A centralized reading of these imaging diagnostic procedures will be performed in a CRO by 3 readers who will be blinded to [^{18}F]CTT1057 PET/CT scan results, but not to other patient data collected in

clinical database. The majority rule (2/3 readers) will be used as a final outcome of the reads. Further details will be provided in the Imaging Charter.

In addition, the imaging diagnostic procedures included in CTS level 2 will be read by local nuclear medicine physicians or radiologists with expertise in reading oncology PET/CT scans as per SoC, who will be blinded to the [^{18}F]CTT1057 PET/CT scan results, but not to other patient data. [redacted] The criteria to be applied for PET positivity are detailed in Section 4.1.

SoC imaging data to be documented in eCRF will include the outcome of assessments, i.e. if negative or positive for PCa tumor or metastases, regions where lesions are identified, number and location of the lesions. For lesions that are visually positive on the [^{68}Ga]Ga-PSMA-11 PET but not considered as PCa, their characteristics will be documented (i.e. non-prostate cancer tumoral or benign, such as inflammatory, degenerative, necrotic, other). For CT/MRI lesion size measurements RECIST 1.1 guidelines will be applicable (Section 16.2).

Post-baseline PET imaging assessments

PET imaging assessments as described in Table 8-1 should be performed at the timepoints, at Day 1 and approximately at Day 15. The following steps will take place on each PET imaging day:

[^{68}Ga]Ga-PSMA-11 PET imaging day (as part of the imaging component of CTS):

1. Participant will be asked to drink 1-2 glasses of water before arrival at the clinic
2. Participants 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 a single dose of approximately 150 MBq of [^{68}Ga]Ga-PSMA-11, administered doses must not be lower than 111MBq or higher than 185MBq in any case then flushed by 10 ml of saline. For [^{18}F]CTT1057 administration, please see below
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 patient to void, an urethral catheterization will be considered
6. Approximately 50 to 100 minutes (min) later, 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 participant will be allowed to void again, and uretheral 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 approximately 120+60 min post-injection (p.i.)

8. Vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be recorded again at the completion of the study (prior to participant discharge)
9. Participant will be discharged with the reminder of the safety follow up as described in the Informed Consent Form (ICF).

[^{18}F]CTT1057 (investigational imaging agent) PET imaging day:

1. Participant will be asked to drink 1-2 glasses of water before arrival at the clinic
2. Participants 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 patient 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 participant will be asked to void again, and uretheral 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 approximately [redacted]
8. Vital signs (body temperature, blood pressure, heart rate, respiratory rate) will be recorded again at the completion of the study (prior to participant discharge)
9. Participant will be discharged with the reminder of the safety follow up as described in the Informed Consent Form (ICF).

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, regions where lesions are identified, number and location of the lesions as well as their characteristics.

[^{18}F]CTT1057 PET/CT images will be submitted to the designated imaging CRO for independent central review. All reviewers have to be blinded to patient data (including clinical condition, histopathology and imaging results). Central read results will not be provided to the treating physician/Clinical 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, blinded to [^{68}Ga]Ga-PSMA-11 PET/CT scan results, but not to other patient data. The report from this local reader

will be provided to the treating physician / Clinical Study Investigator to complete the patient management questionnaire 2.

[^{68}Ga]Ga-PSMA-11 PET/CT images will be both centrally and locally read as all the other imaging procedures included in CTS Level 2.

8.3.2 Histopathology assessments

In the cases where pathology will be available (from prospective biopsy or salvage surgery performed within 8 weeks after the completion of [^{18}F]CTT1057 PET/CT scan and after the completion of [^{68}Ga]Ga-PSMA-11 PET/CT scan), assessments by the local pathologists will be performed as per SoC, and results are to be provided within 2 weeks of the biopsy. Pathologists will be blinded to any PSMA-PET data (i.e. both PET/CT scans), but not to other patient data.

Pathology data to be documented in eCRF will include among others the procedure/methodology used, the outcome of the assessment, i.e. if negative or positive for adenocarcinoma, if other tumor histological types are present or not and their nature, number, location as well as size of the tumor and/or metastatic lesions within the tissue specimens.

8.3.3 PSA level assessments

For CTS Level 3, increases and decreases of PSA levels will be tracked to assess PSA responses before and after RT (third component of the CTS) as per PCWG3 for participants where pathology or radiological assessments are not available or conclusive.

