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Clinical Development

AAA405

Clinical Trial Protocol CAAA405A12302 / NCT04838626

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

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
12-Oct-2021	Prior to DB lock	Creation of final version	N/A - First version	NA
30-Sep-2022	After PA01, before original IND submission	Incorporating changes made in the protocol amendment v01.	1. Updated surgery timing to ensure that surgery will be performed up to 6 weeks after but not sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan. 2. Updated safety follow-up visit assessments timing to ensure all patients will go through at least a 2-day period to check their safety after PET scan without being confounded by the effects of surgery. 3. Aligned between objectives and endpoints wording, e.g. “evaluated for all regions” removed. 4. Removed that incidence of AEs will be described after PET tracer injection, after PET/CT scans and at 24-72 h after PET/CT scan. 5. Updated the definition of efficacy analysis set about patients who will be evaluable for co-primary endpoints. 6. Alignment with the protocol added regarding the definition of overall study positivity. 7. Clarification added to the definition of TP and FP patients. 8. Clarification added regarding a secondary objective of detection of distant metastasis in PS patients that distant metastatic lesions for prostate cancer are defined in clinical practice as metastasis in extra-PLN or visceral or skeletal location. It was also clarified in the definition of this endpoint that it will be assessed in all patients with an evaluable [^{18}F]CTT1057 PET/CT scan. 9. Removed the sentence about aggregating results among readers for the intra-reader variability calculation. 10. Added 3-day time window for post-baseline lab and vital sign assessments. 11. [redacted]	Section 1.1, 1.2, 2.1.1, 2.2, 2.3.1, 2.4.2, 2.5.1, 2.5.2, 2.6, 2.7.1, 2.8.1, 2.8.3, 2.8.4, 3 and Section 5.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			12. Minor typographical corrections, removal of duplicated wording and minor rewording implemented across the document.	
12-Dec-2023	After dry run review, before DBL	Incorporating changes made in the TFLs amendment v01.	1. Clarification added and modified analyses to be performed regarding patient disposition output to fully align with SC meeting. 2. Added details regarding a supplementary analysis for the primary endpoints. 3. Modified analysis set for calculating [^{18}F]CTT1057 scan inter/intra-reader variability. 4. [redacted] 5. Updated the patient disposition section to include analysis set (if different from FAS), 6. Added grouping information when tabulating primary tumor clinical stage, biopsy Gleason score, radical prostatectomy Gleason score (if applicable) per comments received from SC meetings. 7. Changed the name from AESI to STI to align with RLT program standard. 8. Added minor update to the imputation rule. 9. Minor updates to the estimand wording were made as compared to the protocol for clarification. 10. Replaced “subject” and “patient” with “participant” throughout the document, wherever applicable and appropriate. 11. Updated SAP template version. 12. Minor typographical corrections, removal of duplicated wording and minor rewording implemented across the document.	Section 1.2.1, 2.1.1, 2.2, 2.3, 2.4.2, 2.5.2, 2.5.3, 2.5.4, 2.5.6, 2.6, 2.7.1, 2.8, 2.9 and Section 5.

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List of abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DMS	Document Management System
DRL	Drug Reference Listing
ECG	Electrocardiogram
EFF	Efficacy Analysis Set
eCRS	Electronic Case Retrieval sheet
ePLND	Extended Pelvic Lymph Node Dissection
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
HGLTs	High Level Group Terms
HLT	High Level Terms
HPLC	High-Performance Liquid Chromatography
HR	Heart Rate
IA	Interim Analyses
ICF	Informed Consent Form
IRT	Interactive Response Technology
LN	Lymph Node
LPLV	Last Patient Last Visit
MBq	Mega-Becquerel
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mL	milliliter(s)
NCI	National Cancer Institute
NMQ	Novartis MedDRA Queries
ng	nanogram(s)
PAS	Pharmacokinetic Analysis Set
PCa	Prostate Cancer
PD	Pharmacodynamic(s)
PET	Positron Emission Tomography
PK	Pharmacokinetics
PLN	Pelvic Lymph Node
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PS	Primary Staging
PSA	Prostate Specific Antigen

PSMA	Prostate Specific Membrane Antigen
PT	Preferred Term
RAP	Reporting & Analysis Process
RR	Respiratory Rate
SAF	Safety Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SoC	Standard of Care
SoT	Standard of Truth
STI	Safety Topic of Interest
TFLs	Tables, Figures, Listings
TN	True Negative
TP	True Positive
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CAAA405A12302, a Phase II/III study for evaluation of the diagnostic performance of [^{18}F]CTT1057 PET imaging for the detection of Prostate Specific Membrane Antigen (PSMA) positive tumors using histopathology as a standard of truth (SoT).

The content of this SAP is based on protocol CAAA405A12302 version 01. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

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

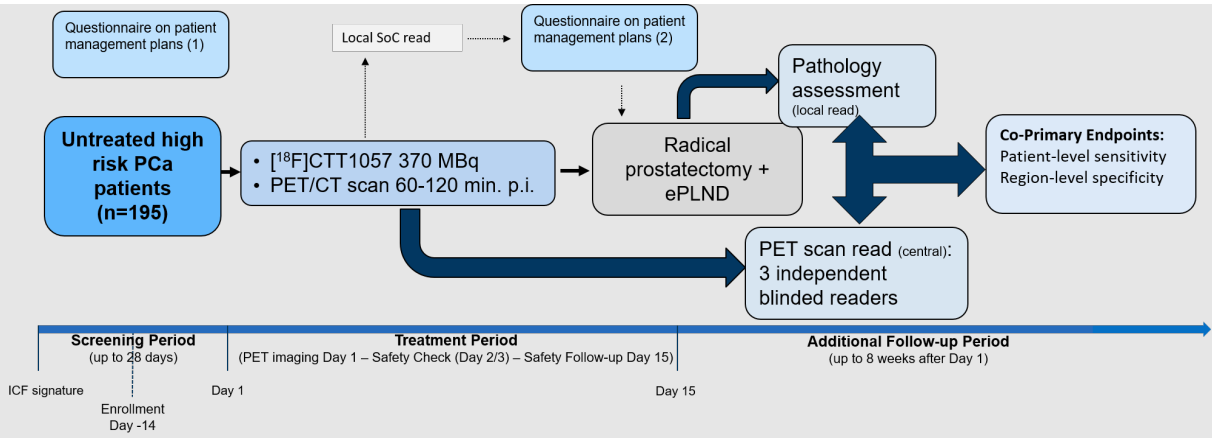
Approximately 195 participants will be enrolled to ensure that at least 156 participants are evaluable for co-primary endpoints. Surgery (radical prostatectomy/ePLND) will be performed up to 6 weeks after [^{18}F]CTT1057 PET/CT but not sooner than 48 hours after the completion of the [^{18}F]CTT1057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

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

Pathology will be assessed by the local pathologists as per Standard of Care (SoC). Pathologists will be blinded to the PET data. For anatomical localization, a sextant anatomic template for the prostate and a left/right template for the PLNs will be used (see appendix Section 16.3 of the protocol). Pathology results should be available within 2 weeks after surgery.

[redacted]. See Figure 1-1 for study design schema. There will be no interim analysis for this study.

