CLINICAL STUDY PROTOCOL

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

LIGHTHOUSE

BED-PSMA-301

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Sponsor: Blue Earth Diagnostics

Blue Earth Diagnostics

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Approval:

Sponsor Signature (Name and Title) Date

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include providing Blue Earth Diagnostics with the information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted Good Clinical Practice principles, applicable regulatory requirements, and to abide by the terms of this protocol.

Protocol Number: BED-PSMA-301

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Protocol Version: 3 Protocol Date: 01-Jul-2020

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LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
BCR	Biochemical recurrence
CI	Confidence interval
COVID-19	Corona Virus Disease-19
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
EAP	Efficacy Analysis Population
EBRT	External beam radiation therapy
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eTMF	Electronic trial master file
EU	European Union
^{18}F	Fluorine-18
FAS	Full Analysis Set
FDA	Food and Drug Administration
FN	False Negative
FP	False Positive
FSP	Full Safety Population
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGG	Gleason Grade Grouping
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICRP	International Commission on Radiological Protection
ID	Identifier
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
LHRH	Luteinizing hormone-releasing hormone
LN(s)	Lymph node(s)

MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NPV	Negative predictive value
PCa	Prostate cancer
PET	Positron emission tomography
PLND	Pelvic lymph node dissection
PP	Per Protocol Population
PPV	Positive predictive value
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
rh	Radiohybrid
RP	Radical prostatectomy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCID	Severe combined immunodeficiency
SoT	Standard of Truth
SOP	Standard Operating Procedure
^{99m}Tc-HDP	^{99m} Technetium-hydroxydiphosphate
^{99m}Tc-MDP	^{99m} Technetium-methyldiphosphonate
TN	True Negative
TP	True Positive
TUM	Technical University of Munich
US	United States
VDR	Verified detection rate

PROTOCOL SYNOPSIS

Study Title	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
Protocol Number	BED-PSMA-301
Phase	3
Sponsor	Blue Earth Diagnostics
Funding Organization	Blue Earth Diagnostics Ltd
Study Design	This is a Phase 3, multi-center, single-arm, diagnostic imaging study designed to evaluate the safety and diagnostic performance of radiohybrid prostate-specific membrane antigen (rhPSMA)-7.3 positron emission tomography (PET) ligand for the detection of N1 and M1 metastases in men with newly diagnosed unfavorable intermediate-, high- or very high-risk prostate cancer (PCa; per National Comprehensive Cancer Network [NCCN] Guidelines Version 1.2020; PROS-2). A number of measures have now been put in place to streamline the study for patients' safety due to the continued impact of the Corona Virus Disease-19 (COVID-19) pandemic on daily life. Consented patients will be screened to determine eligibility for the study up to 28 days (up to 45 days due to the COVID-19 pandemic) before investigational product (IP) administration. Alternatively, this 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 (named "Visit 1 and Visit 2 combined"). In addition to their routine clinical work-up, which may include ^{99m}technetium-biphosphonate bone scan and abdominal/pelvic computed tomography (CT) or magnetic resonance imaging (MRI) and chest CT per local practice, and before the scheduled radical prostatectomy (RP) and pelvic lymph node dissection (PLND), patients will receive 8 mCi (296 MBq) ± 20% rhPSMA-7.3 (^{18}F), delivered as an intravenous (IV) bolus injection, followed by PET imaging. For each patient, the PET imaging results 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 electrocardiogram (ECG), blood safety laboratory tests and focused physical examination. Clinical review of 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). Within 45 days post-IP administration, the patient will receive treatment as follows: • Standard of care surgical treatment of PCa, including PLND; **or** • If the rhPSMA-7.3 (^{18}F) PET scan detects M1 lesion(s): o A biopsy/surgery and/or additional imaging to confirm M1 lesion(s) will be required prior to initiation of treatment.

	Safety will be monitored throughout the study. This will include adverse event (AE) and vital signs monitoring, clinical laboratory evaluations, 12-lead ECG and focused physical examinations performed in all patients. 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. In addition, the standard of care treatment and follow-up procedures to confirm M1 lesions(s) by PET may occur up to 60 days post-IP administration.	
Study Rationale	The purpose of this study is 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 RP with regional PLND. Accurate staging of newly diagnosed PCa assists in directing appropriate treatment strategies. In patients with unfavorable intermediate, high or very high risk PCa, the primary goal of imaging is to detect extra-prostatic disease. The identification of metastatic disease may significantly change the planned treatment regimen from locoregional to systemic therapy. The prostate-specific membrane antigen (PSMA) receptor is over-expressed in the majority of PCa. Although not approved in any country or region, PSMA PET tracers have been used in many centers around the world to image PCa patients. Initial results have demonstrated promising diagnostic performance. The variable production capacity of the radiometal ^{68}Ga represents a practical disadvantage when considering the large number of patients with PCa eligible to undergo PSMA PET imaging. To overcome this shortcoming, ^{18}F-labeled PSMA ligands, such as rhPSMA-7.3 (^{18}F), have been developed. rhPSMA-7.3 (^{18}F) injection is a PET ligand for the detection of PCa. The rhPSMA-7 (^{18}F) isomer mixture and the rhPSMA-7.3 (^{18}F) stereoisomer have already been administered to patients at the Technical University of Munich (TUM). Evaluation of the sensitivity and specificity of rhPSMA-7.3 (^{18}F) imaging by blinded image evaluation (BIE) for detecting regional pelvic lymph node (LN) involvement, compared to histopathology, will be performed as the co-primary endpoints.	
Primary Objective and Endpoints	Objective: To assess the sensitivity and specificity of rhPSMA-7.3 (^{18}F) 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) on a patient level.	Endpoints: • 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.

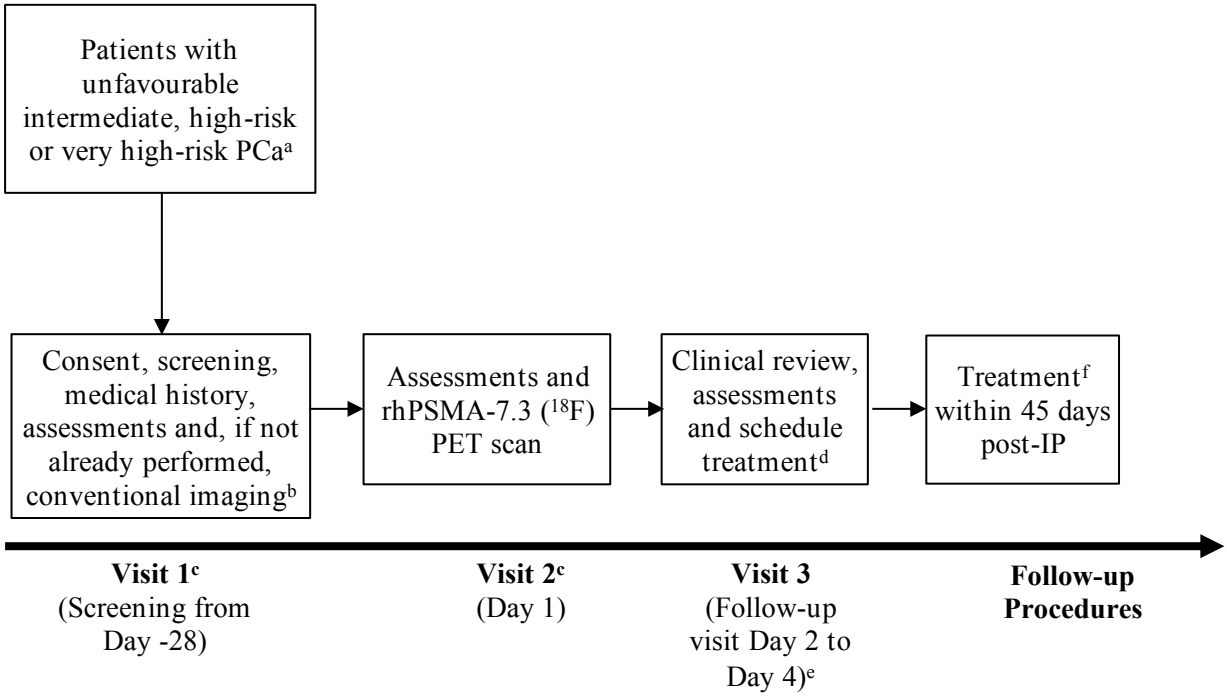
Secondary Objectives and Endpoints	Objective: 1. To assess the Verified Detection Rate (VDR) for M1 disease of rhPSMA-7.3 (^{18}F) PET findings (as determined by central BIE) on a patient level in patients with newly diagnosed unfavorable intermediate-, high-, or very high-risk PCa using histopathology or confirmatory imaging.	Endpoints: 1. Percentage of patients in whom rhPSMA-7.3 (^{18}F) imaging detects at least one verified M1 metastasis, as determined by central BIE.
Secondary Objectives and Endpoints *(Cont.)*	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 False Positive (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 False Negative (FN) patient is defined as having at least one FN region (right or left pelvis), regardless of any coexisting True Negative (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).	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. 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.	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.
Exploratory Objectives and Endpoints	Objective: 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. 2. 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: 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. 2. 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).
Study Sites	This study will be conducted at up to approximately 35 sites in the United States (US) and Europe.	
Investigational Product(s), including control products	IP: 8 mCi (296 MBq) ± 20% rhPSMA-7.3 (^{18}F), delivered as an IV bolus injection with a 10 mL fast 0.9% sodium chloride flush. Control: Not applicable.	
Study and Participant Duration	Study Duration: The total study duration from first site activation to data analysis is estimated to be 15 months. Participant Duration: Will be approximately 90 days (assuming the longest possible participation). Patients will be screened for inclusion into the study up to 28 days (up to 45 days due to the COVID-19 pandemic) before IP administration. Each patient will have a safety visit within 1 to 3 days following IP administration (due to the COVID-19 pandemic, this visit may be conducted within 1 to 5 days post-IP administration). Future study procedures such as surgery, biopsy or further imaging should be scheduled at this visit and based on the results of the PET scan and standard of care. Patients will remain in the study until the results of the histology or confirmatory imaging are obtained in order to satisfy the Standard of Truth (SoT). If confirmatory procedures for suspected M1 disease are required, this should be prior to initiation of treatment.	