RT should commence within approximately 8 weeks of completing the study treatment (i.e. both PET/CT scans) and PSA should be assessed prior to starting the RT and then at approximately 90 days from last day of radiation.

8.3.4 Appropriateness of efficacy assessments

[^{18}F]CTT1057 PET/CT efficacy assessments will be based on a Composite Truth Standard (CTS), as described in Section 3 (in brief: CTS Level 1=pathology, CTS Level 2= imaging diagnostic procedures, CTS Level 3= PSA changes). See Section 1.1 for the rationale of using a CTS in the BCR setting.

For CT/MRI lesion size measurements, applicable RECIST v1.1 guidelines Section 16.2 will be used. For PSA measurements after RT (third component of the CTS) PCWG3 guidelines Section 16.3 will apply. PCWG3 is an international working group of clinical and translational experts in PCa who developed international recognized recommendations.

8.4 Safety

Safety assessments are specified below (Table 8-3) 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.

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 AE section.

Table 8-3 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 site 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 below (Table 8-4).

Table 8-4 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 8-5 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)

Test Category	Test Name
PSA	PSA

8.4.2 Electrocardiogram (ECG)

A standard 12 Lead ECG 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 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. 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.

8.4.3 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 investigational imaging agents.

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

8.5.1 Other Assessments

Patient Management questionnaire will be completed by the treating physician/ Clinical Study Investigator before and within 14 days after having the results of the [^{18}F]CTT1057 PET imaging assessment by an independent local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans. For subjects assigned to sequence 1, questionnaire 2 should be completed before [^{68}Ga]Ga-PSMA-11 PET/CT is performed. Refer to Section 16.4 for details.

9 Study discontinuation and completion

9.1 Discontinuation from study treatment and study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when either one of the two injections of study treatment is not given as planned per protocol and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from Study treatment is required under the following circumstances:

- Participant non-compliance or voluntary withdrawal from study or from study treatment/guardian decision
- Unacceptable toxicity, as assessed by the Investigator, after the first administration of imaging agent that precludes the safe administration of the second imaging agent
- 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
- Any other situation in which continued study participation might result in a safety risk to the participant
- At the Sponsor's or Investigator's discretion.

For study participants for whom it is required to discontinue from study treatment due to unacceptable toxicity resulting in a SAE, refer to Section 10.1.3 for the reporting requirements.

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation of study treatment and record this information in the source documents and relevant eCRF pages.

Participants who discontinue from study treatment can agree to **return for the end of treatment and follow-up visits and any efficacy assessment 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 discontinuation from study treatment, at a minimum, in abbreviated visits, 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.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason. If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

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 from study treatment or discontinue from study or withdraw consent/oppose their use of data or biological samples, 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.

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)
- andNo longer wishes to receive study treatment

and

- Does not want to participate in the study anymore,

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/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 be discontinued 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
- Discontinuation of study compound (i.e. the investigational imaging agent) 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 (e.g. safety follow up period must be completed if applicable with required visits to be performed). The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or 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 randomized and/or treated participants will have a Safety Follow up visit at Day 29. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Please refer to Table 8-1 for the required assessments at this visit.

Additional follow up period will be applicable where SoC additional diagnostic procedures are to be performed. These may include SoC pathology, imaging or other modality disease assessments (CTS Levels 1 or 2) up to 8 weeks after [^{18}F]CTT1057 PET imaging, or three-month follow-up imaging (from baseline) if clinically required for the diagnosis of particular lesion(s).

In addition, for participants at CTS Level 3 (i.e. in case CTS Levels 1 or 2 are not feasible or conclusive), PSA levels to be assessed prior to starting RT and at approx. 90 days from the last day of radiation.

End of Study visit should be done once all post-treatment follow-up assessments are completed and can be done via a phone call.

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. 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, or the imaging agent [^{68}Ga]Ga-PSMA-11. 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 (i.e. discontinuation from 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 study treatment.

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 E15D (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 E15D (2004) Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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 electronic Serious Adverse Event (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 medicinal product/study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment 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

10.2.1 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial and Novartis representatives from the Clinical Trial Team.

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 Electronic Case Report Forms (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, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant will be

tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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 that time 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, on the efficacy analysis set and safety set 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 randomized participants.

The Efficacy Analysis Set (EFF) includes all randomized participants who receive the dose of investigational treatment (i.e. [^{18}F]CTT1057) and have both an evaluable [^{18}F]CTT1057 PET/CT scan imaging, and at least one evaluable CTS assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CTs and CTS procedures.