Figure 1-1 Study design



Screening Period

Written informed consent form (ICF) must be obtained prior to any screening procedures. The participant must be registered in the Interactive Response Technology (IRT) for screening and [^{18}F]CTT1057 requested. All procedures described in the Assessment Schedule as per Table 8-1 of the protocol must be carried out, prioritizing laboratory assessments to allow time to obtain the results at least 14 days prior the planned PET imaging day (Day 1). Eligibility must then be confirmed at the latest on Day -14. The screening period should last up to 28 days.

[^{18}F]CTT1057 PET imaging day

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

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

Safety Check

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

Safety Follow-up

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

Additional Follow-up

Surgery (RP/ePLND) will be scheduled for all participants as planned per SoC on a date that must not be sooner than 48 hours after the completion of the [^{18}F]CTT1057 PET/CT scan, and

no later than 6 weeks after completion of the [^{18}F]CTT1057 PET/CT scan. Final histopathology results have to be obtained within 2 weeks after surgery.

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Evaluate the patient-level sensitivity of [^{18}F]CTT1057	• Sensitivity of [^{18}F]CTT1057 PET imaging, considering PSMA positive patients as those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLN regions, with anatomically localized correspondence with the SoT. See Section 1.2.1 for Primary Estimand.
• Evaluate the region-level specificity of [^{18}F]CTT1057	• Specificity of [^{18}F]CTT1057 PET imaging, defined as proportion of PLN regions that test negative for lymph nodes on [^{18}F]CTT1057 among those that are lymph node negative on the SoT. See Section 1.2.1 for Primary Estimand.
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Evaluate the patient-level specificity of [^{18}F]CTT1057	• Specificity of [^{18}F]CTT1057 PET imaging, considering PSMA negative patients as those who do not show any pathological [^{18}F]CTT1057 uptake either in the primary tumor or PLNs and will be confirmed not having primary tumor or metastatic PLNs with the SoT
• Evaluate the patient-level positive predictive value of [^{18}F]CTT1057	• Proportion of patients who are both [^{18}F]CTT1057 and SoT positive (true positives (TP)) among those who test positive on [^{18}F]CTT1057 (TP+ false positives(FP))
• Evaluate the patient-level negative predictive value of [^{18}F]CTT1057	• Proportion of patients who are both [^{18}F]CTT1057 and SoT negative (true negatives (TN)) among those who test negative on [^{18}F]CTT1057 (TN+ false negatives (FN))
• Evaluate the patient-level accuracy of [^{18}F]CTT1057	• Proportion of patients that are SoT and [^{18}F]CTT1057 positive (TP) and negative (TN) among all patients in EFF(TP+TN+FP+FN)
• Evaluate the region-level sensitivity of [^{18}F]CTT1057 for patients excluding micro-metastasis	• Sensitivity of [^{18}F]CTT1057 PET imaging in the PLN region, excluding from the analysis those lymph nodes showing metastasis <2mm (micro-metastasis)
• Evaluate the region-level sensitivity of [^{18}F]CTT1057	• Proportion of PLN regions that test positive on both [^{18}F]CTT1057 and SoT (TP) among those that are SoT positive (TP+FN)
• Evaluate the region-level positive predictive value of [^{18}F]CTT1057	• Proportion of PLN regions that are SoT and [^{18}F]CTT1057 positive (TP) among those regions that test positive on [^{18}F]CTT1057 (TP+FP)
• Evaluate the region-level negative predictive value of [^{18}F]CTT1057	• Proportion of PLN regions that are SoT and [^{18}F]CTT1057 negative (TN) among those regions that test negative on [^{18}F]CTT1057 (TN+FN)

Objective(s)	Endpoint(s)
• Evaluate the region-level accuracy of [^{18}F]CTT1057	• Proportion of PLN regions that are SoT and [^{18}F]CTT1057 positive (TP) and negative (TN) among all PLN regions assessed [^{18}F]CTT1057 (TP+TN+FP+FN)
• Detection of distant metastasis in PS patients	• Number of distant metastasis (extra-PLN, visceral or skeletal) identified at PET/CT scan per patient, and percentage of patients with at least one distant metastatic lesion identified by PET/CT scan
• Characterize the safety and tolerability of [^{18}F]CTT1057	• Incidence of AEs. Treatment emergent adverse event (TEAE) rate within 14 days of administration
• [^{18}F]CTT1057 scan inter-reader variability	• Inter-reader agreement of [^{18}F]CTT1057 images
• [^{18}F]CTT1057 scan intra-reader variability	• Intra-reader agreement of [^{18}F]CTT1057 images
• To further assess [^{18}F]CTT1057 pharmacokinetics in humans in subset of approximately 10 patients	• Summary statistics of [^{18}F]CTT1057 pharmacokinetic parameters (i.e. Cmax, Tmax, AUClast, AUCinf, T1/2, Vz and CL from blood radioactivity data; quantification of urinary excretion of [^{18}F]CTT1057 from urine data)

[redacted]

1.2.1 Primary estimand(s)

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

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

histopathology results (SoT) in the dissected tissue specimens (primary tumor and PLNs), both at a patient and region level.

The co-primary estimands are described by the following attributes:

Primary estimand 1:

1. Population: Untreated high risk PCa patients according to D'Amico classification (Stage ≥ T2c or PSA level >20ng/ml or Gleason score ≥8) (D'Amico et al 1998), who are scheduled or planned RP and lymph node resection. Further details about the population are provided in Section 5 of the protocol.
2. Variable: Patient level sensitivity, defined as the proportion of participants that test positive on both [^{18}F]CTT1057 and SoT (TP) among those that are SoT positive (TP + FN), considering PSMA positive participants are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor and/or metastatic PLN, with anatomically localized correspondence with the SoT.
3. Treatment (investigational imaging agent) of interest: [^{18}F]CTT1057 injected as a single intravenous dose of approximately 370 MBq and subsequent PET/CT scan. Further details about the investigational imaging agent are provided in Section 6 of the protocol.
4. Intercurrent events:
   - Participants who received the investigational imaging agent [^{18}F]CTT1057 but did not undergo/complete the PET/CT scan for any reasons (e.g. consent withdrawal, PET camera failures, etc.). Details on how to handle intercurrent events are provided in Section 2.5.3.
5. Summary measure: Patient level sensitivity, along with two-sided exact binomial 95% CI. Further details on how the summary measure will be tested are provided in Section 2.5.2.

Primary estimand 2:

1. Population: the same as the primary estimand 1
2. Variables: Regional level specificity, defined as the proportion of PLN regions that test negative on both [^{18}F]CTT1057 and SoT (TN) among those PLN region that test negative on the SoT (TN + FP), considering PSMA negative PLN regions those that do not show any pathological [^{18}F]CTT1057 uptake within the region.
3. Treatment (investigational imaging agent) of interest: the same as the primary estimand 1
4. Intercurrent events: the same as the primary estimand 1
5. Summary measure: Region level specificity, along with two-sided exact binomial 95% CI. Further details on how the summary measure will be tested are provided in Section 2.5.2.

2 Statistical methods

2.1 Data analysis general information

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

Data included in the analysis

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

All events with start date before or on the database lock date and end date after the database lock date will be reported as 'ongoing'. The same rule will be applied to events starting before or on database lock date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. No center effect will be assessed.
Qualitative data (e.g., ECOG, race, etc.) will be summarized by tables; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, height, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, 1st and 3rd quartiles, minimum, and maximum).