Planned Interim Analyses	No formal interim analysis is planned. In order to have inclusion of sufficient numbers of histopathologically positive and negative N1 cases, an interim look will be allowed to ensure a distribution of pN1 disease as would be anticipated in this patient population.
STATISTICS Primary Analysis Plan	The co-primary endpoints for the study are based on the sensitivity and specificity of rhPSMA-7.3 (^{18}F) PET (as determined 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% confidence intervals (CIs) will also be provided. If the predefined sensitivity and specificity goals are met by the same two of three readers (both tests reach statistical significance 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. Secondary and exploratory endpoints will be summarized descriptively, with the exception of consistency of rhPSMA-7.3 (^{18}F) scan interpretation by blinded independent readers which will be presented utilizing Kappa statistics. Two-sided 95% CIs will be presented, where applicable.
Rationale for Number of Patients	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 study [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% (Klevečka, 2008; MSKCC, Nomogram; Internal Report: PSMA: TUM Data Report), a sample size of 300 evaluable patients is expected to provide 75 positive cases and 225 negative cases. 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 inclusion of sufficient numbers of histopathologically 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. Dropouts who fail to complete all study procedures, for reasons other than

	due to adverse reactions/AEs deemed related to IP, will be withdrawn from the study and replaced. No more than 15% of patients enrolled, who did not have M1 disease or EBRT, will be replaced.

Figure 1: Study Schema



COVID-19=Corona Virus Disease-19; CT=computed tomography; EBRT=external beam radiation therapy; eCRF=electronic case report form; ^{18}F=fluorine-18; GGG=Gleason Grade Grouping; IP=investigational product; MRI=magnetic resonance imaging; NCCN=National Comprehensive Cancer Network; PCa=prostate cancer; PET=positron emission tomography; PLND=pelvic lymph node dissection; PSA=prostate-specific antigen; RP=radical prostatectomy; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; ^{99m}Tc-HDP=^{99m}technetium-hydroxydiphosphate; ^{99m}Tc-HDP=^{99m}technetium-methyldiphosphonate.

[a] Unfavorable intermediate-risk (GGG 2 with ≥50% of biopsy cores positive for PCa and/or >1 Intermediate Risk Factor [T2b; T2c; PSA 10-20] **or** Any GGG 3), high-risk or very high-risk disease (per NCCN Guidelines Version 1.2020; PROS-2).

[b] If not already performed within 60 days prior to screening, conventional imaging will be performed as part of routine clinical practice, which may include bone scan (^{99}mTc-HDP, ^{99}mTc-MDP), abdominal/pelvic CT or MRI, and chest CT as per local practice. Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are retrievable and reviewed by the participating institution. Note: baseline conventional imaging performed as part of routine clinical practice should be performed at least 24 hours prior to the investigational rhPSMA-7.3 (^{18}F) PET scan.

[c] Due to the COVID-19 pandemic, for patients who already have baseline conventional imaging, Visit 1 and Visit 2 may be combined (named "Visit 1 and Visit 2 combined") if judged by the investigator to be necessary to decrease potential exposure to SARS-CoV-2 for patients. For all patients enrolled through the Visit 1 and Visit 2 combined pathway, pre-screening via telephone contact with the patient is required prior to Day 1 to review the study eligibility criteria, obtain initial consent (remote consent is acceptable if permitted under local regulations and approvals), to promote study visit compliance and to ensure patient understanding of the combined study visit and planned IP administration, as well as ask about baseline conventional imaging that may already have been performed or needs to be scheduled. Full written informed consent will be taken on Day 1 (Visit 1 and Visit 2 combined). For sites with on-site manufacturing, the visits may be combined if mutually agreed by the Radiopharmacy and investigator even post-COVID-19 pandemic restrictions.
Alternatively, the time from Visit 1 (initial screening) to Visit 2 (rhPSMA-7.3 (^{18}F) PET scan) may be extended up to 45 days due to the COVID-19 pandemic.

[d] 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 RP, the patient may proceed to EBRT and the rationale for this change of management will be documented on the eCRF.
Patients in whom the rhPSMA-7.3 (^{18}F) PET shows M1 metastatic disease 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 treatment decision may be altered, based on the responsible physician's clinical judgement. This change will be documented on the eCRF. Any confirmatory procedure for suspected M1 disease, as described above, should be performed prior to initiation of treatment.

[e] Within 1 to 3 days post-IP administration, the patient must return to the clinic for safety follow-up. Clinical review of imaging results and discussion of further procedures/treatments with the patient should also take place at this visit if

feasible. In cases where the rhPSMA-7.3 (^{18}F) PET imaging results are not available, imaging results and further procedures/treatment plan should be discussed with the patient within 7 days after rhPSMA-7.3 (^{18}F) imaging (this may be conducted by telephone at the clinician's discretion). Details of this review will be entered under Visit 3 on the eCRF.
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.

[f] Due to the COVID-19 pandemic, the time period from Visit 2 to the scheduled surgery and/or follow procedures (e.g. to confirm M1 lesion(s)) may be extended up to 60 days.

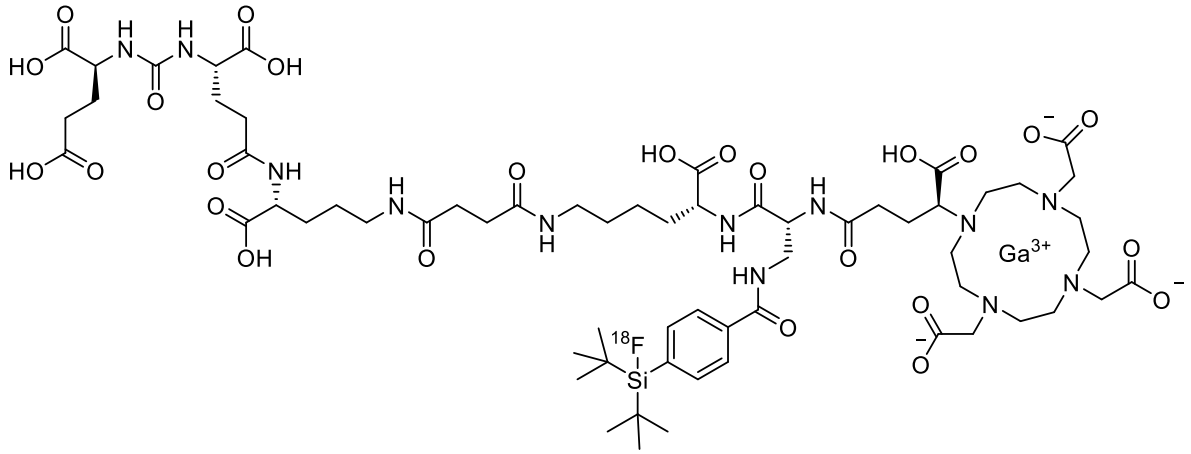
1 BACKGROUND

The investigational product (IP) is fluorine-18 (^{18}F) radiohybrid prostate-specific membrane antigen (rhPSMA)-7.3 injection, a positron emission tomography (PET) ligand for the detection of prostate cancer (PCa).

It is designed to target the extracellular epitope of the prostate-specific membrane antigen (PSMA) molecule and is administered as a single intravenous (IV) bolus microdose (i.e. the mass dose administered is less than 100 µg/patient).

