Statistical Analysis Plan

Version 3.0 01 October 2021

Protocol Title: Prospective, Phase 3, multi center, single-arm, imaging study investigating the safety and diagnostic performance of rhPSMA-7.3 (^{18}F) PET ligand in men with newly diagnosed prostate cancer

Protocol Number: BED-PSMA-301

Compound Number: Flotufolastat (18F) injection

Short Title: LIGHTHOUSE

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Blue Earth Diagnostics

BED-PSMA-301

A prospective, Phase 3, multi center, single-arm, imaging study investigating the safety and diagnostic performance of rhPSMA-7.3 (^{18}F) PET ligand in men with newly diagnosed prostate cancer

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Version: 3.0

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SPONSOR SIGNATURE PAGE

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Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

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REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	03 July 2020	Finalized document
2.0	18 Aug 2021	Added BMI Wording: Replaced consensus between blinded readers with majority of blinded readers. Added that within analysis of subcategories, categories with low counts may be collapsed. Removed second exploratory objective and endpoint Updated first exploratory endpoint to use cluster binary data estimation of Confidence Interval
3.0	Date of Last Signature	Changed TEAE definition from on or before Visit 3 to on or before Day 4. Changed medications and/procedures starting after Day 4 not to be summarized. Changed summaries of TEAE leading to death, serious adverse events, and discontinuation will only display TEAE.

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
BIE	blinded image evaluation
CI	Confidence interval
CSP	Clinical Study Protocol
COVID-19	Coronavirus disease 2019
CT	Computed tomography
DRM	Data Review Meeting
EBRT	External beam radiation therapy
EAP	Efficacy Analysis Population
ECG	electrocardiogram
eCRF	electronic Case Report Form
EEP	Extended Efficacy Population
FAS	Full Analysis Set
FN	False Negative
FP	False Positive
FSP	Full Safety Population
GGG	Gleason Grade Grouping
IP	Investigational product
IMP	Investigational Medicinal Product
IV	Intravenous
LN	Lymph Node
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NPV	Negative Predictive Value
PCa	Prostate Cancer
PET	Positron emission tomography
PLND	Pelvic lymph node dissection
PP	Per Protocol Population

Abbreviation / Acronym	Definition / Expansion
PPV	Positive predictive value
PSA	prostate-specific antigen
PT	Preferred Term
RP	Radical prostatectomy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedures
SoT	Standard of Truth
TEAE	Treatment-emergent adverse event
TLFs	Tables, Listings and Figures,
TN	True Negative
TP	True Positive
VDR	Verified Detection Rate
WHO-DD	WHO Drug Global

1 INTRODUCTION

Prostate cancer (PCa) is the most prevalent cancer in men in the developed world and the third leading cause of death (Jemal, 2011). It is most commonly diagnosed in men aged 65 years and over and in its early stages it is largely asymptomatic, with tumors detected by identification of increased levels of prostate-specific antigen (PSA) in peripheral blood. If detected early, and when the disease is organ confined, the 5-year survival rate approaches 100%.

Accurate staging of newly diagnosed PCa assists in directing appropriate treatment strategies. The National Comprehensive Cancer Network (NCCN Guidelines; Version 1.2020; PROS-2) recommend bone imaging and abdominal/pelvic imaging as the initial work-up in patients with newly-diagnosed high- and very high-risk PCa, as well as in a subgroup of patients with unfavorable intermediate-risk PCa. The primary goal of such imaging is to detect extra-prostatic disease (M1: non-regional nodal involvement, bone, or other sites [UICC, TNM Classification of Malignant Tumours]); the identification of which would likely significantly change the planned treatment regimen from locoregional to systemic therapy.

The overwhelming need for improved imaging should focus on the identification of N1 (metastasis in regional node(s)) and M1 disease, which may potentially have a meaningful impact on patient treatment and outcomes. Ideally, a staging technique that detects extra-prostatic disease should: 1) image the whole body, 2) not be limited to the skeleton, and 3) be both sensitive and specific for identifying PCa extent.

This study is designed to assess the performance of rhPSMA-7.3 (^{18}F) for detecting N1 and M1 disease in patients with newly diagnosed PCa eligible for curative intent, standard of care locoregional therapy, who have elected to undergo radical prostatectomy (RP) with regional pelvic lymph node dissection (PLND). Evaluation of the sensitivity and specificity of rhPSMA-7.3 (^{18}F) imaging by central blinded image evaluation (BIE) for detecting regional pelvic lymph node (LN) involvement, compared to histopathology, will be performed as the co-primary endpoints. Therefore, only patients who are scheduled to undergo RP and a PLND will be included in this study.

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data and outlines the statistical programming specifications for the Tables, Listings and Figures (TLFs). It describes the variables and populations, anticipated data transformations and manipulations and other details of the analyses not provided in the Clinical Study Protocol (CSP). In case of discrepancies between Study Protocol and SAP the SAP supersedes the Study Protocol.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 3.0 (July 01, 2020)
- Electronic Case Report Form (eCRF), Version 4.0 (February 8, 2021)

- Invicro Independent Review Charter (IRC), Version 2.0 (June 18, 2021)
- Invicro Technical Operations Manual Version 4.0 (August 04, 2020)
- Invicro Review Session Methodology: Conventional Imaging Version 1.0 (June 08, 2021)

The following guidance document has been used:

Guidance for Industry and FDA Staff - Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests (13 March 2007)

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (^{18}F) positron emission tomography (PET) in detecting N1 disease (as determined by the central BIE) on a patient level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND. At least one positive pelvic LN on PET (N1) and one positive LN as determined by histopathology (pN1) on the same side of the pelvis (left or right) will be deemed a True Positive (TP) at the patient level. In patients who have no TP regions (left or right), the translation of varying combinations of False Positive (FP), True Negative (TN) and False Negative (FN) regions to patient level categorizations is described in detail in Section 4.13.

2.2 Secondary Objective(s)

The secondary objectives of the study are:

1. To assess the Verified Detection Rate (VDR) for M1 disease of rhPSMA-7.3 (^{18}F) PET findings (as determined by central BIE) on a patient level in patients with newly diagnosed unfavorable intermediate-, high-, or very high-risk PCa using histopathology or confirmatory imaging.
2. To assess the VDR for M1 disease of rhPSMA-7.3 (^{18}F) PET findings (as determined by central BIE) on a patient level in patients with negative conventional imaging.
3. To assess the positive predictive value (PPV) of rhPSMA-7.3 (^{18}F) PET for N1 and M1 lesions (as determined by central BIE) compared to histopathology or confirmatory imaging (M1 lesions only).
4. To assess the PPV of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a patient level in which a FP patient is defined as having at least one FP region (right or left pelvis), regardless of any coexisting TP findings.
5. To assess the negative predictive value (NPV) of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a patient level in which a FN patient is defined as having at least one FN region (right or left pelvis), regardless of any coexisting TN findings.
6. To assess the impact of rhPSMA-7.3 (^{18}F) PET BIE on a) upstaging patients planned for RP or b) converting planned RP to external beam radiation therapy (EBRT).

7. To determine the inter- and intra-reader agreement of rhPSMA-7.3 (^{18}F) scan interpretation by blinded independent readers.
8. To assess the safety of rhPSMA-7.3 (^{18}F) injection in patients.