2.1.1 General definitions

Investigational PET imaging agent: [^{18}F]CTT1057

Study treatment: a single injection intravenously (i.v.) of approximately 370 MBq (range 266 – 407 MBq) [^{18}F]CTT1057 whether the PET/CT scan was acquired or not.

Date of administration of investigational PET imaging agents

The date of administration of investigational PET imaging agent is defined as the date when a non-zero dose of investigational PET imaging agent is administered and recorded on the study treatment (e)CRF. The date of administration of study treatment will also be referred as start of investigational PET imaging agent.

Study day

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

The study day is defined as:

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

The reference date for all assessments (safety, efficacy, pk, etc) is the start of study treatment.

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

Time unit

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

Baseline

For safety evaluations, the last available assessment prior to the administration of [^{18}F]CTT1057 (on or before the start of the study treatment date/time) is defined as "baseline" assessment. If participants have no value as defined above, the baseline result will be set to matching missing.

Efficacy evaluations will not include any comparisons between baseline and post-baseline values, and therefore a baseline definition for efficacy evaluations does not apply.

On-treatment assessment/event and observation periods

For adverse event reporting, the overall observation period will be divided into three mutually exclusive segments:

1. **Pre-treatment period:** from day of participant's informed consent to the day and time before dosing of study medication.
2. **On-treatment period:** from day of dosing of study medication to 14 days after dosing of study medication.
3. **Post-treatment period:** starting 15 days after dosing of study medication.

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).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments

In order to summarize weight, vital signs, ECGs, and laboratory tests collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If there are multiple assessments on the same date, then the worst

case will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Table 2-1 Time windows

Time Window	Planned Visit Timing	Time Window Definition
On treatment		
Baseline (pre-treatment)	On or before Study Day 1*	Before Study Day 1, or on Study Day 1 but prior to [^{18}F]CTT1057 injection
Day 1	Study Day 1	Date of [^{18}F]CTT1057 injection
Day 15	Study Day 15	14 – 17 days after the date of [^{18}F]CTT1057 injection

*Study Day 1 = the date of [^{18}F]CTT1057 injection

Electrocardiograms (ECGs) (for the PK subset) and vital signs will be assessed pre-injection, post-injection/ pre-imaging and post-imaging on Study Day 1. Their results will be presented by timepoint.

2.2 Analysis sets

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

The **Efficacy Analysis Set (EFF)** includes all enrolled participants who receive the dose of investigational treatment (i.e. [18F]CTT1057), have both an evaluable [18F]CTT1057 PET/CT scan and histopathology assessment, and have not received any prohibited systemic antineoplastic therapy before the completion of PET/CT and surgery.

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

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

Approximately 10 participants from the same site are expected to provide at least one evaluable PK parameter.

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

The number (%) of participants in each analysis set will be summarized and information about analysis sets for each participant will be displayed in a listing.

2.2.1 Subgroup of interest

The co-primary efficacy endpoints will be summarized by the following subgroups:

(a) PSA level at baseline (from central laboratory)

- PSA ≤ 20 ng/mL
- PSA > 20 ng/mL

(b) Gleason Score

- Grade Group 1 Gleason score ≤ 6
- Grade Group 2 Gleason score 7 (or 3 + 4 = 7)
- Grade Group 3 Gleason score 7 (or 4 + 3 = 7)
- Grade Group 4 Gleason score 8
- Grade Group 5 Gleason score 9 or 10

(c) Number of pelvic lymph nodes (PLNs) dissected during the surgery

- PLNs < 12
- PLNs ≥ 12

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Enrollment by country or subdivision and center will be summarized for all screened participants. The number (%) of screen failures and the reasons for screen failure will also be displayed. For participants screened more than once, the data from the last screening visit will be used in the summaries.

The following summaries will be provided (with % based on the total number of FAS participants unless otherwise specified):

- Number (%) of participants who were screened, and number (%) who were screened but not enrolled with the reasons for participants not enrolled (based on the 'Disposition' page and with % based on all screened participants)
  - Number (%) of participants who were not enrolled related to COVID-19 and primary relationships to COVID-19 (based on the 'Disposition' page and with % based on all screened participants)
- Number of participants (%) who were enrolled (i.e. FAS, based on the 'Subject ID' page)
- Number of participants (%) who completed study treatment phase (PET imaging completed)
- Number of participants (%) who were discontinued from study treatment phase and reason for discontinuation
  - Number of participants (%) who were discontinued from study treatment phase related to COVID-19 and relationship to COVID-19

- Number of participants (%) who were dosed with [^{18}F]CTT1057 but not scanned and reason for not scanned
- Number of participants (%) who were not dosed with [^{18}F]CTT1057 and reason for not dosed
  - Number of participants (%) who were not dosed with [^{18}F]CTT1057 related to COVID-19 and relationship to COVID-19
- Number (%) of participants who completed the study (based on the 'Disposition' page)
- Number (%) of participants who discontinued the study and the reason for discontinuation (based on the 'Disposition' page)
  - Number (%) of participants who discontinued the study related to COVID-19 and primary relationships to COVID-19 (based on the 'Disposition' page)

Protocol deviations

The number (%) of participants in the FAS with any confirmed protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan). All protocol deviations will be listed. For all important protocol deviations, the relationship to COVID-19 will also be captured.

2.3.2 Demographics and other baseline characteristics

The FAS and EFF will be used for all baseline and demographic summaries and listings unless otherwise specified. Listings will be provided using the FAS.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. Age groups: < 65 and ≥ 65 years, race, ethnicity, ECOG others as applicable) will be summarized by frequency counts and percentages; the number and percentage of participants with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index (BMI), PSA level at screening from central laboratory) will be summarized by descriptive statistics (N, mean, median, 1st and 3rd quartile, standard deviation, minimum and maximum). BMI (kg/m^2) will be calculated as weight[kg] / (height[m^2]) using weight at Baseline.

Diagnosis and extent of cancer

Diagnosis and extent of cancer will be summarized and listed. This analysis will include the following: PSA level at time of initial diagnosis (ng/mL), primary tumor clinical stage (i.e. T2c or less, T3, T3a, T3b, T4 and Tx), biopsy predominant histology/cytology, percentage of each histological type/pattern, biopsy Gleason score (i.e. ≤ 6, 7 (3+4), 7 (4+3), 8, and 9 or 10), time since initial diagnosis (in months). Note: biopsy Gleason score will be displayed along with the score details for each score combination in the table.