The molecular structure of the drug substance comprises a PSMA binding motif, a peptide spacer, an ^{18}F-radiolabeled silicon fluoride acceptor moiety and a gallium chelator complex (Figure 2).

Figure 2: Structure of rhPSMA-7.3 (^{18}F)



1.1 Overview of Non-clinical Studies

A non-clinical biodistribution and dosimetry study has been performed (Internal Report: BEDPSMADEV002), in which 100 pmol rhPSMA-7.3 (^{18}F) (N=27) was administered IV to severe combined immunodeficiency (SCID) male mice. Animals were sacrificed at 10, 60, 120, 180 and 300 minutes post-administration, with urine and blood samples collected immediately after sacrifice and tissues harvested and weighed for the measurement of ^{18}F radioactivity. Human dosimetry was calculated by extrapolation from the mouse biodistribution data using scaling factors to account for the differences between animals and humans. The data demonstrated that for rhPSMA-7.3 (^{18}F), the largest accumulation of radioactivity was in the kidney, spleen, lung, liver and heart. Clearance from the blood and clearance to the urine was rapid for rhPSMA-7.3 (^{18}F), but there was a relatively slow build-up of radioactivity in the kidney. Using a 3.5-hour bladder voiding interval, as recommended by the International Commission on Radiological Protection (ICRP, 1992), the effective dose for humans extrapolated from the animal data was 21.7 µSv/MBq for rhPSMA-7.3 (^{18}F). Using a 1.0-hour bladder voiding interval, based on the time at which patients will be encouraged to void in the clinical setting, the effective dose for humans was 12.8 µSv/MBq. Based on these data, an injection of 8 mCi (296 MBq) ± 20% for a clinical scan would result in a favorable radiation effective dose of less than 5 mSv, assuming a 1-hour voiding interval.

Consistent with the development of a radiodiagnostic agent, rhPSMA-7.3 (^{18}F) is not designed to elicit pharmacological activity and an *in vitro* secondary pharmacology screen has confirmed there is no unintended pharmacological activity in a panel of 44 potential targets. A concentration of 5 µg/mL was used in the *in vitro* pharmacology profiling which compares to a maximum concentration in human plasma of 0.04 µg/mL (based on 2500 mL plasma and a maximum human dose of 100 µg). In a pivotal single IV bolus dose extended toxicity study in rats to determine tolerance and potential target organ toxicity to rhPSMA-7.3 at IV dosages of 0, 0.1, 1 and 10 mg/kg, the no-observed-adverse-effect-level was the maximum dose administered of 10 mg/kg (allometrically scaled human dose equivalent of 1.6 mg/kg). This represents a 1000-fold multiple of the maximum clinical microdose of 100 µg based on a 60 kg human. No target organs of toxicity were identified. Systemic exposure demonstrated rat plasma concentrations above the intended maximum human actual dose. *In vitro* protein binding in rat and human indicated moderate binding of 75% and 82% in rat and human, respectively, with no concentration dependence. *In vitro* human cytochrome P450 (CYP) reaction phenotyping indicated rhPSMA-7.3 is not metabolized. *In vitro* rhPSMA-7.3 does not inhibit or induce human CYP isoforms and is not a substrate or inhibitor of human drug transporters suggesting drug interaction with rhPSMA-7.3 is unlikely.

Further details of the non-clinical studies performed with rhPSMA-7.3 or rhPSMA-7.3 (^{18}F) are provided in the rhPSMA-7.3 (^{18}F) Investigator's Brochure (IB).

1.2 Overview of Clinical Studies

Although no PSMA-targeted imaging agents are licensed as radiodiagnostic agents for use in either Europe or the United States (US), they are widely used by many imaging centers (Rowe, 2018). This includes use of rhPSMA-7.3 (^{18}F) (single diastereoisomer), as well as rhPSMA-7 (^{18}F) (a mixture of four diastereoisomers, including rhPSMA-7.3 [^{18}F]), at the Technical University of Munich (TUM). To date, data for rhPSMA-7 (^{18}F), administered under the physician's personal responsibility, (exempt from a manufacturing authorization as per Section 13, Subsection 2b of the German Medicinal Products Act), have been reported. In a retrospective, non-interventional review of data from patients (N=1189) with known or suspected PCa who underwent a clinically indicated rhPSMA-7 (^{18}F) PET/computed tomography (CT) or PET/magnetic resonance imaging (MRI) scans at TUM, diagnostic performance, biodistribution and safety data for rhPSMA-7 (^{18}F) were analyzed (Internal Report: PSMA: TUM Data Report). Data sources included hospital records and imaging results, as well as routine follow-up data. Given the retrospective nature of the data collection, informed consent was not obtained from each individual patient; thus, routine clinical data included in the study database were totally anonymized and only aggregated anonymized data from chart review were available for analysis.

No clinical data on rhPSMA-7.3 (^{18}F) diagnostic performance are currently available; however, clinical data available for rhPSMA-7 (^{18}F) are broadly expected to be consistent with that of the rhPSMA-7.3 (^{18}F) isomer alone. The single isomer product (rhPSMA-7.3 [^{18}F]) is being developed as it is preferable to a diastereoisomer mix for the purposes of manufacturing control.

A total of 1189 patients, with known or suspected PCa, underwent a clinically indicated rhPSMA-7 (^{18}F) PET/CT or PET/MRI scan at TUM between 30 June 2017 and 30 June 2018. Based on the retrospective chart review, rhPSMA-7 (^{18}F) was well-tolerated, with no safety concerns identified. A total of 58 consecutive patients with high risk PCa (defined by D'Amico, 1998) staged with rhPSMA-7 (^{18}F) PET/CT or PET/MRI were analyzed. Results

were compared to histopathological findings (patient-based analysis; template region based analysis; right- versus left-based analysis). For the patient-based analysis, the sensitivity, specificity and accuracy of rhPSMA-7 (^{18}F) PET were 72.2%, 92.5% and 86.2%, respectively. For morphological imaging, values were 50.0%, 72.5% and 65.5%, respectively. On receiver operating characteristic analyses, rhPSMA-7 (^{18}F) PET performed statistically significantly better than morphological imaging in the patient-based analyses (area under the curve of 0.858 versus 0.649; p=0.012). For the template region-based and the right- versus left-based analysis, similar results were obtained with rhPSMA-7 (^{18}F) PET compared to morphological imaging. These efficacy data demonstrated that rhPSMA-7 (^{18}F) PET imaging is superior to morphological imaging for N-staging of primary high risk PCa.

Furthermore, rhPSMA-7 (^{18}F) PET imaging offers excellent detection rates in early biochemical recurrence (BCR) after radical prostatectomy (RP; 423/532 had positive findings on rhPSMA-7 (^{18}F) PET/CT imaging, including 333/418 and 90/114 patients with and without pelvic lymph node dissection (PLND), respectively, and 185/225 and 238/307 patients with and without salvage external beam radiation therapy [EBRT], respectively), as well as in early BCR after primary radiation therapy with curative intent (60/65 had positive findings on rhPSMA-7 (^{18}F) PET/CT imaging).

Further details of the clinical studies performed or planned for rhPSMA-7.3 (^{18}F) are provided in the rhPSMA-7.3 (^{18}F) IB.

2 STUDY RATIONALE

rhPSMA-7.3 (^{18}F) injection is a PET ligand for the detection of PCa. The rhPSMA-7 (^{18}F) isomer mixture and the rhPSMA-7.3 (^{18}F) stereoisomer have already been administered to patients at the TUM (see Section 1.2). To date, several hundred patients with PCa have been imaged clinically with rhPSMA (^{18}F), which has informed the design of this proposed study. rhPSMA-7.3 (^{18}F) is currently being formally evaluated by Blue Earth Diagnostics in a Phase 1, open label, study designed to assess the safety, biodistribution and internal radiation dosimetry of rhPSMA-7.3 (^{18}F) injection in healthy volunteers, and to assess safety and investigate the imaging characteristics in patients with PCa (Study BED-PSMA-101; EudraCT No. 2018-004703-39).

Prostate cancer 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 recently updated 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 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.

Various retrospective studies have evaluated the utility of bone scans as a staging tool, with an incidence of bone metastases ranging from 3.5% (Ito, 2013) or 6.4% (De Nunzio, 2013) up to 20% (Chong, 2014) reported in patients with intermediate- and high-risk PCa. A false-positive rate of these bone scans of 20% has been reported (Chong, 2014), with MRI proving no better at detecting bone metastases. Specifically, a recent publication highlights the low probability of finding bone metastases on a staging MRI of the pelvis, with bone metastases identified in only 1.5% (57 of 3765) of cases and only in those with intermediate- and high-risk PCa (Vargas, 2017).