2.3 Exploratory Objective(s)

The exploratory objectives of the study are:

1. To assess the sensitivity and specificity of rhPSMA-7.3 (^{18}F) PET in detecting nodal metastases (as determined by central BIE) on a regional level compared to the histopathology of pelvic lymphatic tissue removed during RP and PLND.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a prospective, Phase 3, multi-center, single-arm, diagnostic imaging study designed to evaluate the safety and diagnostic performance of rhPSMA-7.3 (^{18}F) PET ligand for the detection of N1 and M1 metastases in men with newly diagnosed unfavorable intermediate-, high- or very high-risk PCa (per NCCN Guidelines Version 1.2020; PROS-2).

Up to approximately 375 patients will be enrolled into the study to ensure inclusion of at least 300 evaluable patients undergoing RP and PLND. Consented patients will be screened at Visit 1 to determine eligibility for the study up to 28 days (up to 45 days due to the Coronavirus Disease-2019 [COVID-19] pandemic) before Investigational product (IP) administration at Visit 2. Due to the COVID-19 pandemic, Visit 1 and Visit 2 may be combined. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be assigned a patient identifier (ID) and entered into the study at screening. In addition to their routine clinical work-up, which may include ^{99m}technetium-biphosphonate and abdominal/pelvic computed tomography (CT) or magnetic resonance imaging (MRI) and chest CT per local practice, and before the scheduled RP, patients will be administered a dose of rhPSMA-7.3 (^{18}F), an administered activity of 8 mCi (296 MBq) ± 20% delivered as an intravenous (IV) bolus injection with a 10 mL fast 0.9% sodium chloride flush, followed by PET imaging.

Note: The screening/eligibility evaluation may take place on the day of rhPSMA-7.3 (^{18}F) administration (with pre-screening via telephone), if necessary, to ensure the safety of enrolled patients (see Visit 1 and 2 combined; CSP Section 10.3). Alternatively, the time from Visit 1 (initial screening) to Visit 2 (rhPSMA-7.3 (^{18}F) PET scan) may be extended to 45 days due to the COVID-19 pandemic.

The PET imaging results for each patient will be reported to the responsible physician prior to the planned RP. If safe and feasible, within 1 to 3 days post-IP administration, the patient must return to the clinic for safety follow-up including an electrocardiogram (ECG), blood safety laboratory tests and a focused physical examination. Clinical review of the imaging results and discussion of further procedures/treatments with the patient should also take place at this visit if the results are available. In cases where the rhPSMA-7.3 (^{18}F) PET imaging results are not available at the safety

follow-up visit, imaging results and further procedures/treatment plan should be discussed with the patient within 7 days after rhPSMA-7.3 (^{18}F) imaging (this review may be conducted by telephone at the clinician's discretion). Note: due to the COVID-19 pandemic, the post-IP safety follow-up (laboratory and ECG assessments and focused physical examination) may be conducted within 1 to 5 days post-IP administration to ensure the safety of enrolled patients.

Within 45 days post-IP administration (may be extended to 60 days due to the COVID-19 pandemic), the patient will receive treatment as follows, with further detail provided in CSP Section 9.1.6.

- Standard of care surgical treatment of PCa, including a PLND; or
- If the rhPSMA-7.3 (^{18}F) PET scan detects M1 lesion(s):
    - A biopsy/surgery and/or additional imaging to confirm M1 lesion(s) will be required prior to initiation of treatment.

Safety will include adverse events (AEs) and vital signs monitoring, clinical laboratory evaluations, 12-lead ECG and focused physical examinations performed in all patients.

3.2 Endpoints

3.2.1 Primary Efficacy Endpoint

The co-primary endpoints for this study will be the:

- Sensitivity of rhPSMA-7.3 (^{18}F) PET (as determined by central BIE) for detecting pelvic LN metastases compared to surgical pathology on a patient level.
- Specificity of rhPSMA-7.3 (^{18}F) PET (as determined by central BIE) for detecting pelvic LN metastases compared to surgical pathology on a patient level

3.2.2 Secondary Efficacy Endpoints

The secondary endpoints for this study will be:

1. Percentage of patients in whom rhPSMA-7.3 (^{18}F) imaging detects at least one verified M1 metastasis, as determined by central BIE.
2. Percentage of patients with negative conventional imaging for M1 disease in whom rhPSMA-7.3 (^{18}F) PET detects at least one verified M1 metastasis, as determined by central BIE.
3. Patient level PPV of rhPSMA-7.3 (^{18}F) PET BIE for N1 and M1 lesions compared to histopathology or confirmatory imaging (M1 lesions only).
4. PPV of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a patient level in which a FP patient is defined as having at least one FP region (right or left pelvis), regardless of any coexisting TP findings.
5. NPV of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a patient level in which a FN patient is defined as having at least one FN region (right or left pelvis), regardless of any coexisting TN findings.
6.

a. The percentage of patients being upstaged to N1 or M1 disease;
b. The percentage of patients in whom planned RP is converted to EBRT.

7. Kappa statistic for the agreement between and within blinded independent readers on the interpretation of rhPSMA-7.3 (^{18}F) scans.
8. Safety (AEs, vital signs clinical laboratory evaluations, 12-lead ECG and focused physical examinations) of rhPSMA-7.3 (^{18}F) injection in patients

3.2.3 Exploratory Efficacy Endpoints

1. Diagnostic performance (sensitivity and specificity) of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a regional level.

3.2.4 Safety Variables

In all patients, safety evaluations will include AE monitoring and reporting from the time of informed consent throughout the study.
Vital sign assessments will also be conducted at screening and pre- and post-IP administration on the day of rhPSMA-7.3 (^{18}F) injection.
In addition, a focused physical examination will be performed at screening and at the safety follow-up visit within 1 to 3 days post-IP administration (may occur within 1 to 5 days post-IP administration due to the COVID-19 pandemic), and a 12-lead ECG will be performed pre-IP administration on the day of rhPSMA-7.3 (^{18}F) injection and at the safety follow-up visit within 1 to 3 days post-IP administration (may occur within 1 to 5 days post-IP administration due to the COVID-19 pandemic). Baseline blood safety laboratory tests, including hematology (full blood count), biochemistry (urea and electrolytes, liver function tests) and coagulation will be performed pre-IP administration on the day of rhPSMA-7.3 (^{18}F) injection and repeated at the safety follow-up visit within 1 to 3 days post-IP administration (may occur within 1 to 5 days post-IP administration due to the COVID-19 pandemic).

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Presentation Considerations

'Baseline' is defined as the last available pre-IP administration assessment.
'End of Study' is defined as the last available post-IP administration assessment.

'Study Day' will be calculated relative to the date of rhPSMA-7.3 (^{18}F) injection day, and is equal to:

- Assessment Date – IP Administration Date + 1 if the assessment date is on or after IP administration date.
- Assessment Date – IP Administration Date, if the assessment date is before IP administration date.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data (e.g. counts) that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In case the rules result in more than four decimal places, the number of decimal places reported shall be four for any summary statistic, irrespective of the previous rules.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals (CIs) of continuous variables will be presented to one more decimal place than the raw data. CIs of proportions will be presented to three decimal places (e.g. 1/3 will be a proportion of 0.333) and exact intervals (Clopper-Pearson) will be employed unless specified otherwise. CI for percentages will be to one decimal place.

4.3 Software

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment.

4.4 Study Patients

4.4.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion as per CONSORT guidance.
The following summaries will be provided:

- A summary of the number of patients screened for entry into the study and the number and percentage of patients excluded prior to IP administration by major reason and overall (Analysis set: All enrolled Patients)
- A summary of the number of patients enrolled (See section 4.5) per center, and per country (Analysis set: Full Analysis Set [FAS]).
- A summary of the number of patients who received IP, number of patients who had an evaluable PET scan following IP administration, and the number and percentage of patients withdrawing from the study and completing each phase. (Analysis set: FAS).
- A summary of withdrawals from the study and from IP administration by major reason (Analysis set: FAS).