Derivation:

Time since initial diagnosis to PET scan (in months) = (date of PET scan – date of first prostate cancer diagnosis + 1) / 30.4375

ECOG Performance Status

ECOG performance status at baseline will be presented in a summary table and will be listed.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on eCRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC), preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

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

2.4.1 Study treatment / compliance

The following exposure information of [^{18}F]CTT1057 as reported in the '[^{18}F]CTT1057 study treatment injection' page of the eCRF will be summarized (with % based on the total number of SAF participants unless otherwise specified):

- Descriptive statistics of radioactivity dose administered (MBq)
- Number (%) of participants who were dosed but with problems (i.e. extravasation) in administration
- Number (%) of participants with dose administered outside the planned range (i.e. < 266 MBq or > 407 MBq)
- Time (in minutes) from injection to full-body PET imaging acquisition start time (based on the '[^{18}F]CTT1057 PET/CT Imaging - Local reads' page)
- Number (%) of participants with additional pelvic PET imaging acquisition, with time (in minutes) from injection to additional pelvic PET imaging acquisition start time, if applicable (based on the '[^{18}F]CTT1057 PET/CT Imaging - Local reads' page)
- Time (in days) from full-body PET imaging acquisition start time to the date of surgery (based on the '[^{18}F]CTT1057 PET/CT Imaging - Local reads' page and the 'Radical prostatectomy and ePLN dissection - Local histopathology assessment' page)

Participant level listings of doses administered or not, along with reasons if not administered will be produced using the FAS.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of participants who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized. Prior anti-neoplastic medications will be summarized by total number of regimens, setting (e.g. neo-adjuvant, adjuvant, metastatic, etc.), and also by lowest ATC class and preferred term. Prior anti-neoplastic radiotherapies will be summarized by method (i.e. external beam vs. internal

beam) and setting (e.g. neo-adjuvant, adjuvant, metastatic, etc.). Prior anti-neoplastic surgeries will be summarized by procedure (i.e. radical prostatectomy vs. other) and residual disease (e.g. yes, no, etc.).

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery using the FAS.

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

The above summary tables will be provided using the FAS and EFF.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a participant coinciding with the study treatment period. Concomitant therapy includes medications (other than study drugs) /therapies/procedures starting on or after the start date of study treatment or medications/therapies/procedures starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications/therapies/procedures starting on or after the start of study treatment but no later than 14 days after study treatment
2. Medications/therapies/procedures starting prior to start of study treatment and continuing after the start of study treatment.

The number of participants (%) who received diuretics (e.g. Furosemide) as concomitant medication on the day of PET/CT will also be summarized.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 14 days after the last date of study treatment will be flagged in the listing. The SAF will be used for all concomitant medication tables and listings.

2.5 Analysis supporting primary objective(s)

The primary objectives of the study are to evaluate patient-level sensitivity of [^{18}F]CTT1057and region-level specificity of [^{18}F]CTT1057.

2.5.1 Primary endpoint(s)

The co-primary endpoints evaluated for participants in the EFF are the following:

Patient-level Sensitivity of [^{18}F]CTT1057 PET imaging, defined as the proportion of participants that test positive on both [^{18}F]CTT1057 and SoT (TP) among those that are SoT

positive (TP + FN), considering PSMA positive participants are those who show at least one pathological [^{18}F]CTT1057 uptake either in the primary tumor (prostate region) and/or metastatic PLN region, with anatomically localized correspondence with the SoT. See Section 1.2.1 for Primary Estimand.

Region-level Specificity of [18F]CTT1057 PET imaging, defined as the proportion of PLN regions that test negative on both [^{18}F]CTT1057 and SoT (TN) among those PLN regions that test negative on the SoT (TN + FP), considering PSMA negative PLN regions are those which do not show any pathological [18F]CTT1057 uptake within the region. See Section 1.2.1 for Primary Estimand.

[redacted]

2.5.2 Statistical hypothesis, model, and method of analysis

To address the co-primary efficacy objectives:

Patient-level sensitivity along with two-sided exact binomial 95% CIs will be calculated.

The lower bound of the 95% CI for patient-level sensitivity should be greater than 0.50 to attain the first co-primary endpoint.

Region-level specificity along with two-sided exact binomial 95% CIs will be calculated. Only pelvic lymph node regions will be used to calculate the specificity. The lower bound of the 95% CI for specificity should be greater than 0.70 for the study to attain the second co-primary endpoint.

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.

2.5.3 Handling of intercurrent events

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

- Participants who receive the investigational imaging agent [^{18}F]CTT1057 but do not undergo/complete the [^{18}F]CTT1057 PET/CT scan for any reason (e.g. drop out, PET camera failures, etc) will not be used for the co-primary endpoint analyses. Note that safety data for these participants will be collected after the administration of the investigational imaging agent and will be summarized.

2.5.4 Handling of missing values not related to intercurrent event

This is a diagnostic study, where the co-primary endpoints are calculated on the basis of one-time imaging assessment. Missing data will not be imputed.

2.5.5 Sensitivity analyses

Not applicable

2.5.6 Supplementary analyses

As supplementary analyses performed for the EFF, patient-level sensitivity and region-level specificity and the corresponding 95% CIs will be obtained from a covariate-adjusted logistic regression model. Candidate covariates include categorized PSA level at baseline, diagnostic biopsy Gleason score, and categorized number of PLNs dissected as given below.

- PSA level
  - PSA ≤ 20 ng/mL
  - PSA > 20 ng/mL
- Gleason Score
  - Grade Group 1 Gleason score ≤ 6
  - Grade Group 2 Gleason score 7 (or 3 + 4 = 7)
  - Grade Group 3 Gleason score 7 (or 4 + 3 = 7)
  - Grade Group 4 Gleason score 8
  - Grade Group 5 Gleason score 9 or 10
- Number of PLNs dissected
  - Number of PLNs < 12
  - Number of PLNs >= 12

Estimates of patient-level sensitivity and region-level specificity and the corresponding 95% CIs will be obtained from the logistic regression model adjusting for covariates. The p-values from the Type III tests for each candidate covariate in the full model will be provided. The patient-level sensitivity and region-level specificity (and their 95% CIs) for each level of the covariates estimated from the full model including all candidate covariates as well as the final model including only statistically significant covariates (p-value < 0.05) will be displayed. In the case that there are no statistically significant covariates identified from the full model, patient-level sensitivity and region-level specificity (and their 95% CIs) from the unadjusted logistic regression model will be provided.

2.6 Analysis supporting secondary objectives

The secondary efficacy objectives are to:

- Evaluate the patient-level specificity of [^{18}F]CTT1057
- Evaluate the patient-level positive predictive value of [^{18}F]CTT1057
- Evaluate the patient-level negative predictive value of [^{18}F]CTT1057
- Evaluate the patient-level accuracy of [^{18}F]CTT1057
- Evaluate the region-level sensitivity of [^{18}F]CTT1057 for patients excluding micro-metastasis
- Evaluate the region-level sensitivity of [^{18}F]CTT1057
- Evaluate the region-level positive predictive value of [^{18}F]CTT1057
- Evaluate the region-level negative predictive value of [^{18}F]CTT1057
- Evaluate the region-level accuracy of [^{18}F]CTT1057
- Detection of distant metastasis in PS patients
- Characterize the safety and tolerability of [^{18}F]CTT1057

- [^{18}F]CTT1057 scan inter-reader variability
- [^{18}F]CTT1057 scan intra-reader variability
- To further assess [^{18}F]CTT1057 pharmacokinetics in humans in a subset of approximately 10 patients

2.6.1 Secondary endpoint(s)

Secondary endpoints are defined for the EFF unless otherwise specified with details given as follows:

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

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

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

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

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

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

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

Two-sided exact binomial 95% CIs for diagnostic performance parameters will be calculated.

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

Region-level sensitivity will also be presented, excluding PLNs showing metastasis < 2 mm (micro-metastasis).