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

The [^{68}Ga]Ga-PSMA-11 Safety Set (Ga-SAF) includes all participants who received [^{68}Ga]Ga-PSMA-11. Participants will be analyzed according to the study treatment received.

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 dose of [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 will be summarized by means of descriptive statistics using the F-SAF and Ga-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 EFF

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

The co-primary endpoints of the study are region-level CLR and patient-level PPV

- Region-level CLR is defined as the proportion of regions containing at least one TP lesion (exactly localized correspondence between PET imaging and the reference standard), regardless of any co-existent FP findings within the same region, out of all regions containing at least one PET-positive finding.

- Patient-level PPV is defined as the proportion of patients who have at least one TP lesion (exactly localized correspondence between PET imaging and the reference standard), regardless of any co-existent FP findings, out of all patients who are PET/CT scan positive.

Centralized imaging assessments (CTS Level 2) will be used as reference standard if pathology (CTS Level 1) is not available for a lesion, inconclusive or negative (for biopsy only).

12.4.2 Statistical model, hypothesis, and method of analysis

To address the co-primary efficacy objectives:

Region-level CLR and its 95% CI will be calculated using logistic random-effects models taking into account the correlation among regions within one patient. .The lower bound of the 95% CI for CLR should be greater than 0.5 to attain the first co-primary endpoint.

Patient-level PPV and its 95% CI will be calculated based on the binomial distribution. The lower bound of the 95% CI for patient-level PPV should be greater than 0.2 to attain the second co-primary endpoint.

12.4.3 Handling of remaining intercurrent events of primary estimand

The primary analyses 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 PET/CT scan for any reasons: they will not be used for the co-primary endpoint analyses, but safety data will be collected as planned 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, co-primary endpoints are 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

The lower level of CTS will be used to verify positivity or negativity for the sensitivity analysis. For instance, if pathology (CTS Level 1) is used as true standard for primary estimand, imaging component of CTS (Level 2) will be used as true standard for sensitivity analysis for primary estimand. However, for those using changes in PSA level (CTS Level 3) as the true standard for primary estimand, their positivity status cannot be replaced by another component of CTS for sensitivity analysis.

12.4.6 Supplementary analysis

As supplementary analyses performed in the EFF, the region-level CLR and patient-level PPV and 95% CIs will be obtained from covariate adjusted logistic regression model. Important covariate will be specified in the SAP.

Subgroup analyses for region-level CLR and patient-level PPV will be performed:

- patients with prior radical prostatectomy

- patients with prior curative intent radiation therapy

If the co-primary endpoints 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 and related endpoints are described in Table 2-1.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Following secondary endpoints, centralized imaging assessment will be used as reference standard if pathology assessment is not available for a lesion.

Patient-level sensitivity is defined as the proportion of TP patients among those who are TP or FN

Patient-level specificity is defined as the proportion of TN patients among those who are TN 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 scanned patients (regardless of TP, TN, FP, FN)

Patient-level correct detection rate is defined as the proportion of TP patients among all scanned patients (regardless of TP, TN, FP, FN)

Patient-level detection rate is defined as the proportion of TP and FP patients among all scanned patients (regardless of TP, TN, FP, FN)

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

- PSMA TP patients are those who have at least one TP lesion with anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the CTS.
- PSMA TN patients are those who do not show any pathological [^{18}F]CTT1057 uptake and will be confirmed NOT having any lesions with the CTS.
- PSMA FP patients are those who show at least one pathological [^{18}F]CTT1057 uptake but will be verified NOT having any lesions with the CTS or none is correctly localized in anatomical location by the CTS.
- PSMA FN patients are those who do not show any pathological [^{18}F]CTT1057 uptake but will be confirmed having at least one with the CTS.

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 among three readers determinations and will be assessed by Fleiss' Kappa statistic. Details of calculation of Fleiss' Kappa statistic in SAP.

[^{18}F]CTT1057 scan intra-reader variability is defined as within-reader agreement for two different time points and will be assessed by Cohen's Kappa statistic. A subset of imaging reading will be performed at two different time points by each reader. See details in imaging charter. Details of calculation of Cohen's Kappa statistic in SAP.