By-patient listings of eligibility details, enrollment details, visit dates (including impact of COVID-19 on visits), withdrawal/study completion details (including reason for discontinuation and time since IP administration prior to discontinuation) will be provided.

4.4.2 Protocol Deviations

Protocol deviations will be handled in accordance with Parexel Standard Operating Procedures (SOPs).

Protocol deviations occur when the patient, investigator, or Sponsor fails to adhere to protocol requirements or where there is a significant non-compliance to ICH-GCP, affecting patient safety or the scientific value of the trial.

Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The impact of major protocol deviations on the efficacy and/or safety results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by major protocol deviations at a Data Review Meeting (DRM) shortly before database lock. Results and population assignments will be summarized in a DRM report which will be signed off by all relevant scientific experts.

Major protocol deviations and any action to be taken regarding the exclusion of patients or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification which is agreed and signed off before analysis.
Major protocol deviations which lead to withdrawal and replacement of the patient include, but not limited to:

- Failure to meet inclusion/exclusion criteria (see CSP Sections 6.2 and 6.3).
- Use of a prohibited concomitant medication (see CSP Section 7.1).
- IP administration but no subsequent PET scan.
- Significant non-compliance with IP administration.

Patients will be withdrawn from the study and be included in the All Enrolled Patients and Full Safety Population as applicable.
Deviations due to COVID-19 will be listed separately.

A by-patient listing of major protocol deviations will be provided.
A summary of the number and percentage of patients with a major protocol deviation by type of deviation (Analysis set: FAS) will be provided.

4.5 Analysis Sets

All enrolled patients: all patients who signed the informed consent form.

Full Analysis Set (FAS): all patients who were scheduled to receive the rhPSMA-7.3 (^{18}F) injection having met the inclusion/exclusion criteria.

Full Safety Population (FSP): all patients who received the rhPSMA-7.3 (^{18}F) injection.

Efficacy Analysis Population (EAP): all patients who received rhPSMA-7.3 (^{18}F) injection followed by a PET/CT scan and who underwent RP and PLND.

Extended Efficacy Population (EEP): all patients who received rhPSMA-7.3 (^{18}F) injection followed by a PET/CT scan. This population includes M0 and M1 patients independent of performance of RP and PLND and will be used for M1 related efficacy and Kappa statistics.

Per Protocol Population (PP): All patients in the EAP population who have histology available from surgery that allows SoT determination, and without any major protocol deviations that will affect the evaluations of the PET scan or histology.

The primary analysis will be based on the EAP. The FSP will be used for all safety summaries.

Upon database release, protocol deviation and analysis set outputs will be produced and will be to BED for review. An analysis set classification meeting will be arranged to discuss the outputs and to decide which patients and/or patient data will be excluded from certain analyses. Decisions made regarding the exclusion of patients and/or patient data from the analyses, and the agreement of population inclusion for each patient, will be made prior to database lock and will be documented and approved by the Sponsor.

A by-patient listing of analysis set details will be provided. This listing will include: center, country, patient identifier, and inclusion/exclusion flag for each set and reason for exclusion from

each set. All enrolled patients will appear on this listing. If patient data have been partially excluded, visit will also appear on this listing.

The number and percentage of patients in each population will be provided using all enrolled patients.

4.6 Demographic and Other Baseline Characteristics

4.6.1 Demographics

All demographics (e.g. age [including age groups of <65, ≥65 and the subgroup of ≥75], sex, race, height, weight and BMI at screening and on Day 1) and baseline characteristics will be listed, and their baseline characteristics summarized (with weight and BMI on day 1) using the FAS, FSP, EAP, EEP and PP.

BMI will be calculated as $BMI(kg/m^2) = \frac{weight\ (kg)}{height\ (m)^2}$

4.6.2 Baseline conventional imaging

Baseline conventional imaging will be taken from imaging performed within the 60 days before screening or will be performed prior to IP administration.
The imaging results classified as baseline (above) will be summarized using FAS, EAP, EEP and PP by imaging modality and as positive or negative for detection of N1 or M1 disease. Patients with more than one baseline scan will be summarized for the combination of baseline scans and include all applicable anatomical areas covered. A listing will contain all these baseline parameters and include the imaging modality (CT, MRI, bone Scan, etc).

4.6.3 Prostate Cancer History

Prostate cancer history will be summarized using the FAS, FSP, EAP, EEP and PP for time of initial prostate cancer diagnosis to informed consent (in months), for TNM stage, total Gleason score (Frequencies), Gleason Grade Group (GGG) based on prostate biopsy, most recent PSA including frequency by categorization (0-0.5, >0.5-1.0, >1.0-2.0, >2.0-5.0, >5.0-10.0, >10.0 [ug/L]).
This same information will be listed by patient.

Gleason Grade Group is defined by the International Society of Urological Pathologists, and the categories are as follows:

- Grade Group 1 is defined as Total Gleason score ⩽6
- Grade Group 2 is defined as Gleason score 3+4=7
- Grade Group 3 is defined as Gleason score 4+3=7
- Grade Group 4 is defined as Total Gleason score of 8
- Grade Group 5 is defined as Total Gleason scores 9-10

TNM staging will be displayed at observed level and combined at levels T2, T3, T4, M0, M1, MX, where each of these contain underlying categories (i.e. T2 -All contains subjects with observed at T2, T2a, T2b, T2c)

4.6.4 Baseline Risk Category

Risk Category will be assigned using the NCCN Guidelines, version 1.2020; PROS-2. A listing of risk category and underlying variables will be provided. Risk category will be summarized into categories using the EAP. Risk Categories are shown in Table 1. Per the CSP, risk categories of unfavorable intermediate-risk, high-risk or very high-risk are expected.

Table 1: Risk Categories from NCCN guidelines.

Risk Group	Clinical/Pathologic Features
Very Low	T1c AND Grade Group 1 AND PSA <10 ng/mL AND Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND PSA density < 0.15 ng/mL/g
Low	Has all following but does not qualify for very low risk T1-T2a AND Grade Group 1 AND PSA < 10 ng/mL
Favorable intermediate	No High or Very High-risk features 1 Intermediate Risk Factors and Grade Group 1 or 2 and <50% biopsy cores positive
Unfavorable Intermediate	No High or Very High-risk features 2 or 3 Intermediate Risk Factors. and/or Grade Group 3 and/or ≥50% biopsy cores positive
High	No very-high risk features and has at least one high-risk feature: T3a OR Grade Group 4 or Grade Group 5 OR PSA>20 ng/mL
Very High	Has at least one of the following T3b-T4 OR Primary Gleason pattern 5 OR 2 or 3 high-risk features >4 cores with Grade Group 4 or 5

Intermediate risk factors are: T2b-T2c, PSA 10-20 ng/mL, Grade Group 2 or 3

In this study, the risk groups will be categorized into:

- "High or Very High Risk" – defined as meeting any one of these criteria: T-stage T3 (including T3a and T3b) or T4, Gleason Grade Group 4 or 5, Primary Gleason pattern 5, or PSA >20ng/mL
- "Not High or Very High Risk" – defined as not meeting any of the criteria meeting the high or very high-risk criteria.