In the absence of confirmed M1 disease, PLND at the time of RP is recommended to assess for nodal disease and predict patient outcome (Moschini, 2016; Swanson, 2006). Furthermore, in cases where disease is limited to the prostate and regional lymph nodes (LNs; N1 disease), removal of regional LN metastases is performed with curative intent. Similarly, diagnosis of M1 disease beyond the field of surgery or radiotherapy allows both the patient and clinician to make more informed decisions about appropriate adjuvant, often systemic, treatments (Roach, 2018). Several methods to predict the absence or presence of M1 disease have been used with limited success, including nomograms, CT, MRI and PET imaging (Cagiannos, 2003; Schiavina, 2008; Park, 2015; Zarzour, 2017).

With respect to the detection of N1 disease, a recent meta-analysis of 24 studies including 2928 patients demonstrated a pooled overall sensitivity of MRI for the detection of LN metastases of only 56% (Woo, 2018). PET using ^{11}C-choline did not perform materially better, with a sensitivity of 59% for the detection of LN metastases (Huang, 2018). A variety

of studies have recently evaluated ^{68}Ga-PSMA-11 PET or ^{18}F-DCFPyL PSMA PET as a decision-making aid in the prediction of N1 disease (Table 1). Although specificity was relatively high in these studies, the sensitivity compared to LN dissection and pathological examination was rather low, with point estimates ranging from 31% to 71%.

Table 1: Evaluation of ^{68}Ga-PSMA-11 PET and ^{18}F-DCFPyL PSMA PET in N1 Disease

Tracer	Study	Sensitivity	Specificity	No. Patients
^{68}Ga-PSMA	van Kalmthout, 2019; prospective, controlled study	42% (27% to 58%)[a]	91% (79% to 97%)[a]	96
^{68}Ga-PSMA	Pooled analysis of four studies (Von Eyben, 2018)	61% (47% to 72%)[a]	97% (85% to 99%)[a]	224
^{18}F-DCFPyL	Gorin, 2018; prospective; controlled study	71% (29% to 96%)[a]	89% (65% to 99%)[a]	25
^{18}F-DCFPyL	OSPREY [NCT02981368]; prospective controlled clinical trial	31% to 42%[b] (19% to 30%)[c]	96% to 99%[b] (94% to 96%)[c]	268

CI=confidence interval; PET=positron emission tomography; PSMA=prostate-specific membrane antigen
a 95% CI
b range of point estimates among three readers
c range of lower bound of the 95% CIs for three readers (upper bound of CIs not reported).

The overwhelming need for improved imaging should focus on the identification of N1 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.

The PSMA receptor is a 100 kD transmembrane glycoprotein that is over-expressed in the majority of PCa (Israeli, 1994; Silver, 1997; Osborne, 2013). Peptidomimetic glu-ureido-based PSMA inhibitors, initially described in 2001 (Kozikowski, 2001), bind to a carboxypeptidase active site on the extracellular motif of the PSMA receptor. Although not approved in any country or region, in the last 5 years, many centers around the world have imaged patients using PSMA PET tracers based on this targeting technology (Perera, 2016). Whilst these initial results have demonstrated promising diagnostic performance, there remains no licensed or approved PSMA PET imaging agents. Ongoing clinical use of these technologies is only through compassionate use and research protocols. The variable production capacity of the radiometal ^{68}Ga represents a practical disadvantage when considering the large number of patients with PCa eligible to undergo PSMA PET imaging. To overcome this shortcoming, ^{18}F-labeled PSMA ligands have also been developed.

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 RP with regional PLND. Evaluation of the sensitivity and specificity of rhPSMA-7.3 (^{18}F) imaging by central BIE for detecting regional pelvic LN involvement, compared to histopathology, will be performed as the co-primary endpoints. Therefore, only patients who choose to undergo RP and a PLND will be included in this study.

2.1 Risk-benefit Assessment

2.1.1 Benefits

As rhPSMA-7.3 (^{18}F) represents approximately 39% of the rhPSMA-7 (^{18}F) mixture, clinical data obtained to date with rhPSMA-7 (^{18}F) are relevant to the understanding of rhPSMA-7.3 (^{18}F).

rhPSMA-7 (^{18}F) has been shown to be an effective PET radiotracer and is considered an improvement over morphological imaging for staging of primary high-risk PCa in terms of diagnostic accuracy (Internal Report: PSMA: TUM Data Report). rhPSMA-7 (^{18}F) PET also showed good detection rates in early BCR of PCa after RP or curative radiation therapy (Internal Report: PSMA: TUM Data Report). The data compare favorably with those published for ^{68}Ga-PSMA-11, the most widely used small-molecule inhibitor of PSMA used for PCa imaging (Rowe, 2016).

The rhPSMA-7.3 (^{18}F) PET scans may provide further clinical information regarding the patient's disease status that may not have been appreciated by routine clinical testing. If such information arises, this will be reported back to the responsible clinician to help direct the patient's further management. This may provide a direct benefit to the patient.

2.1.2 Risks

The risks from the imaging studies to patients mainly relate to the IV injection and the radiation emitted by the radiopharmaceutical and the CT transmission scan (when the PET scan is acquired on a PET/CT scanner). Intravenous injection carries a small risk of infection and hematoma.

A non-clinical biodistribution and dosimetry study has been performed (see Section 1.1). Using a 1.0-hour bladder voiding interval, based on the time at which patients will be encouraged to void in the clinical setting, the effective dose for humans extrapolated from the animal data was 12.8 µSv/MBq for rhPSMA-7.3 (^{18}F). The administered activity in this study will be 8 mCi 296 MBq ± 20%. Based on the results of the non-clinical study, this would result in an effective dose of less than 5 mSv. Full details are in the Study Imaging Manual. rhPSMA-7.3 (^{18}F) is currently being formally evaluated by Blue Earth Diagnostics in a Phase 1, open-label, study designed to assess the safety, biodistribution and internal radiation dosimetry of rhPSMA-7.3 (^{18}F) injection in healthy volunteers, and to assess safety and investigate the imaging characteristics in patients with PCa (Study BED-PSMA-101; EudraCT No. 2018-004703-39).

The maximum effective dose due to the CT transmission scan on a PET/CT scanner will vary from site-to-site, but as a guide a dose of 7 mSv would be expected. The effective dose due to the CT acquisition will be in accordance with ALARA (**As Low As Reasonably Achievable**) principles. The estimated total dose of 12 mSv (PET and CT transmission scan) is in line with other common nuclear medicine procedures.

Patients in whom the rhPSMA-7.3 (^{18}F) PET shows M1 metastatic disease will be asked to undergo a biopsy or confirmatory imaging of the PET-positive lesion(s) to confirm the presence of a metastasis.

A CT-guided biopsy may be required in these patients; mean effective doses of between 4.3 and 13.9 mSv have been reported (Guberina, 2018) during CT-guided biopsies and is dependent on the organ region and CT-scanner generation. A biopsy will cause discomfort and pain and may incidentally lead to complications, like prolonged bleeding at the site of the biopsy or infection.

Confirmatory imaging may include the use of diagnostic ultrasound, CT or PET (see Section 9.1.8). Examples of effective doses from such procedures are as follows: abdominal/pelvic CT, 6 to 8 mSv (McCollough, 2015); chest CT, 7 mSv (McCollough, 2015); ^{18}F-sodium fluoride PET, 8.9 mSv (Beheshti, 2015).

As with all imaging techniques, there is the risk that the PET scan may provide a False Positive image (FP; giving the appearance of cancer) in sites where it is not present, due to other events in the body or False Negative (FN; failing to detect a nidus of cancer). Thus, patients should continue to be reviewed and may require other investigations, to confirm scan findings.

To date, rhPSMA-7 (^{18}F) has been administered to over 1200 patients undergoing clinically indicated rhPSMA-7 (^{18}F) PET/CT or PET/MRI scan in a single center (formal data available for 1189 patients). rhPSMA-7 (^{18}F) was well tolerated in these patients, and adverse events (AEs) primarily related to the underlying tumor, with few serious adverse events (SAEs) and only three events with a possible causal association with rhPSMA-7 (^{18}F). This is consistent with AE reporting for other PSMA agents in the literature (Literature Review of PSMA for the Detection and Management of Prostate Cancer, data on file). In addition, as of 15 February 2019, rhPSMA-7.3 (^{18}F) has been administered at TUM, under the physician's personal responsibility, to a total of 558 men with known or suspected PCa. Although 35 patients had AEs or SAEs within the 30-day observation period, there were no reports of adverse reactions or serious adverse reactions attributed to injection of rhPSMA-7.3 (^{18}F) (M Eiber, TUM; personal communication).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to assess the sensitivity and specificity of rhPSMA-7.3 (^{18}F) 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 FP, True Negative (TN) and FN regions to patient level categorizations is described in detail in Section 16.4.