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

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

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

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

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

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

Two-sided exact binomial 95% CIs for diagnostic performance parameters will be calculated.

[^{18}F]CTT1057 scan inter-reader variability is defined as the agreement rate among reader determinations and will be assessed by Fleiss' Kappa statistic. See details given in Section 2.6.2.

[^{18}F]CTT1057 scan intra-reader variability is defined as the within-reader agreement rate and will be assessed by Cohen's Kappa statistic. See details given in Section 2.6.2.

Detection number of distant metastasis is defined as number of distant metastasis (extra-PLN, visceral or skeletal) identified at PET scan for each participant in all participants with an evaluable [^{18}F]CTT1057 PET/CT scan. Summary statistics will be provided by region, i.e. extra-PLN, visceral and skeletal.

Detection rate of distant metastasis is defined as **the** percentage of participants with at least one distant metastatic lesion (extra-PLN, visceral or skeletal) identified by PET scan in all participants with an evaluable [^{18}F]CTT1057 PET/CT scan. **Detection number of distant metastasis** will be presented and used to calculate **Detection rate of distant metastasis,** along with two-sided exact binomial 95% CIs for detection rate will be calculated.

Characterize the safety and tolerability of [18F]CTT1057
Further discussion of the safety and tolerability endpoints to support the secondary objective analysis is included in Section 2.8.

Pharmacokinetics in humans in subset of approximately 10 patients

Further discussion of the pharmacokinetics analysis is included in Section 2.9.

2.6.2 Statistical hypothesis, model, and method of analysis

Patient-level diagnostic performance parameters include:

- Patient-level specificity
- Patient-level positive predictive value
- Patient-level negative predictive value
- Patient-level accuracy
- Detection rate of distant metastasis evaluated for all other regions (i.e. extra PLN, skeletal and visceral)

See details given in Section 2.6.1.

Region-level diagnostic performance parameters include:

- Region-level sensitivity including and excluding micro-metastasis
- Region-level positive predictive value
- Region-level negative predictive value
- Region-level accuracy

See details given in Section 2.6.1.

[^{18}F]CTT1057 scan inter-reader variability will be assessed by Fleiss' Kappa (κ_1) statistic (Fleiss 1971) defined below:

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

Let N represent the total number of participants who have evaluable PET/CT, n the number of central readings per participant $n = 3$ (OBJ), and $k = 2$ the number of outcome categories (OBJ) into which assignments are made. Participants $i = 1, \ldots, N$ by $j = 1, \ldots, k$ OBJ n_{ij} OBJ i OBJ represent the number of readers who assigned the OBJ j participant to the jth category. Then

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

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

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

Based on the contingency table as described above, a Fleiss's Kappa statistic and corresponding 95% confidence interval will be estimated based on asymptotic estimation of the standard error (i.e.

$$\widehat{se}(\kappa_1) = \frac{\sqrt{2}}{\sum_{j=1}^{k} p_j(1-p_j)\sqrt{Nn(n-1)}} \sqrt{\left(\sum_{j=1}^{k} p_j \, (1 - p_j)\right)^2 - \sum_{j=1}^{k} p_j(1-p_j)(1-2p_j)}$$

(Fleiss, Nee, Landis 1979; Fleiss J, Levin B, Paik MC 2003) and the normality assumption (i.e. 95% CI

can be calculated as: $\kappa_1 \pm 1.96\widehat{se}(\kappa_1)$). An additional table will be presented to show the distribution of agreements with the number (%) of scans agreed by two readers and the number (%) of scans agreed by all three readers. Inter-reader variability will be calculated for the SAF.

[^{18}F]CTT1057 scan intra-reader variability will be assessed by Cohen's Kappa (κ_2) statistic. To assess the intra-reader variability, each of the three readers will re-read the same 20 randomly selected cases (with evaluable PET/CT) but each case will be presented to each reader in a random order. The readers will not reference any previous read results nor discuss any of these cases at any time during the read process. Each reader will use the same method to read the randomly presented cases as they did in the previous reads. Intra-reader agreement will first be evaluated separately for each of the 3 readers using Cohen's kappa statistic (κ_2) as described below:

Step 1: A 2 by 2 contingency table (e.g. Table 2-2) will be calculated to summarize the frequency of concordance and discordance for patient-level positivity or negativity. The counts in the table will add up to 20 in total (i.e. a + b+ c + d = 20).

Table 2-2 Example 2 by 2 contingency table for each reader

		New Reads	
		Positive	Negative
Original Reads	Positive	a	b
	Negative	c	d

Step 2: Based on the contingency tables described above, a simple agreement rate, i.e. $\frac{a+d}{a+b+c+d}$ and its corresponding 95% confidence interval (Agresti A, Coull BA 1998) will be estimated based on normal approximation.

Step 3: Finally, a Cohen's kappa statistic (κ_2) and its corresponding 95% confidence interval will be estimated (Cohen J 1960; Cohen J 1968; Fleiss J, Levin B, Paik MC 2003) using the formula $\kappa_2 \pm 1.96SE$, where $SE = \sqrt{\frac{p_o(1-p_o)}{N(1-p_e)^2}}$ (McHugh M 2012). Let N denote the number of re-reads ($N = 20$), k the number of categories ($k = 2$), $n_{i1}$the number of times the original reads were assigned to i ($i = 1, \dots, k$) and $n_{i2}$the number of times the re-read were assigned to i ($i = 1, \dots, k$). Then Cohen's kappa can be calculated as $\kappa_2 = \frac{p_o - p_e}{1-p_e}$, where p_o is the relative agreements among the original and re-reads ($p_o = \frac{a+d}{a+b+c+d}$ in Table 2-2) and $p_e = \sum_{i=1}^{k} \frac{n_{i1}}{N}\frac{n_{i2}}{N}$ ($p_e = \frac{a+b}{N}\frac{a+c}{N} + \frac{c+d}{N}\frac{b+d}{N}$ in Table 2-2). Intra-reader variability will be calculated for the SAF.

2.6.3 Handling of intercurrent events

Though no secondary estimands are defined for the study, intercurrent events defined in the primary estimands will impact secondary endpoints analysis. Thus they will be handled in the same way as in primary estimands analyses. Participants who receive the investigational

imaging agent [^{18}F]CTT1057 but do not undergo/complete the [^{18}F]CTT1057 PET/CT scan for any reasons (e.g. drop out, PET camera failures, etc) will not be used for the secondary efficacy endpoint analysis, but safety data for these participants will be collected after the administration of the investigational imaging agent and will be summarized.