4.6.5 Medical history

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher – the data will be listed and include start date, end date, ongoing at study start, Preferred Term (PT) and System Organ Class (SOC). Medical history will also be summarized using FSP by SOC and PT.

4.7 Prior and Concomitant Medications and Procedures

Medication and/or procedure start and stop dates will be compared to the date of IP administration to allow medications/procedures to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications and/or procedures starting after Day 4 will be listed but will not be classified or summarized.

Medications/procedures that start and stop prior to the date of dose of IP administration will be classified as Prior only. If a medication/procedure starts before the date of IP administration and stops on or after the date of IP administration, then the medication/procedure will be classified as both Prior and Concomitant. Medications/procedures will be classified as Concomitant only if they have a start date on or after the date of first dose of study medication.

If medication/procedure start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of IP administration. Medications/procedures will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication/procedure started prior to the IP administration. If there is clear evidence to suggest that the medication/procedure started prior to the IP administration, the medication/procedure will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication/procedure stopped prior to the IP administration. If there is clear evidence to suggest that the medication/procedure stopped prior to the IP administration, the medication will be assumed to be Prior only.

Medications will be coded using WHODrug Global Dictionary and summarized by ATC code (levels 2 and 4) and Preferred term and listed by patient using the FSP. In case of missing level 4 coding the level 3 coding will be used.

Procedures will be summarized by System Organ Class (SOC) and Preferred Term (PT) using MedDRA dictionary and listed by patient.

All prior and concomitant medications and procedures will be listed by patient. Concomitant medications will be summarized using the FSP.

4.8 Exposure and Treatment Compliance

A patient listing of rhPSMA-7.3 (^{18}F) administration including total administered activity, injection site reactions, local imaging results, incidental findings, and evaluations of the independent blinded central PET readers will be provided.

A summary of total administered activity will be provided using the FAS and PP. All activity will be converted to MBq using the conversion 1mCi=37 MBq.

4.9 rhPSMA-7.3 (^{18}F) Image reading

Each rhPSMA-7.3 (^{18}F) image will initially be read by a site-based local reader, and the results will be listed including incidental findings. In addition, for the primary endpoint analysis, imaging will be read by three blinded independent PET readers (see the study Independent Review Charter for further details). The results of the blinded PET readers will be used in the primary analysis, thus requiring each (statistical) analysis to be performed three times. In addition, the majority interpretation will be displayed.

Table 2 Derivation of Overall Interpretation (2 out of 3 readers consensus)

Reader 1	Reader 2	Reader 3	Majority
Positive	Positive	Positive	Positive
Positive	Positive	Negative	Positive
Negative	Negative	Positive	Negative
Negative	Negative	Negative	Negative

PET imaging results (i.e. positive/negative) will be summarized using the EEP by anatomical location by category and anatomical location within category. Categories will be prostate, pelvic lymph nodes, lymph nodes outside of pelvis, soft tissue/parenchyma and bones, as well as extra-pelvic (which would include lymph nodes outside of pelvis, soft tissue/parenchyma and bones together). All categories will be presented in the summary, but anatomical locations will only be presented where data are collected, i.e. lesion investigated in that anatomical location.

4.10 Biopsy/Surgery

If the rhPSMA-7.3 (^{18}F) PET shows M1 metastatic disease, the patient will be asked to undergo a biopsy or confirmatory imaging of the PET-positive lesion(s) to confirm the presence of a metastasis. If a surgical intervention of this lesion is carried out as part of the treatment, this may substitute for a biopsy. If the patient has proven M1 metastatic disease, the disease management may be altered, based on the responsible physician's clinical judgement. This change in disease management will be documented on the eCRF.

If rhPSMA-7.3 (^{18}F) PET does not detect M1 disease, the patient will undergo the scheduled RP and PLND. In patients without M1 lesions identified and in whom the patient and physician believe, after obtaining the results of the rhPSMA-7.3 (^{18}F) PET, that EBRT would be a better therapeutic option than surgery, the patient may proceed to EBRT and the rationale for this change of disease management will be documented on the eCRF.

The regional PLND must be performed by a suitably qualified surgeon and should include, at minimum, resection of lymphatic tissue for histological analysis from the following nodal groups: 1) hypogastric (internal iliac), 2) external iliac, and 3) obturator LNs. Extended LN dissection may be performed if clinically appropriate and the anatomical regions (e.g. presacral, common iliac, peri-rectal) with left/right designations, should be recorded on the eCRF. The location of the dissected material shall be marked in order to allow matching with their anatomical origin (left and right pelvis); the left and the right side of the specimen shall be clearly marked. The dissected LNs will be sectioned and analyzed by a pathologist for the presence or absence of PCa according to standard of care at the clinical site. The number of lymph nodes sampled and found positive for PCa will be registered and summarized.
Patients with PET M1 will be summarized using the EEP by confirmatory method(s), result of confirmation, change in disease management, surgery (radical prostatectomy and pelvic lymph node dissection) performed, Lymph node dissection and (additional) treatment received. All counts will be presented including percentage of patients categorized as PET M1.

Patients will be summarized using the EEP by surgery (RP and PLND) received, extended lymph node dissection and (additional) treatment received. All counts will be presented including the percentage of patients categorized as PET M0.

Results by patient will be listed for both M0 and M1 patients. A display of Histopathology of Pelvic Lymph Nodes and a display of confirmatory procedures will be created for all patients. For M1 patients, a listing of PSMA Positive M1 Lesions (by anatomic location), including method (Biopsy/histopathology, CT Scan, MRI, Bone scan, Other) and result, will be created.
A summary will be provided on methods to obtain standard of truth.

4.11 TNM staging and Gleason score

In addition to baseline values (Section 4.6.3), baseline and post-surgery staging will be summarized for TNM stage, primary and secondary and total Gleason score similar to baseline using the EEP. In addition, for GGG, a shift table will be presented from baseline to final staging.

4.12 Standard of Truth

Histology or confirmatory imaging will be used as the Standard of Truth (SoT), as defined below.

1. Histology
    a. Histology of surgically removed pelvic LNs;
    b. Histology obtained by biopsy of M1 lesion.
2. Confirmatory Imaging
    a. In patients without available histopathology, confirmatory conventional imaging is acceptable as proof of M1 disease in case of unequivocal findings (e.g. sclerotic bone lesions on CT, positive bone lesions on bone scan, evidently enlarged LNs radiologically considered metastases, lesions in the liver representing metastases as determined by ultrasound, CT or MRI, multiple pulmonary nodules on CT).

b. Confirmatory imaging for proof of M1 disease will be read centrally. Three central reviewers will review all submitted imaging and reach consensus on the nature of the target lesion. Reads of the confirmatory imaging as SoT will be directed by rhPSMA-7.3 (^{18}F) PET findings (for confirmation of lesion location only). A brief summary of clinical information will be available to the SoT readers (e.g. 67-year-old male with newly diagnosed, localized prostate cancer prior to rhPSMA-7.3 (^{18}F) scan). Readers will be blinded to all other information. Further details are given in the study Independent Review Charter.

3. Baseline Conventional Imaging only
   a. If M1 lesion identified by blinded PET reader but not site reader, or if M1 lesion is identified by site reader but no histology or no confirmatory imaging is available, then only conventional imaging at baseline will be used to determine the SoT.

SoT will be listed next to the results of the blinded independent reads and include method (Histology/Confirmatory Imaging/Baseline Imaging only), anatomical location and Result(s) using the EEP. Histology SoT will be assessed based on local reads of the PET scan, and these results will be included irrespective of BIE reading. The SoT will be summarized by method and anatomical location.