3.2 Secondary Objectives

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 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.

3.3 Exploratory Objectives

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.
2. 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.

4 STUDY DESIGN

4.1 Study Overview

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 Corona Virus Disease-19 [COVID-19] pandemic) before IP administration at Visit 2. 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 CT or 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 IV bolus injection with a 10 mL fast 0.9% sodium chloride flush, followed by PET imaging.

Note: Due to the COVID-19 pandemic, for patients who already have baseline conventional imaging, 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 Visit 2 combined; Section 10.3). Alternatively, the time from Visit 1 (initial screening) to Visit 2 (rhPSMA-7.3 (^{18}F) PET scan) may be extended up 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 electrocardiogram (ECG), blood safety laboratory tests and focused physical examination. Clinical review of 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 up to 60 days due to the COVID-19 pandemic), the patient will receive treatment as follows, with further detail provided in 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 be monitored throughout the study. This will include AE and vital signs monitoring, clinical laboratory evaluations, 12-lead ECG and focused physical examinations performed in all patients.

An overview of the study is provided in the study schema (Figure 1).

4.2 Sub-studies

Not applicable.

5 CRITERIA FOR EVALUATION

5.1 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.

5.2 Secondary 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.

5.3 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.
2. 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).

5.4 Safety Evaluations

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, 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. 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.

Note: due to the COVID-19 pandemic, the 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.

6 PATIENT SELECTION

6.1 Study Population

Treatment naïve patients with a diagnosis of unfavorable intermediate-, high-risk or very high-risk PCa (per NCCN Guidelines Version 1.2020; PROS-2), scheduled to receive standard of care surgical treatment for PCa, including a PLND, who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

In order to have inclusion of sufficient numbers of histopathologically 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 suspendedInclusion Criteria

1. Patient willing to provide signed informed consent and willing to comply with all required study schedule events, where safe and feasible.
2. Patient is male and aged >18 years old.
3. Histologically confirmed adenocarcinoma of the prostate.
4. Candidate for RP with PLND and scheduled to undergo the surgical procedure.
5. Patient with either:
   a) Unfavorable intermediate-risk disease, defined as:
      – Any Gleason Grade Grouping [GGG] 3, **or**
      – GGG 2 with ≥50% of biopsy cores positive for PCa **and/or** >1 Intermediate Risk Factor [T2b; T2c; PSA 10-20]

      or
   b) High-risk or very high-risk disease (per NCCN Guidelines Version 1.2020; PROS-2).

6.2 Exclusion Criteria

1. Patients with any medical condition or circumstance (including receiving an IP) that the investigator believes may compromise the data collected or lead to a failure to fulfil the study requirements.
2. Patients who are planned to have an x-ray contrast agent or other PET radiotracer <24 hours prior to the PET scan.
3. Patients currently receiving, or with a prior history of, androgen deprivation therapy (ADT; defined as surgical orchidectomy; luteinizing hormone-releasing hormone [LHRH] agonist alone [continuous or intermittent]; LHRH antagonist alone [continuous or intermittent]; administration or use of a first generation or second generation anti-androgen alone or in combination with an LHRH agonist/antagonist).
4. Patients participating in an interventional clinical trial within 30 days and having received an IP within five biological half-lives prior to administration of rhPSMA-7.3 (^{18}F).
5. Patients with known hypersensitivity to the active substance or to any of the excipients of the IP.

7 CONCURRENT MEDICATIONS

As medically feasible, all patients should be maintained on the same medications without change throughout the entire study period.

Concomitant medications will be recorded at screening and any changes in administration will be noted.

7.1 Prohibited Medications

The following medications are prohibited during the study and administration will be considered a protocol violation:

- X-ray contrast agent <24 hours prior to the rhPSMA-7.3 (^{18}F) PET scan.
- Any other PET imaging agent within 24 hours prior to the rhPSMA-7.3 (^{18}F) PET scan.
- The initiation of any therapy should not occur until after definitive pathology or imaging results are obtained satisfying the Standard of Truth (SoT) assessment.

8 STUDY TREATMENTS

As manufacturing and supply of IP will be site-specific, the Study Pharmacy Manual provides additional information for the IP (rhPSMA-7.3 [^{18}F] injection).

8.1 Method of Assigning Patients to Treatment Groups

Not applicable. This is a single-arm study.

8.2 Blinding

Not applicable. This is an open-label study.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

The IP – rhPSMA-7.3 (^{18}F) – is a PET imaging radiopharmaceutical formulated as a solution for injection. It is designed to target the extracellular epitope of the PSMA molecule and is administered as a single IV bolus microdose (i.e. the mass dose administered is less than 100 µg/patient).

The molecular structure of the drug substance comprises a PSMA binding motif, a peptide spacer, an ^{18}F-radiolabeled silicon fluoride acceptor moiety and a gallium chelator complex (Figure 2, Section 1).

Company Code:	rhPSMA-7.3 (^{18}F)
Chemical Name:	Gallium 2,2',2''-(10-((3*S*,7*S*,12*R*,26*R*,34*S*)-1,3,7,12,26,34-hexacarboxy-29-((4-(di-tert-buty-[^{18}F]fluorosilyl)benzamido)methyl)-5,10,17,20,28,31-hexaoxo-4,6,11,16,21,27,30-heptaazatetratriacontan-34-yl)-1,4,6,10-tetraazacyclododecane-1,4,7-triyl)triacetate
Molecular Formula:	$C_{63}H_{96}{}^{18}FGaN_{12}O_{25}Si$

8.3.2 Formulation of Control Product

Not applicable. This is a single-arm study.

8.3.3 Packaging and Labeling

rhPSMA-7.3 (^{18}F) is supplied as a sterile, aqueous solution for IV administration. The product is supplied either in a multi-dose vial sealed with a synthetic rubber closure and aluminum overseal or in a single unit dose syringe depending on the manufacturing location. The product label will be region-specific and will include the following information: batch number, product expiry date/time, total product volume (dispensed), radioactive concentration and/or total radioactivity (activity in mCi and/or MBq) and calibration date and time.

8.4 Supply of IP at the Site

Each vial or syringe is transported in a lead or tungsten shield. The quality control analysis of a sample of the drug product may be performed in parallel with transportation of the drug

product to the study site. The investigator (or nominated deputy) will receive release information for the drug product. Only product for which confirmation of release has been received shall be used. Where the product is transported as a single patient dose, the dose will be measured in a radionuclide dose calibrator before administration. Where the product is transported in its original container the volume of injection for each patient is calculated and withdrawn into a shielded syringe immediately before injection. The calculation is based on the radioactive content, the half-life of ^{18}F (109.8 mins), the reference date and time, the prescribed dose and the time of injection.

8.4.1 Dispensing

When the study site receives the dose and prior to administration, the activity in the syringe will be measured in a dose calibrator. Should the activity be less than 6.4 mCi (236 MBq), the volume required exceed 10 mL (US sites) or 6 mL (European sites) undiluted material or the IP be past the expiry date and time, the scan should not be performed. The dose can be diluted in the syringe to a maximum volume of 10 mL with 0.9% saline (as required). After administration, residual radioactivity in the injection device shall be measured using a radionuclide dose calibrator.

8.4.2 Administration Instructions

Patients will receive a dose with an administered activity of 8 mCi (296 MBq) ± 20% of rhPSMA-7.3 (^{18}F), delivered as an IV bolus injection with a 10 mL fast 0.9% sodium chloride flush, followed by PET imaging. Full details are provided in the Study Imaging Manual.

8.4.3 Storage

The shelf-life of rhPSMA-7.3 (^{18}F) injection is up to 10 hours from the end of synthesis and the product must not be used beyond this limit. rhPSMA-7.3 (^{18}F) injection should be stored at room temperature in a shielded container.

All non-radioactive containers (shielding, transport cans) must be returned to the manufacturing site. Containers that are radioactive or that contained radioactive products must be disposed of at either the study site or another designated facility, with prior approval from the Sponsor, after the study and after overall drug accountability has been completed by the Sponsor or its representative.

Waste must be disposed of according to Federal, State and local regulations for radioactive material. Imaging sites must comply with all applicable regulations.

Precautions for the safe handling of radioactive materials should be observed.

8.5 IP Accountability

An accurate and current accounting of the dispensing and return/disposal of IP for each patient will be recorded on the IP Accountability Record. The study monitor will verify this document throughout the course of the study.

8.6 Measures of Treatment Compliance

Participants will receive the rhPSMA-7.3 (^{18}F) injection under direct supervision of study personnel. Each administration volume and total radioactivity injected will be checked. The batch number and activity per administration (determined by the radioactivity in the injection

device before and after administration, with measurement date and time) will be recorded in each patient's electronic case report form (eCRF)/source document.