2.6.4 Handling of missing values not related to intercurrent event

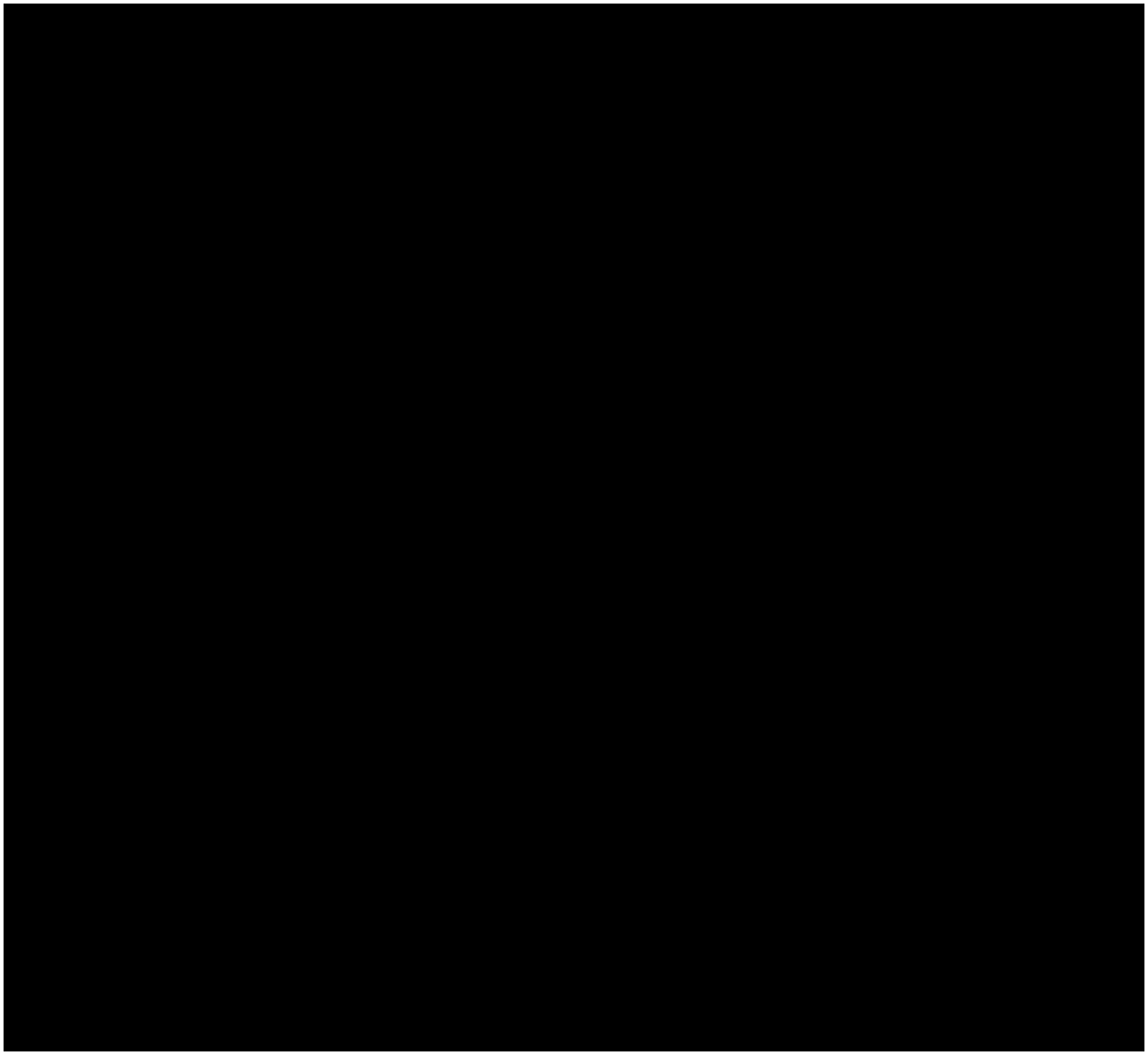
This is a diagnostic study, where the secondary endpoints are calculated on the basis of a one-time imaging assessment. Missing data will not be imputed.

2.6.5 Sensitivity analyses

No sensitivity analyses are planned for the secondary endpoints.

2.6.6 Supplementary analyses

No supplementary analyses are planned for the secondary endpoints.



2.8 Safety analyses

All safety analyses will be based on the safety set.

2.8.1 Adverse events (AEs)

Adverse events are coded using MedDRA terminology. The latest MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. AE summaries will include all AEs that started or worsened during the on-treatment period. (See Section 2.1.1) All AEs that started or worsened within 14 days after the [^{18}F]CTT1057 dose, and adverse events that were reported as related to [^{18}F]CTT1057 irrespective of time of onset will be regarded as treatment emergent AEs.

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

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency.

The following adverse event summaries will be produced: overview of all adverse events and deaths (number and % of participants who died, with any AE, any SAE, any dose change, drug withdrawn, etc.), AEs by SOC and PT, by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose change, and leading to fatal outcome. In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term). To help evaluate the impact of the COVID-19 on the safety, the incidence of COVID-19 related adverse event preferred terms will be presented. All COVID-related AEs will be included in the listings.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables for on-treatment emergent adverse events which are not serious adverse events with an incidence of greater than 5% and on-treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by SOC and PT for the SAF.

- If for the same participant, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT: a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

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

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs, e.g. AE relationship to study drug, AE outcome, etc. All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected outside of the on-treatment period will be flagged.

2.8.1.1 Safety topics of interest / grouping of AEs

A safety topic of interest (STI) is a grouping of adverse events that are of scientific and medical concern specific to the tracer [^{18}F]CTT1057. These groupings are defined using MedDRA terms,

SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. STI will be defined at the project level and may be regularly updated. The grouping of AEs in STI according to project standards will be specified in the electronic Case Retrieval Sheet (eCRS). For each specified STI, the number and percentage of participants with at least one event of the STI occurring during on-treatment period will be summarized.

STIs will be summarized by grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc. A listing of all grouping levels down to the MedDRA preferred terms used to define each STI will be generated. All the analyses will be carried out for the SAF.

2.8.2 Deaths

Two separate summaries, one for on-treatment and the other for all deaths (including post-treatment deaths) will be produced, by system organ class and preferred term. The number of deaths resulting from SAEs suspected to be related to study treatment will also be summarized. See details given in Section 2.8.1.

All deaths will be listed, post-treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

2.8.3 Laboratory data

Laboratory data from all sources (central and local laboratories) will be combined for the analysis. The summaries will include all assessments available for the lab parameter collected prior to (baseline) and during the on-treatment period (14 + 3 day-window) after the study treatment administration.

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.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

The number and percentage of participants with an abnormal ECG (clinically significant) at screening will be presented. ECG data will be read and interpreted locally. A listing of all ECG assessments will be produced. These analyses will be performed for the FAS.

In addition, for the approximately 10 PK subset participants:
Specified parameters PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant in the PK subset on treatment day (Day 1) at pre-injection, post-injection/pre-imaging, and post-imaging and at Safety follow-up Day 15.

The number and percentage of PK subset participants with notable ECG values will be presented.
- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 60 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: body temperature, blood pressure, pulse rate, respiratory rate.

Data handling

Vital signs collected prior to (baseline) and on-treatment (14 + 3 day-window after the study treatment administration) will be summarized. Values measured outside of the on-treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs, the clinically notable vital sign criteria are provided in Table 2-3 below.

Table 2-3 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	Increase	**Decrease**
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Body temperature (°C)	>= 39.1	-
Pulse rate (bpm)	> 100 with increase from baseline of > 25%	< 60 with decrease from baseline > 25%
Respiratory rate	> 22 breaths per minute	<14 breaths per minute

The number and percentage of participants with notable vital sign values (high/low) will be presented. Descriptive statistics will be tabulated for baseline, at each post-baseline time point and changes from baseline at each post-baseline time point for each vital sign measure.

A listing of all vital sign assessments will be produced and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.9 Pharmacokinetic endpoints

All PK analyses will be carried out on the PAS.