Change in patient management plans attributed to the [^{18}F]CTT1057 PET/CT scan is defined as the percentage of patients who undergo a change in intended treatment plan attributed to the PET/CT scan as assessed by pre imaging questionnaire 1 and post imaging questionnaire 2

Numbers and percentage of patients on each category of treatment plan: surgery, radiation alone, radiation alone with change in radiation treatment plan (only applicable for questionnaire 2), radiation plus ADT, ADT alone, observation/surveillance, other (free text box) in two questionnaires will be calculated.

Treatment plan change is defined as a pair of categories (one category of questionnaire 1, one category of questionnaire 2)

Numbers and percentage of patients on the treatment change defined above will be calculated.

The following secondary endpoints, centralized imaging assessment will be used as reference standard if pathology assessment is not available for a lesion.

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

Region-level specificity is defined as the proportion of TN regions among those that are TN or FP

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

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

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

- PSMA TP regions are regions containing at least one TP lesion (anatomically localized correspondence between [^{18}F]CTT1057 PET imaging and the CTS).
- PSMA TN regions are regions containing no lesions with pathological [^{18}F]CTT1057 uptake and confirmed by CTS.
- PSMA FP regions are regions containing lesions with pathological [^{18}F]CTT1057 uptake but will be verified negative by CTS or none is correctly localized in anatomical location by the CTS.
- PSMA FN regions are regions containing no lesions with pathological [^{18}F]CTT1057 uptake but will be confirmed having at least one lesions with the CTS.

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

95% CI for region-level diagnostic performance parameters will be calculated using logistic random-effects models taking into account the correlation among regions within one patient.

For different regions (i.e. prostate region, PLN, extra-PLN, skeletal, visceral), 95% CI for region-level diagnostic performance parameters will be calculated based on the binomial distribution respectively.

Patient-level positive predictive value will be also calculated for different categorical PSA levels.

Concordance between [^{18}F]CTT1057 and [^{68}Ga]Ga-PSMA-11 for detection of lesions, positive percent agreement will be calculated to assess the concordance.

12.5.2 Safety endpoints

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs). [^{18}F]CTT1057 treatment-emergent AEs, [^{68}Ga]Ga-PSMA-11 treatment-emergent AEs will be presented using F-SAF and Ga-SAF separately.

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 treatment
2. On-treatment period: from day of dosing of study medication to approximately 14 days after dosing of study treatment.
3. Post-treatment period: starting at day 15 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 treatment emergent adverse events (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, other significant adverse events leading to drug interruption, and adverse events leading to drug withdrawn.

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 adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, 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

All ECG data will be listed by participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by visit/time.

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) 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.

[redacted]

12.7 Interim analyses

Not applicable

12.8 Sample size calculation

Overall, approximately 190 participants will be enrolled to ensure at least 152 participants are evaluable (i.e. have both an evaluable [18F]CTT1057 PET/CT scan imaging, and at least one evaluable CTS assessment and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CTs and CTS procedures), which will be required for the

calculation of the co-primary endpoints. 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 190 patients. The sample size calculation is based on the co-primary endpoints of region-level CLR and the patient-level PPV of [^{18}F]CTT1057.

The assumptions for sample size calculations are based on the estimates from data available from prior studies.

The primary endpoint is to evaluate region-level CLR (prostate region, PLN, extra-PLN, skeletal, visceral) and patient-level PPV of [^{18}F]CTT1057 PET for detection of tumor location confirmed by histopathology/biopsy. Based on the results of previous studies, the following distribution of disease across regions are anticipated: Prostate bed: 30%, pelvis: 15%; extrapelvic soft tissue: 20%; bone metastases: 35% (Eiber et al 2015, Ceci et al 2015, Van Leeuwen et al 2016). It is anticipated that the CLR for the five regions and for all regions combined using conventional imaging ranges from 30-60%. An overall CLR for [^{18}F]CTT1057 PET of at most 50% will be considered as unacceptably low. Hence, the null hypothesis that the CLR is at most 50% will be tested against the alternative hypothesis that the CLR is greater than 50%.

The BCR population targeted in this study is expected to have similar PSA values than prior studies (Morris et al 2020) of approved diagnostic PET agents for PCa such as [^{18}F]-fluciclovine, which had a 27% PPV for patients with PSA values that were less than 1.78, as noted in their summary basis of approval. Thus, a patient-level PPV of 20% will be considered as unacceptably low. The [^{18}F]CTT1057 positive patient rate (detection rate) for the study population is 80% based on [^{18}F]-fluciclovine studies. The sample size calculation will be performed based on the null and alternative hypotheses as follows.