4.13 Hemipelvis Region Categorization and Patient Level Categorization

At least one positive pelvic LN on PET (N1) and one positive LN as determined by histopathology (pN1) on the same side of the pelvis (left or right), as depicted in Table 3, will be deemed a TP on a patient level.

Table 3 Hemipelvis Region Categorization Method

	At Least One Pathology-positive LN in the Region	No Pathology-positive LN in the Region
At Least One PET-Positive LN in the Region	True Positive (TP) region	False Positive (FP) region
No PET-positive LN in the Region	False Negative (FN) region	True Negative (TN) region

LN=lymph node; PET=positron emission tomography.

For patients who have no TP regions, Table 4 depicts the method for assigning patient level categorizations based on by-region results (i.e. for the different possible hemipelvis combinations of TN, FN and FP regions).

Two analyses will be performed based on the classification of patients with one positive region and one negative region. The primary analysis will include patients as FN if they only had one positive region by histopathology and it was missed by PET. Full diagnostic statistics will be provided for both patient level classifications.

Table 4: Translation of Region Level to Patient Level Categorizations in Patients with No TP Regions

a)

Patient Level Categorization	At Least one True Negative (TN) Region	At Least one False Negative (FN) Region	At Least one False Positive (FP) Region
True Negative (TN)	Yes	No	No
False Negative (FN)	Yes	Yes	No
False Negative (FN)	No	Yes	No
False Positive (FP)	Yes	No	Yes
False Positive (FP)	No	No	Yes
False Negative (FN) for Primary Analysis; False Positive (FP) for Secondary Analysis*	No	Yes	Yes

PPV=positive predictive value.

* Patient contributes to the primary efficacy analysis for Sensitivity (False Negative categorization) and a secondary analysis of PPV (False Positive categorization).

b)

Histopathology	PET Patient Level Classification			
	True Positive (TP)	**False Negative (FN)**	**False Positive (FP)**	**True Negative (TN)**
Two Positive Regions	1 or 2 positive regions on PET	Both regions negative on PET	NA	NA
One Positive Region; One Negative Region	PET is correct on positive region	Primary analysis: PET is negative on the positive region Secondary analysis: PET is negative on both regions only	Primary analysis: NA Secondary analysis: PET is negative on histopathology positive region and PET is positive on histopathology negative region	NA
Two Negative Regions	NA	NA	PET-positive on one or two regions	PET is negative on both regions

NA=cell classification is not applicable; PET=positron emission tomography.

Results of the Hemipelvis Categorization will be listed by region and summarized by region status using the EAP. This summary will include a category for missing Hemipelvis Categorization.
The patient's by region and patient level classification will be listed including classification for the secondary analysis (Section 4.14.3.4 and 4.14.3.5).
A cross table of patients PET image diagnostic and SoT diagnostic will be provided.

4.14 Efficacy Evaluation

Unless otherwise stated, all efficacy evaluations will be done using the EAP as defined in Section 4.5.

4.14.1 Analysis and Data Conventions

The primary hypothesis involves a joint assessment of sensitivity and specificity against individual performance goals:
H_0: Sensitivity ≤ Se_0 or Specificity ≤ Sp_0 *versus* H_1: Sensitivity > Se_0 and Specificity > Sp_0
Where Se_0 and Sp_0 are performance goals for sensitivity and specificity, respectively. Performance goals of 22.5% (Se_0) for sensitivity and 82.5% (Sp_0) were selected based on the low sensitivity but high specificity of other PSMA ligands used for lymph node staging.

The definition of Sensitivity will be:
True Positive / (True Positive + False Negative)
The definition of Specificity will be:
True Negative / (True Negative + False Positive)

Additional analysis will be performed for PPV and NPV.
The definition of PPV will be:
True Positive / (True Positive + False Positive)
The definition of NPV will be:
True Negative / (True Negative + False Negative)

The sensitivity, specificity, PPV and NPV, together with the corresponding 95% CIs, will be estimated for each of the three blinded PET readers. All analyses performed for the three blinded PET readers will be repeated for their majority evaluation (Section 4.9).

4.14.1.1 Adjustments for Covariates

Not applicable.

4.14.1.2 Handling of Dropouts or Missing Data

Missing evaluation results in the biopsy/surgery will be assigned the worst value. Hence, a side with a positive rhPSMA-7.3 (^{18}F) PET will be considered as false positive (i.e. SoT will be set to negative), while a side with negative rhPSMA-7.3 (^{18}F) PET will be a false negative (i.e. SoT set to positive).

The number and percentage of patients with missing data for the biopsy/surgery will be summarized by major reason, as indicated in Section 4.13.

Imputation of missing dates for concomitant medications and procedures is described in Section 4.7, imputation of missing dates for AEs is described in Section 4.15.1.

4.14.1.3 Interim Analyses

Using the first 150 patients an interim analysis of safety data will be created. The actual outputs for this are indicated in the shells.

4.14.1.4 Examination of Subgroups

The attributes of the primary efficacy variable will be examined across subgroups based on:

- PCa risk categories (high- or very high-risk vs not high or very high risk).
- Most recent PSA values (0- 0.5, >0.5-1.0, >1.0-2.0, >2.0-5.0, >5.0-10.0,>10.0 [ng/mL])
- Race (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, White, Not Reported, Other)
- Age (<65, >=65 and >=75)

The analysis within subgroups will involve the confidence intervals (CI) but not the hypothesis testing. For each of these analyses, if a category has low counts (less than 10) it may be collapsed with another category, for ordinal parameters only with neighboring categories.

A cross table of N1 disease status from rhPSMA-7.3 (^{18}F) PET against to histopathology of pelvic LNs will be provided by risk category and associated 95% CI for Sensitivity and Specificity will be presented.

4.14.1.5 Clustered binary data estimate of variance

4.14.1.5.1 Sensitivity

Following Zhou et al. the following estimators will be used:

$$\widehat{Se} = \sum_{i=1}^{I} N_i * \widehat{Se_\iota} \Big/ \sum_{i=1}^{I} N_i$$

$$\widehat{Var}(\widehat{Se}) = \frac{1}{I(\mathrm{I}-1)} \sum_{i=1}^{I} \left[\frac{N_i}{\overline{N}} \left(\widehat{Se_\iota} - \widehat{Se} \right)^2 \right]$$

With:

Se	: Sensitivity
i	: individual patient
I	: total number of patients
N_i	: Number of elements (True Positive + False Negative) for patient i
$\widehat{Se_i}$	: Sensitivity for patient *i*
$\overline{\mathrm{N}}$	: Mean cluster size

The example in Zhou et al. is coded in SAS in Appendix 6.1.

An asymptotic normal distribution for the sampling distribution of $\widehat{PPV}$ is assumed and the 95% confidence interval will be derived as:

$$\widehat{Se} \pm Z_{1-\alpha/2} \sqrt{\widehat{Var}(\widehat{Se})}$$

where $Z_{1-\alpha/2}$ is the upper 1-α/2 value for the standard normal distribution.