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

of radioactivity concentration to mass concentration will not be possible due to missing information of mass concentration of the drug product during the manufacturing process.

Radioactivity concentration in blood will be calculated using the following formula:

$$RDCNNDB = \left({}^{ACTMENDC}/_{SAMPVOL}\right) / DURSFLT1$$

where, RDCNNDB is radioactivity concentration in blood (not decay corrected), ACTMENDC is radioactivity measured (not decay corrected), SAMPVOL is volume of the sample measured, and DURSFLT1 is gamma counter calibration factor.

Decay correction of the radioactivity concentration in blood will be performed using the following formula:

$$RDCNDCB = RDCNNDB \times e^{-\lambda \cdot (RDACTDAT\&TIM - ECSTDTC)}$$

where, RDCNDCB is radioactivity concentration in blood (decay corrected), λ is decay constant, RDACTDAT&TIM is radioactivity measurement date and time, and ECSTDTC is dose administered date and time.

Decay constant (λ) is calculated using the following formula:

$$\lambda = {}^{ln2}/_{t_{1/2}}$$

where, t1/2 is half-life of 18-F which is 109.7 min.

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

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin® (Version 8 or higher): Cmax, Tmax, AUClast, AUCinf, $T_{1/2}$, Vz and CL (Table 2-4).

Table 2-4 Non-compartmental pharmacokinetic parameters

AUC%Extrap[1]	Area under the plasma concentration-time curve extrapolated from the time t to infinity as a percentage of total AUC (%)
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
Clast[2]	Last measurable concentration (mass x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood serum, or other body fluid drug concentration

	after single dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time)
Tlast[2]	Last measurable concentration sampling (time)
Rsqadj[1]	Square of the correlation coefficient associated with lambda_z
CL	The total body clearance (CL) of drug from plasma, blood serum, or other body fluid drug concentration (volume x time^{-1})
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)

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

The elimination of the compound in urine will be evaluated based on decay-corrected urine radioactivity concentration data obtained by measuring the urine samples drawn at pre-defined time points (Table 8-7 of the protocol) using a calibrated gamma-counting device. Urine elimination data will be expressed as the percentage of injected activity (%ID) in each specified time interval and also as cumulative %ID excreted up to the end of each time interval. Urine elimination data will be listed by participants. Descriptive summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum.

Radioactivity concentration in urine will be calculated using the following formula:

$$RDCNNDU = \left({}^{ACTMENDC}/_{SAMPVOL}\right) / DURSFLT1$$

where, RDCNNDU is radioactivity concentration in urine (not decay corrected), ACTMENDC is radioactivity measured (not decay corrected), SAMPVOL is volume of the sample measured, and DURSFLT1 is gamma counter calibration factor.

Decay correction of the radioactivity concentration in urine will be performed using the following formula:

$$RDCNDCU = RDCNNDB \times e^{-\lambda \cdot (RDACTDAT\&TIM - ECSTDTC)}$$

where, RDCNDCU is radioactivity concentration in urine (decay corrected), λ is decay constant, RDACTDAT&TIM is radioactivity measurement date and time, and ECSTDTC is dose administered date and time.

Decay constant (λ) is calculated using the following formula:

$$\lambda = {}^{ln2}/_{t_{1/2}}$$

where, t1/2 is half-life of 18-F which is 109.7 min.

The percentage of injected activity (%ID) will be calculated using the following formula:

$$PCTINDS = \left({RDCNDCU \times SAMPCOL}/{ECDOSE \times 1000}\right) \times 100(\%)$$

where, PCTINDS is percentage of injected activity (%ID) in urine, and ECDOSE is decay-corrected administered dose (MBq).

2.10 PD and PK/PD analyses

No PD and PK/PD analyses are planned in the study.

2.11 Patient-reported outcomes

No patient-reported outcomes analyses are planned in the study.

2.12 Biomarkers

No biomarker analyses are planned in the study.

[redacted]

2.14 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

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

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

3.1 Primary endpoint(s)

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

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

In PS patients before surgery, both the primary tumor and the metastatic PLN are expressing PSMA, which is the target for [^{18}F]CTT1057 binding. After surgery, pathology of both the primary tumor and the dissected pelvic LN will be used as a SoT. A patient-level analysis would

allow to identify positive lesions in both regions. A region-level analysis for sensitivity is not considered appropriate for the primary endpoint as 156 PLN would be needed in order to determine, approximately 520 participants would have to receive the radioactive investigational PET tracer to yield 156 participants with positive PLN. In order to limit the number of participants exposed to radiation for this purpose and given that both the primary tumor and affected PLN are [^{18}F]CTT1057 targets, sensitivity is proposed to be analyzed on the patient level. Region-level sensitivity is included as a secondary endpoint. On the other hand, specificity can be assessed on the regional level (at the PLN region) since a sufficient number of participants with negative PLN are expected to be obtained at pathology.

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

A large variability in sensitivity of PSMA-PET in the primary staging setting has been reported. Two recent systematic reviews of [^{68}Ga]PSMA PET /CT diagnostic accuracy focused on the PS population using pathology as SoT, sensitivity of 33–99% across studies has been reported (Corfield et al 2018), as well as pooled sensitivity and specificity ranges of 23-100% and 67-100% respectively (Petersen and Zacho 2020). Recent preliminary data on the diagnostic efficacy of F-18-rhPSMA-7.3 PET imaging in PS patients compared to histopathology (n=56) reported a 95% CI low bound patient. A meta-analysis on the diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with PCa). A study evaluating the diagnostic value of [^{68}Ga]PSMA PET versus CT and MRI for lymph node staging in 130 consecutive patients who got RP and PLN).

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

Patient-level sensitivity

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

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

Region-level specificity

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

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

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

4 Change to protocol specified analyses

Minor updates to the estimand wording were made as compared to the protocol for clarification.

Blood mass concentration data were planned to be summarized per protocol as part of the PK analysis, however the conversion of radioactivity concentration to mass concentration will not be possible due to missing information of mass concentration of the drug product during the manufacturing process. Section 2.9 of the SAP clarifies the analyses that will be summarized.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

5.1.2 AE, ConMeds and safety assessment date imputation

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

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

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

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

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

Missing Element	Rule (*=date of dose administration plus 15 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

If imputed end date is < start date, set end date = start date.

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

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.3 Other imputations

For the date of initial diagnosis, missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

5.2 AEs coding/grading

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

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

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

5.3 Laboratory parameters derivations

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

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

Imputation Rules

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

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

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

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

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

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

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

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

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Patient-level sensitivity and two-sided exact binomial 95% CIs will be calculated.

Only pelvic lymph node regions will be used to calculate the specificity. Region-level specificity and two-sided exact binomial 95% CIs will be calculated.

Exact binomial confidence intervals (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934).

The supplementary analyses for the co-primary endpoints of patient-level sensitivity and region-level specificity and the corresponding 95% CIs will be calculated based on a covariate-adjusted logistic regression model. The LOGISTIC procedure in SAS will be used to implement the logistic regression model adjusting for covariates. This analysis will be applied to each of the three central reader via the (BY READER) statement.