- Region-level CLR:

Correlated binary test results occur in this situation where each experimental unit (patient) consists of five correlated regions. Lee and Dubin developed a sample size formula for clustered binary data (Lee and Dubin 1994). They propose estimating the binary proportion by assigning equal weights to clusters regardless of their sizes to simplify the derivation of their sample size formula. The weighted estimator for region-level CLR is approximately Gaussian distributed with a variance of a beta distribution (beta-binomial model).

The null Hypothesis H0: region-level CLR p = 0.5 will be tested against the alternative hypothesis H1: p >0.5 Assuming a CLR of 0.58 under the alternative hypothesis, a total sample size of 172 enrolled participants would achieve 90% statistical power to detect a change in CLR of 0.08 using a one-sided test at a target significance level of 2.5%.This sample size includes an adjustment for a dropout rate of 0.20.

To determine the sample size n such that the type I error of one-sided testing H0 is 0.025 and with power 0.9 to reject H0 if alternative H1 is true. By the standard normal approximation, the sample size is given

$$n = \frac{\sigma^2 (Z_\alpha - Z_{1-\beta})^2}{(p_1 - p_0)^2}$$

where σ^2 the variance of a beta distribution, Z_a is the upper a quantile of the standard normal distribution, p_0 is the CLR 0.5 under null hypothesis, p_1 is 0.58 the achievable CLR.

Suppose there is no information on the within-cluster correlation of test results. In this case, a uniform distribution seems reasonable, setting parameters in the beta distribution alpha=1 and beta=1. Then σ^2 is 1/12

Under these assumptions, 137 patients will be necessary to ensure the 90% power, taking into account 20% dropout rate, a total of 172 patients will be recruited for this endpoint of the study.

The lower bound of the 95% CI for CRL should be greater than 0.5 to be considered success.

- Patient-level PPV

The null Hypothesis H0: patient-level PPV p = 0.2 will be tested against the alternative hypothesis H1: p >0.2 Assuming a patient-level PPV of 0.33 under the alternative hypothesis, a total sample size of 190 enrolled participants (which includes 152 [^{18}F]CTT1057 scanned patients based on 80% [^{18}F]CTT1057 positive patient rate) would achieve 90% statistical power to detect a change in patient-level PPV of 0.13 using a one-sided binomial test at a target significance level of 2.5%.This sample size includes an adjustment for a dropout rate of 20%. The lower bound of the 95% CI for patient-level PPV should be greater than 0.2 to be considered success.

A total sample size of 190 patients can ensure 92.7% statistical power for region-level CLR and 90% statistical power for patient-level PPV resulting in an overall study statistical power of at least 83.4% (0.927*0.9).

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 GCP, 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.

15 References

References are available upon request

[^{68}Ga]Ga-PSMA-11 U.S Prescribing Information (USPI) FDA (Internet) Available from: accessdata.fda.gov/drugsatfda_docs/label/2020/212642s000lbl.pdf (Accessed Dec-2020).

Afshar-Oromieh A, Avtzi E, Giesel FL, et al (2015) The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging; 42:197-209.

Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al (2017) Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging; 44:1258-68.

Afshar-Oromieh A, Malcher A, Eder M, et al (2013) PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging; 40:486-95.

Afshar-Oromieh A, Zechmann CM, Malcher A, et al (2014) Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging; 41:11-20.

Behr S, Aggarwal R, Flavell R, et al (2017) Comparison of a novel fluorine-18 labeled PSMA-targeting agent, CTT1057, to gallium-68 PSMA-11 in patients with prostate cancer [abstract]. J Nucl Med; 58 Suppl 1:733A.

Behr SC, Aggarwal R, VanBrocklin HF, et al (2019) Phase I Study of CTT1057, an 18F-Labeled Imaging Agent with Phosphoramidate Core Targeting Prostate-Specific Membrane Antigen in Prostate Cancer. J Nucl Med; 60(7):910-6.

Blomqvist L, Carlsson S, Gjertsson P, et al (2014) Limited evidence for the use of imaging to detect prostate cancer: a systematic review. Eur J Radiol; 83:1601-6.

Boellaard R, Delgado-Bolton R, Oyen WJG, et al (2015) FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging; 42:328-54.

Bostwick DG, Pacelli A, Blute M, et al (1998) Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer; 82(11):2256-61.