4.14.1.5.2 Additional Confidence interval Sensitivity

Normal approximation in constructing 95% CIs might lead to bounds exceed [0, 1] for $\widehat{PPV}$. Hence an additional CI will be derived. Logit transformation will be applied to *PPV* and Delta Method (Casella and Berger, 2021) will be utilized to obtain to approximate the variance of $logit(PPV)$. Accordingly, the asymptotical distribution of $logit(PPV)$ is

$$\sqrt{n}\left[log\left(\frac{\widehat{Se}}{1-\widehat{Se}}\right) - log\left(\frac{Se}{1-se}\right)\right] \xrightarrow{d} \mathrm{N}\left(0, \frac{1}{[Se(1-Se)]^2} Var\,(Se)\right).$$

Accordingly, an asymptotic normal distribution for the sampling distribution of $logit(\widehat{Se})$ is assumed and the 95% confidence interval will be derived as:

$$logit(\widehat{Se}) \pm Z_{1-\alpha/2}\sqrt{\widehat{Var}(logit(\widehat{Se}))}$$

where $Z_{1-\alpha/2}$ is the upper 1-α/2 value for the standard normal distribution and $\sqrt{\widehat{Var}(logit(\widehat{Se}))} \approx \frac{1}{[\widehat{Se}(1-\widehat{Se})]^2}\widehat{Var}(\widehat{Se})$. Lower and upper confidence intervals values will be reported in [0,1] scale by the logit inverse transformation, as follows

$$CI_{[0,1]\,scale} = \frac{e^{CI\_logit}}{1 + e^{CI\_logit}}$$

4.14.1.5.3 Specificity

The formulas for sensitivity can be used with appropriate substitution.
Sensitivity=True Positive / (True Positive + False Negative)
Specificity=True Negative / (True Negative + False Positive)

4.14.2 Primary Efficacy Variable

The co-primary endpoints for the study are based on the sensitivity and specificity of rhPSMA-7.3 (^{18}F) PET (by central BIE) in detecting N1 disease compared to histopathology of pelvic LNs. The primary analysis involves a joint assessment of sensitivity and specificity against individual performance goals:

H_0: Sensitivity ≤ Se_0 or Specificity ≤ Sp_0 *versus* H_1: Sensitivity > Se_0 and Specificity > Sp_0

Where Se_0 and Sp_0 are performance goals for sensitivity and specificity, respectively. Performance goals of 22.5% (Se_0) for sensitivity and 82.5% (Sp_0) for specificity were selected based on the low sensitivity but high specificity of other PSMA ligands used for LN staging. The analyses for sensitivity and specificity will be performed using one-sided 0.025 exact binomial tests. In addition to the rates, exact two-sided 95% CIs will also be provided. If the predefined sensitivity and specificity goals are met by the same two of three blinded independent readers (both tests reach statistical significance [P<0.05] for the same two readers), the study will be considered to have successfully demonstrated the effectiveness of the rhPSMA-7.3 (^{18}F) in detecting N1 disease.
The TP, FP, TN and FN regions will be categorized according to Table 3 (Section 4.13) using a right and left hemipelvis regional classification method. For the primary analysis, patients who have one TP region will be categorized as a TP patient.

For patients who have no TP regions, Table 4 depicts the method for assigning patient level categorizations based on by-region results (i.e. for the different possible hemipelvis combinations of TN, FN and FP regions).
Classification will be summarized via a cross table of region status using the layout of Table 4b.
A summary of frequency of PET Patient level Classifications will be supplied including estimates and CI of Sensitivity and Specificity according to each blinded reader. Sensitivity and Specificity will be plotted for each reader including CI and performance goals.

The primary analysis will be repeated using the PP following methods of the primary analysis:
A summary of frequency of PET Patient level Classifications will be supplied including estimates and CI of Sensitivity and Specificity according to each blinded reader. Frequencies will be displayed in a bar chart. Sensitivity and Specificity will be plotted for each reader including CI and performance goals.

4.14.2.1 Sensitivity Analysis; patients with FN and FP results
The primary efficacy analysis will be repeated with a reclassification of patients with one FN and one FP region. In particular, in the sensitivity analysis, these patients will be classified as FN. The results will be displayed in a summary of frequency of PET Patient level Classifications including estimates and CI of Sensitivity and Specificity according to each blinded reader. Frequencies will be displayed in a bar chart. Sensitivity and Specificity will be plotted for each reader including CI and performance goals.

4.14.3 Secondary Efficacy Variables

All secondary efficacy variables will be analyzed descriptively, with the exception of item 7; Kappa statistic.
Patient pathway through the study (PET scan, M0/M1, subsequent RP-PLND (Yes/No) and additional steps will be summarized and listed.
The following items are presented per secondary efficacy variable.

4.14.3.1 Percentage of patients in whom rhPSMA-7.3 (^{18}F) imaging detects at least one verified M1 metastasis, as determined by central BIE.
This analysis concerns patients in the EEP with rhPSMA-7.3 (^{18}F) imaging and confirmation tested (biopsy or additional imaging).
The percentage of patients with at least one M1 metastasis will be provided for each blinded independent reader. M1 metastasis requires the reader to identify a positive lesion in one of the three following locations: lymph nodes outside the pelvis, soft tissue/parenchyma or the bones. Patients will be counted to have M1 metastasis for this variable if a BIE detects M1 on the rhPSMA-7.3 (^{18}F) and M1 is confirmed (biopsy, additional imaging) at the same location.
Patients where M1 was not verified (e.g. because the local reader did not detect M1) will be included in this analysis, as long as the BIE reader has detected M1 – in this case, the patients' metastasis will be considered as not verified. An additional table will be made using the EEP to summarize for each blinded reader the number of patients who have M1 by BIE and the presence / absence of confirmation of M1 metastasis.

The endpoint for the secondary objective 1 of Verified Detection Rate (VDR) for M1 disease on a patient level is the percentage of patients with True-Positive M1 disease in the EEP.

VDR = (TP)/(TP+FP+TN+FN)
where:

- TP = BIE PET positive and SoT positive
- FP = either: (1) BIE PET positive and SoT negative or (2) BIE PET positive and SoT not done or not proven (NB: If site PET = M0, we would still have baseline imaging and so will count in SoT)
- FN = BIE PET negative and SoT positive
- TN = either: (1) BIE PET negative and SoT negative or (2) BIE PET negative and SoT not done

Results for M1 detections by central, blinded readers will be reported overall and by SOT method used (histopathology, and imaging only) to confirm M1 detection as True Positive or False Positive.

4.14.3.2 Percentage of patients with negative conventional imaging for M1 disease in whom rhPSMA-7.3 (^{18}F) PET detects at least one verified M1 metastasis, as determined by central BIE.

This analysis concerns patients in the EEP with rhPSMA-7.3 (^{18}F) imaging and confirmation tested (biopsy or additional imaging) and with conventional imaging yielding negative M1 disease.
The patients counted in this variable are a subset of 'Percentage of patients in whom rhPSMA-7.3 (^{18}F) imaging detects at least one verified M1 metastasis, as determined by central BIE', where both the numerator and denominator are only counting patients with negative conventional imaging (according to investigator assessment) for M1 disease.

The endpoint for the secondary objective 2 of Verified Detection Rate (VDR) for M1 disease on a patient level with negative conventional imaging is the percentage of patients with negative conventional imaging (according to investigator assessment) for M1 disease and with True-Positive M1 disease according to rhPSMA-7.3 (^{18}F) PET in the EEP.

4.14.3.3 Patient level PPV of rhPSMA-7.3 (^{18}F) PET BIE for N1 and M1 lesions compared to histopathology or confirmatory imaging (M1 lesions only).

This analysis concerns EEP patients with rhPSMA-7.3 (^{18}F) imaging and either N1 or M1 lesions detected.