The predicted probability and 100 (1-α)% confidence limits for patient-level sensitivity P_{Sens} for each central reader can be obtained from SAS using the logistic regression model with covariates.

$$Logit\ (P_{Sens}) = \log\left\{\frac{P_{Sens}}{1-P_{Sens}}\right\} = \alpha + \beta_1 X_{PSA} + \beta_2 X_{Gleason\ Grp\ 2} + \beta_3 X_{Gleason\ Grp\ 3} + \beta_4 X_{Gleason\ Grp\ 4} + \beta_5 X_{Gleason\ Grp\ 5} + \beta_6 X_{PLNs}$$

The predicted probability and 100 (1-α)% confidence limits for region-level specificity P_{Spec} for each central reader can be obtained from SAS using the logistic regression model with covariates.

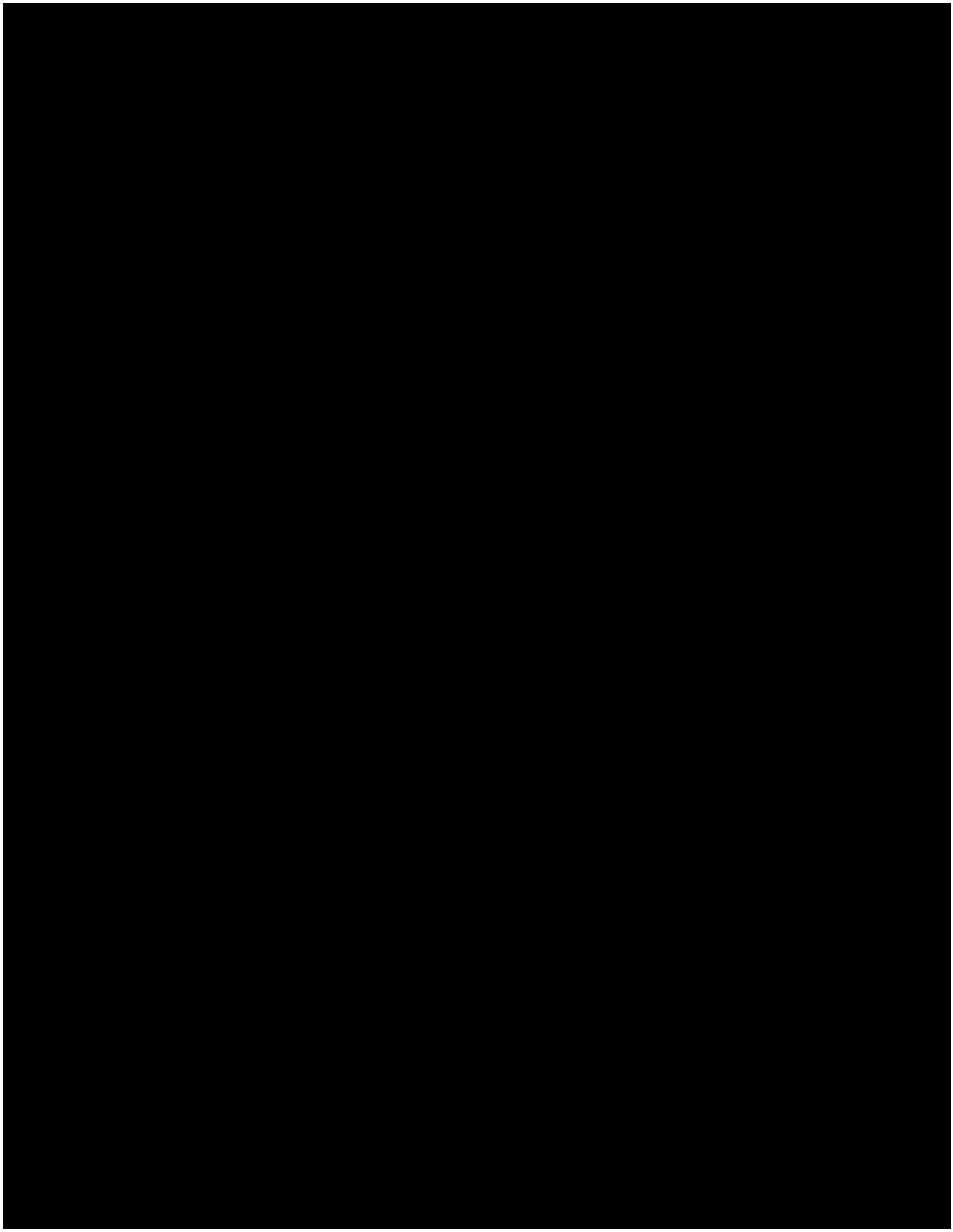
$$Logit\ (P_{Spec}) = \log\left\{\frac{P_{Spec}}{1-P_{Spec}}\right\} = \alpha + \beta_1 X_{PSA} + \beta_2 X_{Gleason\ Grp\ 2} + \beta_3 X_{Gleason\ Grp\ 3} + \beta_4 X_{Gleason\ Grp\ 4} + \beta_5 X_{Gleason\ Grp\ 5} + \beta_6 X_{PLNs}$$

5.4.2 Analysis supporting secondary objective(s)

For patient-level efficacy endpoints, their estimation and two-sided exact binomial 95% CIs will be calculated (implemented using SAS procedure FREQ with EXACT statement for one-way tables) (Clopper and Pearson 1934).

Only pelvic lymph node regions will be used to calculate region-level efficacy endpoints, and their estimation and two-sided exact binomial 95% CIs will also be calculated.

For inter- and intra-reader variability, 95% CIs will be calculated based on normal approximation with details given in Section 2.6.2.



6 Reference

Agresti A, Coull, BA (1998) Approximate is better than "Exact" for interval estimation of binomial proportions. The American Statistician: 52(2):119-26.Cohen, J. (1960). A coefficient of agreement for nominal scales. Educational and psychological measurement; 20(1): 37-46.

Cohen, J. (1968). Weighted kappa: nominal scale agreement provision for scaled disagreement or partial credit. Psychological bulletin; 70(4): 213.Corfield J, Perera M, Bolton D, et al (2018) 68Ga-prostate specific membrane antigen (PSMA) positron emission tomography (PET) for primary staging of high-risk prostate cancer: a systematic review. World J Urol; 36:519-27.

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

D'Amico AV, Whittington R, Malkowicz SB, et al (1998) Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA; 280(11):969-74.

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.

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

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

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

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.

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.

Maurer T, Gschwend JE, Rauscher I, et al (2016) Diagnostic Efficacy of (^{68})Gallium-PSMA Positron Emission Tomography Compared to Conventional Imaging for Lymph Node Staging of 130 Consecutive Patients with Intermediate to High Risk Prostate Cancer. J Urol; 195:1436-43.

Maurer T, Langbein T, Kroenke M, et al (2020) Diagnostic efficacy of ^{18}F-RHPSMA-7.3 imaging for n-staging patients with high-risk prostate cancer [abstract]. J Urol; 203 Suppl 4:e952A

McHugh, M (2012) Interrater reliability: the kappa statistic. Biochemia Medica; 22(3): 276-282.

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

Woythal N, Arsenic R, Kempkensteffen C, et al (2018) Immunohistochemical Validation of PSMA Expression Measured by 68Ga-PSMA PET/CT in Primary Prostate Cancer. J Nucl Med; 59(2):238-43.