Bott SRJ (2004) Management of recurrent disease after radical prostatectomy. Prostate Cancer and Prostatic Dis; 7:211-6.

Bravaccini S, Puccetti M, Bocchini M, et al (2018) PSMA expression: a potential ally for the pathologist in prostate cancer diagnosis. Sci Rep; 8:4254.

Bray F, Ren JS, Masuyer E, et al (2013) Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer; 132:1133-45.

Budäus L, Leyh-Bannurah SR, Salomon G, et al (2016) Initial Experience of (68)Ga-PSMA PET/CT Imaging in High-risk Prostate Cancer Patients Prior to Radical Prostatectomy. Eur Urol; 69:393-6.

Calais J, Kishan AU, Cao M, et al (2018) Potential Impact of 68Ga-PSMA-11 PET/CT on the Planning of Definitive Radiation Therapy for Prostate Cancer. J Nucl Med; 59(11):1714-21.

Ceci F, Uprimny C, Nilica B, et al (2015) (68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? Eur J Nucl Med Mol Imaging; 42:1284-94.

Chantadisai M, Buschner G, Krönke M, et al (2020) Positive predictive value and correct detection rate of 18F-rhPSMA-7 PET in biochemically recurrent prostate cancer validated by composite reference standard. J Nucl Med; 12:1-38.

Conti M, Eriksson L (2016) Physics of pure and non-pure positron emitters for PET: a review and a discussion. EJNMMI Physics; 3(1):1-17.

Cookson MS, Aus G, Burnett AL, et al (2007) Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol;177(2):540-5.

Eiber M, Maurer T, Souvatzoglou M, et al (2015) Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med; 56(5):668-74.

Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer; 45:228-47.

Fendler WP, Calais J, Eiber M, et al (2019) Assessment of ^{68}Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer: A Prospective Single-Arm Clinical Trial. JAMA Oncol; 5(6):856-63.

Ghosh A, Heston WDW (2004) Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem; 91:528-39.

Haffner MC, Kronberger IE, Ross JS, et al (2009) Prostate-specific membrane antigen expression in the neovasculature of gastric and colorectal cancers. Hum Pathol; 40:1754-61.

Han S, Woo S, Kim YJ, et al (2018) Impact of 68Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol; 74:179-90.

Hope TA, Goodman JZ, Allen IE, et al (2019) Metaanalysis of 68Ga-PSMA-11 PET Accuracy for the Detection of Prostate Cancer Validated by Histopathology. J Nucl Med; 60(6):786-93.

Hricak H, Dooms GC, Jeffrey RB, et al (1987) Prostatic carcinoma: staging by clinical assessment, CT, and MR imaging. Radiology; 162:331-6.

Hupe MC, Philippi C, Roth D, et al (2018) Expression of Prostate-Specific Membrane Antigen (PSMA) on Biopsies Is an Independent Risk Stratifier of Prostate Cancer Patients at Time of Initial Diagnosis. Front Oncol; 8:623.

Hövels AM, Heesakkers RAM, Adang EM, et al (2008) The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol; 63:387-95.

ICH E2D (2004) Clinical Safety Data Management: Definitions and Standards for expedited reporting (Internet) Available from: ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002807.pdf (Accessed 15 January 2021).

Isbarn H, Wanner M, Salomon G, et al (2010) Long-term data on the survival of patients with prostate cancer treated with radical prostatectomy in the prostate-specific antigen era. BJU Int; 106:37-43.

Jani AB (2006) Management strategies for locally advanced prostate cancer. Drugs Aging; 23(2):119-29.

Kaushik A, Jaimini A, Tripathi M, et al (2015) Estimation of radiation dose to patients from (18) FDG whole body PET/CT investigations using dynamic PET scan protocol. Indian J Med Res; 142:721-31.

Kuten J, Fahoum I, Savin Z, et al (2020) Head-to-Head Comparison of 68Ga-PSMA-11 with 18F-PSMA-1007 PET/CT in Staging Prostate Cancer Using Histopathology and Immunohistochemical Analysis as a Reference Standard. J Nucl Med; 61(4):527-32.

Lee EW, Dubin N (1994) Estimation and sample size considerations for clustered binary responses. Stat Med; 13:1241-52.

Malvezzi M, Carioli G, Bertuccio P, et al (2019) European cancer mortality predictions for the year 2019 with focus on breast cancer. Ann Oncol; 30(5):781-7.