PPV of N1 lesions is the proportion of patients with a positive PET BIE finding in pelvic lymph nodes and confirmed by histopathology, out of the patients with a positive PET BIE finding in pelvic lymph nodes.

PPV of M1 lesions is the proportion of patients with a positive PET BIE finding in other (extra-pelvic) areas and confirmed by SoT (histopathology or confirmatory imaging (as determined by central SoT)), out of the patients with a positive PET BIE finding in other (extra-pelvic) areas.

4.14.3.4 PPV of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a patient level in which a FP patient is defined as having at least one FP region (right or left pelvis), regardless of any coexisting TP findings.

This analysis concerns patients in the EAP where rhPSMA-7.3 (^{18}F) imaging detected pelvic LN metastasis. Regions where rhPSMA-7.3 (^{18}F) imaging detected no LN metastasis are not part of this by definition of PPV, hence only TP and FP regions will be taken into account.

PPV = TP / (TP + FP)

True positives will be all patients with a surgical pathology confirmed positive region and without a false positive region. False Positive patients will be those patients with any rhPSMA-7.3 (^{18}F) PET positive region with negative surgical pathology or no surgical pathology.

4.14.3.5 NPV of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a patient level in which a FN patient is defined as having at least one FN region (right or left pelvis), regardless of any coexisting TN findings.

This analysis concerns patients in the EAP with rhPSMA-7.3 (^{18}F) imaging, where no LN metastases were detected and LN surgical pathology is available.

Regions where rhPSMA-7.3 (^{18}F) imaging detected positive LN are not part of this by definition of NPV, hence only TN and FN regions will be taken into account.

NPV = TN / (TN + FN)

True negatives will be all patients with a surgical pathology confirmed negative region and without a false negative region. False negative patients will be those patients with any rhPSMA-7.3 (^{18}F) PET negative region with positive surgical pathology.

4.14.3.6 Upstaging

a) The percentage of patients being upstaged to N1 or M1 disease;

b) The percentage of patients in whom planned RP is converted to EBRT.

The endpoints will be calculated as follows:

- Upstaging to N1 = Proportion of patients with positive BIE PET finding by BIE and negative conventional imaging finding from local investigator in pelvic lymph nodes, out of all the patients with evaluable scans.

- Upstaging to M1 = Proportion of patients with positive BIE PET finding and negative conventional imaging finding from local investigator in other (extra-pelvic) areas, out of all the patients with evaluable scans.

- Planned RP converted to EBRT = Proportion of patients with positive BIE PET finding and planned RP changed to EBRT by local investigator, out of all the patients with evaluable scans.

4.14.3.7 Kappa statistic for the agreement between and within blinded independent readers on the interpretation of rhPSMA-7.3 (^{18}F) scans.

This analysis concerns all EEP patients.

For this analysis, the patient's categorization to positive or negative by the blinded readers will be used, in pelvic lymph nodes and in extra-pelvic region.

4.14.3.7.1 Inter-reader agreement analysis

The Cohen's kappa statistic will be used to assess pairwise agreement between 2 readers including 95% exact CIs giving three kappa statistics (SAS® nomenclature: simple kappa). In addition, the Fleiss' kappa across the 3 readers including 95% (approximate) CIs will be shown (SAS® nomenclature: overall kappa Coefficient).

This same calculation will be repeated for the regions:

Prostate/Prostate Bed
Pelvic Lymph Nodes
Other
Other: Lymph nodes outside pelvis
Other: Soft Tissue/parenchyma
Other: Bones.

4.14.3.7.2 Intra-reader agreement analysis

Cohen's Kappa will be used to assess intra-reader agreements in the first read and the repeat read of 10% of the randomly selected images for each of the three readers.

This same calculation will be repeated for the regions:

Prostate/Prostate Bed
Pelvic Lymph Nodes
Other
Other: Lymph nodes outside pelvis
Other: Soft Tissue/parenchyma
Other: Bones.

4.14.4 Exploratory Efficacy Variables

4.14.4.1 Diagnostic performance (sensitivity and specificity) of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases compared to surgical pathology on a regional level.

This analysis will be performed using the EAP on all patients who were not diagnosed as M1 in the rhPSMA-7.3 (^{18}F) PET imaging and for all sides where surgical pathology was performed.

In this analysis, each patient will be considered as a cluster, with left hemi-pelvis and right hemi-pelvis considered as two observations within each cluster. Regions will be classified according to Table 3.
The descriptive parts of the primary analysis; cross table, sensitivity and specificity, will be repeated using region level analysis.

4.15 Safety Evaluation

All safety summaries and analyses will be based upon the FSP as defined in Section 4.5.

4.15.1 Adverse Events

For AEs and Serious AEs (SAEs), the MedDRA Version 22.1 or later will be used to code the reported events.

Treatment-emergent adverse events (TEAEs) will be tabulated and are defined as those AEs that either start or worsen in severity on or after the date/time of IP administration and on or before Day 4.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to IP administration or more than 4 days after IP administration.
In particular this means the following rules will be applied until a classification is given:

1. An AE with a missing start date and missing end date will be a TEAE
2. An AE with a missing start date and end date after IP administration will be TEAE
3. A start date with a missing year but month present will be assumed to have a year such that the start date is after informed consent and before Day 90. If these rules conflict then the rule 'after informed consent' prevails.
4. An AE will not be a TEAE if the start date is incomplete and
    a. The end date of the AE is before the dosing date
    b. The end date/time of an AE is before the dosing date/time
    c. The day of the AE end date is missing and the month of the AE end date is before the month of dosing date
5. An AE will not be a TEAE if the AE start day of month is missing and
    a. The last day of the AE start month is before the dosing date
    b. The first day of the AE start month is more than 4 days after dosing

All AE summaries will provide the number of patients reporting at least one AE and the total number of events reported.

The following summaries will be provided:

- A summary of the number and percentage of patients reporting an AE, including counts of TEAEs, IP-related TEAEs, SAEs and IP-related SAEs.

- A summary of the number and percentage of patients reporting a TEAE by SOC, and PT
- A summary of the number and percentage of patients reporting a TEAE by Common Terminology Criteria for Adverse Events (CTCAE) grade, SOC and PT
- A summary of the number and percentage of patients reporting a TEAE by causality, SOC and PT

Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within an SOC and then alphabetically for SOC, and PT within SOC.

For each patient and each adverse event, the worst CTCAE Toxicity grade (Version 5) recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If CTCAE is missing for, the missing category will be used as worst category. If causality is missing, the worst case will be assumed.

A by-patient listing of all adverse events (including non-treatment-emergent events) will be provided. This listing will include center, patient identifier, age, race, adverse event (SOC, PT, and verbatim term), date of onset, date of resolution, duration, CTCAE, seriousness, action taken, outcome and causality.

4.15.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths, SAEs, and Other Significant AEs will be listed and summarized if numbers allow.
The following summaries are planned.

- A summary of the number and percentage of TEAE leading to death
- A summary of the number and percentage of patients reporting a serious TEAE, by SOC and PT
- A summary of the number and percentage of patients with TEAEs leading to discontinuation of study treatment, by SOC and PT

The following listings will be created:

- A by-patient listing of all deaths that occurred during the study
- A by-patient listing of all SAEs
- A by-patient listing of all AEs leading to discontinuation of study treatment

Listings will follow the format described for AEs in Section 4.15.2.

4.15.3 Clinical Laboratory Evaluation

Blood safety laboratory values (hematology, biochemistry and coagulation) will be listed by patient and study time point including changes from baseline. The baseline for the laboratory values will be the pre-dose results obtained on Day 1.