8.7 End of Trial

The end of the trial will be when the last blinded image evaluation has been completed and the database is locked. The end of patient participation is defined as when the last patient has completed all the study procedures and the results of the histology or confirmatory imaging are available in order to satisfy the SoT.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is summarized in Appendix 1.

Written informed consent will be obtained prior to conducting any study-related activities (see Section 18.3). Patients will provide written informed consent and be assessed for eligibility for study participation at screening (performed within 28 days before IP administration [or up to 45 days due to the COVID-19 pandemic]).

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening, with any changes in concomitant medication during the study recorded on the eCRF. The dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (full/partial date of birth/age, gender, ethnicity/race, sex, height, weight, as permitted by local regulations) will be recorded at screening. Weight will also be recorded pre-IP administration on the day of the rhPSMA-7.3 (^{18}F) injection.

9.1.3 Medical History

Relevant medical history, including history of current disease, concomitant disease record, information regarding underlying diseases will be recorded at screening. Histological confirmation of adenocarcinoma of the prostate must be provided at screening.

If not already performed within 60 days prior to screening, conventional imaging as part of routine clinical practice, which may include bone scan (^{99m}technetium-hydroxydiphosphate [^{99m}Tc-HDP], ^{99m}technetium-methyldiphosphonate [^{99m}Tc-MDP]), abdominal/pelvic CT or MRI, and chest CT as per local practice) will be performed. Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are retrievable and reviewed by the participating institution.

Note: baseline conventional imaging performed as part of routine clinical practice should be performed at least 24 hours prior to the investigational rhPSMA-7.3 (^{18}F) PET scan.

9.1.4 Physical Examination

A focused physical examination will be performed by an appropriately licensed and credentialed clinician 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). New abnormal physical exam findings must be documented on the eCRF. Any clinically significant changes (as determined by the site investigator) in physical examination findings should be reported as an AE.

9.1.5 Vital Signs

Vital signs (body temperature, blood pressure, pulse and respiration rates) will be recorded after resting for 5 minutes at screening and pre- and post-IP administration on the day of rhPSMA-7.3 (^{18}F) injection.

In addition, 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).

Any clinically significant changes in vital sign measurements (as determined by the site investigator) should be reported as an AE.

9.1.6 Diagnostic Imaging

All patients will receive an IV bolus of rhPSMA-7.3 (^{18}F) injection and undergo a PET scan as described in the Study Imaging Manual.

For each patient, the PET imaging results will be reported to the responsible physician prior to the planned RP. Within 1 to 3 days post-IP administration, the patient must return to the clinic for safety follow-up (may occur within 1 to 5 days post-IP administration due to the COVID-19 pandemic). Clinical review of imaging results and discussion of further procedures/treatments with the patient should also take place at this visit if feasible. 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 may be conducted by telephone at the clinician's discretion).

Within 45 days post-IP administration (may be extended up to 60 days due to the COVID-19 pandemic), the patient will receive treatment:

- 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.

Image Interpretation

Results of local rhPSMA-7.3 (^{18}F) PET interpretation will be used to guide biopsy/confirmatory procedures, if indicated, as well as for the physician to discuss further procedures/treatments with the patient.

For the evaluation of the co-primary endpoints, rhPSMA-7.3 (^{18}F) PET image data will be appropriately blinded, randomized, and read by 3 trained, independent central PET readers.

9.1.7 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 treatment decision may be altered, based on the responsible physician's clinical judgement. This change 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 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. pre-sacral, common iliac, peri-rectal) with left/right designations, should be recorded on the eCRF (when collected, pre-sacral lymph nodes should be placed in a separate packet from all other specimens and labeled "pre-sacral" prior to pathology assessment). Surgical procedures can be performed open, robotically, or laparoscopically. 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 anatomical origin of these pelvic LN samples will be correlated to rhPSMA-7.3 (^{18}F) PET BIE to determine the sensitivity and specificity of rhPSMA-7.3 (^{18}F) PET for detecting pelvic LN metastases.

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 2, will be deemed a TP on a patient level. A detailed description of patient level categorizations for patients who have no TP regions (left or right) is provided in Section 16.4.

Table 2: 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.

Any confirmatory procedure for suspected M1 disease should be performed prior to initiation of treatment.

9.1.8 Standard of Truth

Histology or confirmatory imaging will be used as the 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, 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 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.

9.1.9 Adverse Events

AEs will be captured for all patients throughout the study. AEs will be monitored and recorded from the time of informed consent until the last study visit. Duration (start and stop dates and times), severity/grade, outcome, treatment and relationship to IP will be recorded on the eCRF. Patients who experience an SAE (or an AE which developed within 3 days of IP administration and that persists at the final visit) will be followed until resolution or stabilization of these events is recorded.

9.2 Clinical Laboratory Measurements

Blood safety laboratory tests, including hematology (full blood count), biochemistry (urea and electrolytes, liver function tests) and coagulation, will be performed at baseline (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). Further details are provided in the Study Laboratory Manual.

Any clinically significant changes (as determined by the site investigator) in clinical laboratory measurements should be reported as an AE.

9.2.1 Hematology

Blood will be obtained and sent to a central laboratory (Eurofins) for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count determinations) for assessment of systemic evidence for infection and/or inflammation.

9.2.2 Biochemistry

Blood will be obtained and sent to central laboratory (Eurofins) for determination of serum sodium, potassium, chloride, bicarbonate, random glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, gamma-glutamyl transferase, albumin and lactate dehydrogenase.

9.2.3 Coagulation

Blood will be obtained and sent to central laboratory (Eurofins) for determination of prothrombin time, activated partial thromboplastin time and international normalized ratio.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Screening; Day -28 [Within 28 Days before IP Administration])

1. Review the study with the patient and obtain written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization (or equivalent, as required), if appropriate.
2. Assign the patient a unique screening number.
3. Review eligibility criteria and confirm patient suitability for enrollment.
4. Record demographics data.
5. Record medical history and concomitant disease record, including a history of PCa, diagnosis date and prior PCa treatments, as well as histological confirmation of adenocarcinoma of the prostate.
6. Record concomitant medications.
7. Perform and record vital signs (omit if Visit 1 and Visit 2 are combined; see Section 10.3).
8. Commence AE monitoring.
9. If not already done within 60 days prior to screening, perform and record conventional imaging as part of routine clinical practice, which may include bone scan (^{99m}Tc-HDP, ^{99m}Tc-MDP), abdominal/pelvic CT or MRI, and chest CT as per local practice. Note: Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are reviewed by the participating institution. Note: baseline conventional imaging performed as part of routine clinical practice should be performed at least 24 hours prior to the investigational rhPSMA-7.3 (^{18}F) PET scan.
10. Perform a focused physical examination.
11. Schedule patient for Visit 2 within 28 days of consent.

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

10.2 Visit 2 (Day 1; IP Administration)

1. Record any changes in concomitant medication since screening (omit if Visit 1 and Visit 2 are combined; see Section 10.3).
2. Perform and record pre-IP administration vital signs.
3. Record patient's body weight pre-IP administration.
4. Perform 12-lead ECG pre-IP administration.
5. Perform baseline blood safety laboratory tests as outlined in Section 9.2.
6. Ask about and record any AEs since screening (omit if Visit 1 and Visit 2 are combined; see Section 10.3).
7. IP administration (IV bolus rhPSMA-7.3 (^{18}F) injection).
8. PET scan as described in the Study Imaging Manual.

9. Record any AEs occurring during the scan process.
10. Perform and record post-IP administration vital signs.
11. Schedule patient for Visit 3 within 1 to 3 days post-IP administration.

    Note: pre-IP administration ECG and blood safety laboratory tests may be performed at Visit 1 if: a) not feasible at the Visit 2 imaging center and b) collected up to 48 hours before IP administration where Visit 1 and Visit 2 are not combined.

10.3 Visit 1 and Visit 2 combined (Day 1; IP Administration)

Due to the COVID-19 pandemic, for patients who already have baseline conventional imaging, Visit 1 and Visit 2 may be combined (named "Visit 1 and Visit 2 combined") if judged by the investigator to be necessary to decrease potential exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for patients.

If Visit 1 and Visit 2 are combined, please complete all the procedures listed under Visit 1 and Visit 2 (Sections 10.1 and 10.2, respectively) after obtaining written informed consent. Omit those procedures identified as not being required if combining visits.

Notes: Visit 1 and Visit 2 combined requires pre-screening via telephone contact prior to Day 1 to review the study eligibility criteria, obtain initial consent (remote consent is acceptable if permitted under local regulations and approvals), to promote study visit compliance and to ensure patient understanding of the combined study visit and planned IP administration, as well as ask about baseline conventional imaging that may already have been performed or needs to be scheduled (note the specified requirement regarding bone scans [Section 10.1]).