Morris MJ, Carroll PR, Saperstein L, et al (2020) Impact of PSMA-targeted imaging with 18F-DCFPyL-PET/CT on clinical management of patients (pts) with biochemically recurrent (BCR) prostate cancer (PCa): Results from a phase III, prospective, multicenter study (CONDOR) [abstract]. J Clin Oncol; 38 (15 Suppl):5501A.

Nanni C, Zanoni L, Pultrone C, et al (2016) (18)F-FACBC (anti1-amino-3-(18)F-fluorocyclobutane-1-carboxylic acid) versus (11)C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging; 43:1601-10.

Odewole OA, Tade FI, Nieh PT, et al (2016) Recurrent prostate cancer detection with anti-3-[(18)F]FACBC PET/CT: comparison with CT. Eur J Nucl Med Mol Imaging; 43:1773-83.

Oh WK, Kantoff PW (1999) Treatment of locally advanced prostate cancer: is chemotherapy the next step? J Clin Oncol; 17(11):3664-75.

Perera M, Papa N, Christidis D, et al (2016) Sensitivity, Specificity, and Predictors of Positive 68Ga-Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol; 70:926-37.

Pernthaler B, Kulnik R, Gstettner C, et al (2019) A Prospective Head-to-Head Comparison of 18F-Fluciclovine With 68Ga-PSMA-11 in Biochemical Recurrence of Prostate Cancer in PET/CT. Clin Nucl Med; 44(10):e566-e73.

Petersen LJ, Zacho HD (2020) PSMA PET for primary lymph node staging of intermediate and high-risk prostate cancer: an expedited systematic review. Cancer Imaging; 20:10.

Prasad V, Steffen IG, Diederichs G, et al (2016) Biodistribution of [(68)Ga]PSMA-HBED-CC in Patients with Prostate Cancer: Characterization of Uptake in Normal Organs and Tumour Lesions. Mol Imaging Biol; 18:428-36.

Roach M, Hanks G, Thames H, et al (2006) Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys;65(4):965-74.

Roscigno M, Sangalli M, Mazzoccoli B, et al (2005) Medical therapy of prostate cancer. A review. Minerva Urol Nefrol; 57(2):71-84.

Ross JS, Sheehan CE, Fisher HAG, et al (2003) Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res.; 9:6357-62.

Scheidler J, Hricak H, Vigneron DB, et al (1999) Prostate cancer: localization with three-dimensional proton MR spectroscopic imaging--clinicopathologic study. Radiology; 213(2):473-80.

Scher HI, Morris MJ, Stadler WM, et al (2016) Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol; 34(12):1402-18.

Schmidt LH, Heitkötter B, Schulze AB, et al (2017) Prostate specific membrane antigen (PSMA) expression in non-small cell lung cancer. PLoS ONE; 12(10):e0186280.

Schwarzenböck S, Souvatzoglou M, Krause BJ (2012) Choline PET and PET/CT in Primary Diagnosis and Staging of Prostate Cancer. Theranostics; 2(3):318-30.

Shinohara K, Wheeler TM, Scardino PT (1989) The appearance of prostate cancer on transrectal ultrasonography: correlation of imaging and pathological examinations. J Urol; 142:76-82.

Siegel RL, Miller KD, Jemal A (2017) Cancer Statistics, 2017. CA Cancer J Clin; 67(1):7-30.

Siegel RL, Miller KD, Jemal A (2018) Cancer Statistics, 2018. CA Cancer J Clin; 68(1):7-30.

Siegel RL, Miller KD, Jemal A (2019) Cancer Statistics, 2019. CA Cancer J Clin; 69(1):7-34.

Smith RA, Andrews K, Brooks D, et al (2016) Cancer screening in the United States, 2016: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin; 66(2):95-114.

Spatz S, Tolkach Y, Jung K, et al (2018) Comprehensive Evaluation of Prostate Specific Membrane Antigen Expression in the Vasculature of Renal Tumors: Implications for Imaging Studies and Prognostic Role. J Urol; 199:370-7.

Stock K, Steinestel K, Wiesch R, et al (2017) Neovascular Prostate-Specific Membrane Antigen Expression Is Associated with Improved Overall Survival under Palliative Chemotherapy in Patients with Pancreatic Ductal Adenocarcinoma. Biomed Res Int; 2847303.