All values outside the clinical reference ranges will be flagged in the data listings. The abnormal values will be flagged with 'L' for values below the lower limit of the clinical reference range and 'H' for values above the upper limit of the clinical reference range and included in the listings.

Descriptive statistics (for non-categorical data including hematology and blood chemistry) will be presented for both individual values (N, mean, SD, median, minimum, maximum) and changes from baseline.

The following summaries will be provided:

- A summary of each laboratory parameter at visit 2 (pre-dose at day 1) and visit 3
- A summary of the change from baseline to visit 3 in each laboratory parameter
- A shift table of the number and percentage of patients experiencing treatment-emergent laboratory abnormalities at baseline vs visit 3, by laboratory parameter

4.15.4 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital signs will be listed, including change from baseline. Baseline will be the last assessment before dosing, this is planned to be Visit 2 (Day 1), but may be any other assessment.
A summary of each vital sign parameter, including change from baseline to visit 3 will be given.

12-lead ECG results will be listed, including change from baseline by patient and time point. Baseline will be the pre-dose assessment at Visit 2 (Day 1). A summary of each ECG parameter, including change from baseline to visit 3 will be given.

Physical examinations results (Normal, Abnormal Not Clinically Significant, Abnormal Clinically Significant) will be listed by patient and time point. Physical examination findings will be summarized by visit.

Heart rate category (<40 bpm, 40-59 bpm, 60-100 bpm, 101-130 bpm, >130 bpm) will be summarized and a shift table will be presented.
Shift tables will be presented for QTc and physical examinations.

4.15.5 Other safety

A summary of injection site reactions during or immediately after the dose will be provided.

4.15.6 Safety Monitoring (Independent Data Monitoring Committee [IDMC], Data Monitoring Committee [DMC], Data and Safety Monitoring Board [DSMB])

Not applicable.

4.16 Determination of Sample Size

A total sample size of approximately 375 patients is planned in order to obtain 300 evaluable patients for analysis of the primary endpoint. Assuming a sensitivity of 40% of PSMA ligands for detecting N1 disease (based on the previous OSPREY [NCT02981368]), a sample size of 75 positive cases provides 90% power to reject the performance goal of 22.5%. Assuming a specificity of 90% for rhPSMA-7.3 (^{18}F) PET, a sample size of 225 negative cases provides 90% power to reject the performance goal of 82.5%. Assuming the true prevalence rate of N1 disease is 25%, a sample size of 300 evaluable patients is expected to provide 75 positive cases and 225 negative cases.

Up to approximately 375 patients with unfavorable intermediate-, high- and very high-risk PCa will be enrolled into the study. Since some patients will have M1 disease and some patients will receive EBRT instead of RP following the PET scan, enrollment of up to approximately 375 patients will ensure inclusion of at least 300 evaluable patients undergoing RP and PLND.

In order to have sufficient numbers of histologically positive and negative cases, an interim look will be allowed to ensure a distribution of pN1 disease as would be anticipated in this patient population. After the inclusion of approximately 150 patients, the percentages of pN0 and pN1 will be monitored. If the percentage of pN1 exceeds 35%, inclusion of very high-risk and/or high-risk patients will be suspended. If the percentage of pN1 is less than 15%, the inclusion of intermediate-risk patients will be suspended.

4.17 Changes in the Conduct of the Study or Planned Analysis

An additional analysis set (Extended Efficacy Population) was created to accommodate analysis of patients where no RP and PLND was performed, such as patients with M1 lesions.

The second exploratory Efficacy objective and endpoint were removed.
Objective:

> To evaluate diagnostic performance of rhPSMA-7.3 (^{18}F) PET (as determined by central BIE) in patients with a) pelvic LN metastatic deposits <5 mm (short axis) and LN metastatic deposits ≥5 mm (short axis) and b) pelvic LN metastatic deposits <10 mm (short axis) and LN metastatic deposits ≥10 mm (short axis), if feasible.

Endpoint:

> Diagnostic performance of rhPSMA-7.3 (^{18}F) PET in patients with a) pelvic LN metastatic deposits <5 mm (short axis) and LN metastatic deposits ≥5 mm (short axis) and b) pelvic LN metastatic deposits <10 mm (short axis) and LN metastatic deposits ≥10 mm (short axis)

Two changes were documented to make the analysis description consistent.

- In Table 4 part b, which originated as table 6b in the CSP, the following text was changed: CSP: "Secondary analysis: PET is negative on True Positive (TP) region and PET is positive on True Negative (TN) region"

SAP: "Secondary analysis: PET is negative in a histopathology positive region, and PET is positive in a histopathology negative region".

- In section 16.4 the text was adapted:
  CSP: "Two analyses will be performed based on the classification of patients with one TP region and one TN region. The primary analysis will include patients as FN if they only had one positive region by histopathology and it was missed by PET. Full diagnostic statistics will be provided for both patient level classifications."
  SAP will interpret this as: "Two analyses will be performed based on the classification of patients with one positive region and one negative region by histopathology. The primary analysis will include patients as FN if they only had one positive region by histopathology and it was missed by PET. Full diagnostic statistics will be provided for both patient level classifications."

5 REFERENCES

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6 Appendix

6.1 SAS program to reproduce data in Zhou et al [10].

```
data one;
input TN     No_Polyps;
Cards;
1      1
2      2
2      2
1      1
2      2
2      2
1      1
1      1
1      1
1      1
2      2
0      1
2      3
2      2
1      1
1      1
1      1
2      2
1      2
0      2
1      1
2      2
2      2
2      2
0      1
;;;;
run;

proc sql;
   create table two as
      select
         TN ,
         No_Polyps,
         TN/No_Polyps as Sei_hat,
         Se_hat,
         No_Polyps/mNo as Ni_N,
         (calculated Ni_N)*(calculated Ni_N)
             * (calculated Sei_hat-Se_hat)* (calculated Sei_hat-Se_hat) as fc,
         sum(calculated fc) as sfc,
         calculated sfc/(n*(n-1)) as varSe_hat
```

```
      from
         (select
            sum(TN) as sTN,
            sum(No_Polyps) as sNo,
            mean(No_Polyps) as mNo,
            count(*) as n,
            calculated sTN/calculated SNo as Se_hat
            from one ) as o,
         one;
quit;

data final;
   set two;
   if _n_=1;
   CI_L = Se_hat - (quantile('NORMAL', .975)*varSe_hat**0.5);
   CI_U = Se_hat + (quantile('NORMAL', .975)*varSe_hat**0.5);
   p_value = 1 - CDF('NORMAL', (Se_hat-0.625)/varSe_hat**0.5);
   keep Se_hat varSe_hat CI_L CI_U  p_value;
run;
data final_logit;
   set final;
   logit_Se_hat = log(Se_hat/(1-Se_hat));
   logit_varSe_hat = varSe_hat*((1/(Se_hat*(1-Se_hat)))**2);
   logit_CI_L = logit_Se_hat - (quantile('NORMAL', .975)*logit_varSe_hat**0.5);
   logit_CI_U = logit_Se_hat + (quantile('NORMAL', .975)*logit_varSe_hat**0.5);
   logit_zero_one_CI_L = (CONSTANT('E')**logit_CI_L)/((CONSTANT('E')**logit_CI_L)+1);
   logit_zero_one_CI_U = (CONSTANT('E')**logit_CI_U)/((CONSTANT('E')**logit_CI_U)+1);
run;
```

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