At sites where IP is not manufactured on-site, IP should be ordered prospectively at least 5 days in advance in accordance with the IP Supply Manual.

For sites with on-site manufacturing, the visits may be combined if mutually agreed by the Radiopharmacy and investigator even post-COVID-19 pandemic restrictions.

10.4 Visit 3 (Day 2 to 4; Follow-up Visit)

1. Perform clinical review of imaging results and discussion of further procedures/treatments with the patient.
2. Record any AEs and changes in concomitant medication since Visit 2.
3. Perform a focused physical examination.
4. Perform repeat blood safety laboratory tests as outlined in Section 9.2.
5. Perform 12-lead ECG.
6. Schedule patient to receive treatment within 45 days post-IP administration.

   Notes:

   a. in cases where the rhPSMA-7.3 (^{18}F) PET imaging results are not available at this visit, the imaging results and further procedures/treatment plan should be reviewed with the patient within 7 days after rhPSMA-7.3 (^{18}F) imaging (this may be conducted by telephone at the clinician's discretion).

   b. to ensure patient safety 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.

Patients will remain in the study until the results of the histology or confirmatory imaging are obtained in order to satisfy the SoT.

10.5 Follow-up Procedures (Within 45 Days after IP Administration])

Within 45 days post-IP administration patient should receive:

- Standard of care surgical treatment for 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.

    Note: due to the COVID-19 pandemic, follow-up procedures including standard of care surgical treatment for PCa, biopsy/surgery and/or additional imaging to confirm M1 lesion(s) may be extended up to 60 days post-IP administration.

10.6 Early Withdrawal

Patient participation in the study is entirely voluntary and patients may refuse to participate or withdraw from the trial, at any time, without prejudice to their future care.

Although patients are not obliged to give a reason(s) for premature withdrawal, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights.

All withdrawals and dropouts of enrolled patients from the study should be reported and explained on the eCRF.

Enrollment will continue until at least 75 positive cases and 225 negative cases have completed all study procedures; therefore, dropouts who fail to complete all study procedures necessary for the primary efficacy analysis, for reasons other than due to adverse reactions/AEs deemed related to IP, will be withdrawn from the study and replaced. No more than 15% of patients enrolled, who did not have M1 disease or EBRT, will be replaced (see Section 13.2).

11 IMAGING PROTOCOL

11.1 PET Scanner

A dedicated hybrid PET scanner (e.g. PET/CT) is mandatory. The selected PET scanner must be qualified by the study management team. Full details are in the Study Imaging Manual (also referred to as the Technical Operations Manual).

11.2 rhPSMA-7.3 (^{18}F) Injection Administration

As rhPSMA-7.3 (^{18}F) represents approximately 39% of rhPSMA-7 (^{18}F), clinical data obtained with rhPSMA-7 (^{18}F) are relevant to the understanding of rhPSMA-7.3 (^{18}F). These clinical data are available from a retrospective study of 1189 patients who underwent rhPSMA-7 (^{18}F) PET scans. Based on these data, it was concluded that use of moderate activities >8 to 10 mCi (297 to 370 MBq) at an early imaging time point (50 to 70 minutes) is likely preferable for rhPSMA-7 (^{18}F) in general use (see rhPSMA-7.3 (^{18}F) IB).

A venous cannula will be inserted and the patient will receive an administered activity not expected to exceed 8 mCi (296 MBq) ± 20% of rhPSMA-7.3 (^{18}F) injection diluted up to 10 mL. The administration will be injected via the cannula with arms down, as an IV bolus injection followed by 10 mL flush with normal saline solution. The participant will then be positioned supine in the scanner, with the arms above the head (if possible), and will be scanned as described in the Study Imaging Manual. The time from the end of injection of rhPSMA-7 (^{18}F) to the start of imaging will be between 50 to 70 minutes.

Full details are in the Study Imaging Manual.

11.3 rhPSMA-7.3 (^{18}F) PET Acquisition

For the PET acquisition, patients will be imaged for approximately 20 minutes. For the CT acquisition (if acquired on a PET/CT scanner), an unenhanced (no IV contrast) CT will be employed. Further details on the PET acquisition are given in the Study Imaging Manual.

11.4 Image Transfer

Following the completion of PET imaging at the study site, the scan data will be sent to the Invicro Imaging Core Lab (Invicro, LLC) using either the iPACS software or on physical media by courier. Full details are in the Study Imaging Manual.

11.5 rhPSMA-7.3 (^{18}F) Image Reads

All local and central readers will undergo training in interpretation of rhPSMA-7 (^{18}F) PET scans, and will have a training set available for reference. Primary evaluation and reporting of the PET scan will be based on the site-based local read (as per standard of care).

12 ADVERSE EVENT REPORTING AND DOCUMENTATION

12.1 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an IP, whether or not related to that IP. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current rhPSMA-7.3 (^{18}F) IB or of greater severity or frequency than expected based on the information in the rhPSMA-7.3 (^{18}F) IB.

The investigator will probe, via discussion with the patient, for the occurrence of AEs during each visit and record the information in the site's source documents. Adverse events will be recorded in the patient eCRF. Adverse events will be described by duration (start and stop dates and times), severity/grade, outcome, treatment and relationship to IP, or if unrelated, the cause.

12.1.1 Severity of Adverse Events

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5 (2017) will be used to assess and grade event severity, including laboratory abnormalities judged to be clinically significant. The severity grading is provided below (Table 3).

Table 3: CTCAE (V5) AE Severity Grading

Severity (Toxicity Grade)	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events.
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If the experience is not covered in the CTCAE criteria, the guidelines shown in Table 4 below will be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe event is not necessarily serious.

Table 4: AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The patient may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The patient is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.
Death (5)	Death related to AE

AE=adverse event.

12.1.2 Relationship of Adverse Events to IP

The relationship of an AE to IP will be assessed using the guidelines outlined in Table 5.

Table 5: Relationship of AEs to IP

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the patient's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined to have no reasonable probability to have relationship to the IP.

AE=adverse event; IP=investigational product.

12.2 Serious Adverse Events (SAEs)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the patient or require intervention to prevent one of the outcomes listed above.

12.2.1 Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to IP) on an SAE Report Form. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

All SAEs must be reported immediately (as soon as possible after the investigator becomes aware of the event but no later than 24 hours) by sending the completed SAE Report Form by email to:

For study sites in the United States: adverse.events@diag.bracco.com

For study sites in Europe: braccodsu@bracco.com

Additional and further requested information (follow-up or corrections to the original event) will be detailed on a new SAE Report Form and emailed to the same address.

12.3 Urgent Safety Measures

An urgent safety measure is an action that the Sponsor and/or investigator may take in order to protect study participants against an immediate hazard to their health or safety (e.g., it is identified that there is a significant higher incidence of death at one investigator site and as a result recruitment is suspended at that site as an urgent safety measure).

An urgent safety measure taken by the investigator must be immediately notified to the Sponsor. For all urgent safety measures, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Regulatory Agency/Competent Authority will be notified in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulations.

Initial notification may be followed by submission of a protocol amendment (see Section 18.2), notification of early termination of the trial within 15 days (if applicable) and notification of AEs and serious adverse reactions (if applicable).

12.4 Medical Monitoring

Matthew Cooney, MD (Parexel) should be contacted directly at the following number to report medical concerns or questions regarding safety.

Phone: +1 216 374 8221

13 DISCONTINUATION AND REPLACEMENT OF PATIENTS

13.1 Discontinuation of IP

Not applicable. rhPSMA-7.3 (^{18}F) is administered as a single IV injection.

13.2 Discontinuation/Withdrawal from the Study

Patients are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice.

An investigator may discontinue or withdraw a patient for any of the following reasons:

- Significant non-compliance/protocol violation requiring discontinuation from the study.
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interests of the patient.
- If the patient meets any of the exclusion criteria (either newly developed or not previously recognized) that precludes further study participation.
- Lost to follow-up (see Section 13.4).
- Sponsor request for early termination of study.

The reason for patient discontinuation or withdrawal from the study will be recorded in the patient's source documents and on the eCRF.

Enrollment will continue until at least 75 positive cases and 225 negative cases have completed all study procedures; therefore, dropouts who fail to complete all study procedures, for reasons other than due to adverse reactions/AEs deemed related to IP, will be withdrawn and replaced. No more than 15% of patients enrolled, who did not have M1 disease or EBRT, will be replaced.

Note: Any patients who withdraw/are withdrawn due to adverse reactions to rhPSMA-7.3 (^{18}F) PET or AEs due to study procedures involved in rhPSMA-7.3 (^{18}F) PET, will not be replaced.