Szabo Z, Mena E, Rowe SP, et al (2015) Initial Evaluation of [(18)F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer. Mol Imaging Biol; 17(4):565-74.

Tanjore Ramanathan J, Lehtipuro S, Sihto H, et al (2020) Prostate-specific membrane antigen expression in the vasculature of primary lung carcinomas associates with faster metastatic dissemination to the brain. J Cell Mol Med; 24:6916-27.

Tolkach Y, Gevensleben H, Bundschuh R, et al (2018) Prostate-specific membrane antigen in breast cancer: a comprehensive evaluation of expression and a case report of radionuclide therapy. Breast Cancer Res Treat; 169:447-55.

Tolkach Y, Goltz D, Kremer A, et al (2019) Prostate-specific membrane antigen expression in hepatocellular carcinoma: potential use for prognosis and diagnostic imaging. Oncotarget; 10(41):4149-60.

Van Leeuwen PJ, Stricker P, Hruby G, et al (2016) (68) Ga-PSMA has a high detection rate of prostate cancer recurrence outside the prostatic fossa in patients being considered for salvage radiation treatment. BJU Int; 117:732-9.

Van Poppel H, Vekemans K, Da Pozzo L, et al (2006) Radical prostatectomy for locally advanced prostate cancer: results of a feasibility study (EORTC 30001). Eur J Cancer; 42:1062-7.

Von Eyben FE, Picchio M, von Eyben R, et al (2018) 68Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus; 4:686-93.

Wang HL, Wang SS, Song WH, et al (2015) Expression of prostate-specific membrane antigen in lung cancer cells and tumor neovasculature endothelial cells and its clinical significance. PLoS ONE; 10(5):e0125924.

Wernicke AG, Edgar MA, Lavi E, et al (2011) Prostate-specific membrane antigen as a potential novel vascular target for treatment of glioblastoma multiforme. Arch Pathol Lab Med; 135:1486-9.

Wernicke AG, Kim S, Liu H, et al (2017) Prostate-specific Membrane Antigen (PSMA) Expression in the Neovasculature of Gynecologic Malignancies: Implications for PSMA-targeted Therapy. Appl Immunohistochem Mol Morphol; 25(4):271-6.

Yaxley JW, Dagher J, Delahunt B, et al (2018) Reconsidering the role of pelvic lymph node dissection with radical prostatectomy for prostate cancer in an era of improving radiological staging techniques. World J Urol; 36:15-20.

Yaxley JW, Raveenthiran S, Nouhaud FX, et al (2019a) Risk of metastatic disease on 68 gallium-prostate-specific membrane antigen positron emission tomography/computed tomography scan for primary staging of 1253 men at the diagnosis of prostate cancer. BJU Int; 124:401-7.

Yaxley JW, Raveenthiran S, Nouhaud FX, et al (2019b) Outcomes of Primary Lymph Node Staging of Intermediate and High Risk Prostate Cancer with 68Ga-PSMA Positron Emission Tomography/Computerized Tomography Compared to Histological Correlation of Pelvic Lymph Node Pathology. J Urol; 201:815-20.

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: Response Evaluation Criteria in Solid Tumors

The latest RECIST guidelines (version 1.1) can be found at the following site:

[project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf]

16.3 Appendix 3: PCWG3

The sections that apply to this trial are the criteria for PSA response and progression, and the criteria for bone lesion "prevent/delay end points" (progression). It is based on the PCWG3 recommendations (Scher et al 2016).

16.4 Appendix 4: Patient Management questionnaire

A questionnaire on the planned patient management will be filled-in by the treating physician/Clinical Study Investigator before (questionnaire 1) and within 14 days after knowing the results of the [^{18}F]CTT1057 PET/CT scan (questionnaire 2).

Options will be given in the questionnaire to capture possible management plan, such as

- Surgery
- Radiation alone
- Radiation alone with change in radiation treatment plan (only applicable for questionnaire 2)
- Radiation plus ADT
- ADT alone
- Observation/surveillance
- Other (free text box)

The results of the [^{18}F]CTT1057 PET/CT scan will be provided to the Study Investigator before the patient undergoes the planned treatment by a local nuclear medicine physician or radiologist with expertise in reading oncology PET/CT scans, who will be blinded to [^{68}Ga]Ga-PSMA-11 data but not to other patient data, in order to reproduce as much as possible the real clinical context to assess the potential clinical impact of the investigational procedure.