13.3 Replacement of Patients

Patients who sign the informed consent form but do not receive the IP may be replaced. Patients who sign the informed consent form and who receive the IP, but subsequently withdraw (or are withdrawn or discontinued from the study) will also be replaced except for patients who withdraw/are withdrawn due to adverse reactions to rhPSMA-7.3 (^{18}F) PET or AEs due to study procedures involved in rhPSMA-7.3 (^{18}F) PET (see Section 13.2).

13.4 Lost to Follow-up

A participant will be considered lost to follow-up if they fail to return for the follow-up visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study assessment:

- The site will attempt to contact the participant three times to reschedule a missed visit, and will counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

13.5 Study Discontinuation or Termination

Patient enrolment may be temporarily halted or stopped if any of the following occur:

- SAE of severe acute hypersensitivity reaction attributed to the IP.
- SAE of death attributed to the IP.
- A new potential safety signal, e.g. multiple severe AEs which are new to the current rhPSMA-7.3 (^{18}F) risk profile.
- Data from other clinical trials which greatly and negatively influence the current rhPSMA-7.3 (^{18}F) benefit/risk assessment.

14 PROTOCOL DEVIATIONS

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

Any non-compliance with the protocol or GCP which is likely to effect to a significant degree the safety or physical or mental integrity of the study patients or the scientific value of the trial should be notified to the Sponsor within one working day.

Protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria (see Sections 0 and 6.2).
- Use of a prohibited concomitant medication (see Section 7.1).
- IP administration but no subsequent PET scan.

The Sponsor will determine if a protocol deviation will result in withdrawal of a patient. Major protocol deviations will be defined and documented in the Statistical Analysis Plan (SAP), which will be written and approved before database lock.

15 DATA SAFETY MONITORING

Not applicable.

16 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed SAP will be written and approved describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

16.1 Data Sets Analyzed

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 by meeting 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 with a PET scan and who got through RP and PLND.

Per Protocol Population (PP): All evaluable patients in the EAP population.

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

16.2 Accountability of Patients and Imaging

The completion status of all patients will be summarized. Further, availability of results of patient disease assessments, completion of visits, and information on image assessments performed will be reported.

16.3 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized: full/partial date of birth/age, gender, ethnicity/race, sex and height. Weight at screening and on Day 1 will be summarized.

Relevant medical history (including history of current disease, concomitant disease record, information regarding underlying diseases) at screening will be also be summarized.

16.4 Analysis of Primary Endpoint(s)

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 $\leq Se_0$ or Specificity $\leq Sp_0$ *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% confidence intervals (CIs) will also be provided. If the predefined sensitivity and specificity goals are met by the same two of three readers (both tests reach statistical significance 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 2 (Section 9.1.7) 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 6a and Table 6b depict 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 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.

Table 6: 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 True Positive (TP) region and PET is positive on True Negative (TN) 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.

Analysis of subgroups will be included in the SAP.

16.5 Analysis of Secondary and Exploratory Endpoint(s)

Secondary and exploratory endpoints will be summarized descriptively, with the exception of consistency of rhPSMA-7.3 (^{18}F) scan interpretation by blinded independent readers which will be presented utilizing Kappa statistics. Two-sided 95% CIs will be presented, where applicable.

Further details will be provided in the SAP.

16.6 Analysis of Safety Endpoint(s)

Safety data will be summarized descriptively. For AEs and SAEs, the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Terms will be used to code the reported events. The number of events, number of patients with one or more event, and percentage of patients with one or more event will be provided for all AEs, related AEs, SAEs, and all related SAEs. For blood safety laboratory tests, vital signs and 12-lead ECG results, the change from baseline results will also be summarized. Focused physical examination findings will be summarized.

16.7 Planned Interim Analysis

No formal interim analysis is planned. As described in Section 16.8, in order to have inclusion of sufficient numbers of histologically positive and negative N1 cases to power the co-primary endpoints, an interim look will be allowed to ensure a distribution of pN1 disease as would be anticipated in this patient population.

16.8 Sample Size and Randomization

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 study [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% (Klevečka, 2008; MSKCC, Nomogram; Internal Report: PSMA: TUM Data Report), 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 inclusion of 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.

17 DATA COLLECTION, RETENTION AND MONITORING

17.1 Data Collection Instruments

The investigator will prepare and maintain adequate and accurate study records and source documents designed to record all observations and other pertinent data on each of the site's study patients. Particular care should be taken to ensure all data points are recorded in source documentation, especially those which are not part of standard practice. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary.

Study personnel at each site will enter data from source documents corresponding to a patient's visit into the protocol-specific eCRF when the information corresponding to that visit is available.

Patients will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, patient number and, where possible, patient initials. Data are pseudo-anonymized as the patient can be identified and as such data remains personal data and within the scope of US, European and UK law (US HIPAA 1996; European Union [EU] General Data Protection Regulation [GDPR] 2018; UK Data Protection Act 2018).

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The investigator is responsible for all information collected on patients enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. A copy of the eCRF will remain at the investigator's site at the completion of the study.

17.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group at Parexel will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting the Food and Drug Administration (FDA) guidelines for the handling and analysis of data for clinical trials.

17.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the electronic data capture (EDC) system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

17.4 Archive of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained.

Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

The end of study electronic trial master file (eTMF) will be archived according to Blue Earth Diagnostics Standard Operating Procedures.

17.5 Availability and Retention of Investigational Records

The investigator/institution should maintain the study documents as specified in Section 8 of ICH-GCP E6 (R2) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution must make available for direct access all requested study-related records.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations (e.g. 25 years per Clinical Trial regulations 536/2014/EC). No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

17.6 Monitoring and Auditing

Monitoring visits will be conducted by representatives of the Sponsor according to ICH-GCP and relevant regulations. By signing this protocol, the investigator grants permission to the Sponsor's and designee's monitors and auditors, as well as the IRB/IEC and regulatory authorities to conduct on-site monitoring and/or auditing and provide direct access to all requested study-related records. If on-site monitoring is not permitted due to restrictions imposed to maintain social distancing due to the COVID-19 pandemic, then the investigator will work remotely with the Sponsor and designee's monitor to facilitate management of the study including review of study-related records.

17.7 Patient Confidentiality

In order to maintain patient confidentiality, only a site number, patient number and, where possible, patient initials will identify all study patients on eCRFs and other documentation submitted to the Sponsor. Additional patient confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be retained for 25 years in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet.

Clinical information will not be released without written permission of the patient, except as necessary for monitoring by Regulatory Authorities. The investigator must also comply with

all applicable privacy regulations (e.g., US HIPAA 1996; EU GDPR 2018; UK Data Protection Act 2018).

18 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

The study will be conducted in accordance with ICH-GCP and all applicable regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the relevant regulatory authority (if applicable) and IRB/IEC, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study must have completed ICH-GCP training, relevant to their role.

18.1 Institutional Review Boards and Independent Ethics Committees

Any documents that the IRB/IEC may need to fulfil its responsibilities (such as protocol, protocol amendments, IB, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC.

The IRB/IECs written unconditional approval/favorable opinion of the study, and any additional local approvals (e.g., hospital management, Administration of Radioactive Substances Advisory Committee etc.), must be obtained prior to shipment of IP to the site and prior to any patients undergoing study-specific procedures. The investigator will obtain assurance of IRB/IEC compliance with regulations.

Note: Regulatory authority approvals may also be required.

The IRB/IEC's SOPs and policies will be followed for the submission of SAEs and progress reports during the conduct of the study.

An end of study notification will be submitted as determined by each countries regulatory requirements.

18.2 Amendments

Any decision to amend the clinical trial application and/or associated documents (e.g. protocol, informed consent form, eCRF, IB etc.) will be made by the Sponsor.

The relevant regulations will be followed to determine what approvals from regulatory, IRB/IEC or local bodies are required. All required approvals will be obtained prior to implementation of the amendment, except as necessary to eliminate immediate safety hazards to patients (see Section 12.3, Urgent Safety Measures), such as amendments made due to the COVID-19 pandemic to ensure patient safety by minimizing potential exposure to SARS-CoV-2. The Contract Research Organization will notify each participating investigator site when the amendment can be implemented.

All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether a new consent needs to be obtained from patients who provided consent, using a previously approved consent form.

18.3 Patient Information and Consent

In obtaining and documenting patient informed consent, the investigator must comply with the applicable regulatory requirement(s), ICH-GCP and the ethical principles that have their origin in the Declaration of Helsinki.

Patient information and consent forms, and any other written material provided to the patient, must be approved by the relevant IRB/IEC (and by any other body as required by national regulations) prior to the start of the study at each study site.

The investigator (or an appropriately qualified designee) will explain the study to the patient or, if the patient is unable to provide informed consent, the patient's legally acceptable representative, and answer any questions that arise. A verbal explanation will be provided in terms suited to the patient's, or patient's legally acceptable representatives, comprehension, of the purposes, procedures, and potential risks of the study and the rights of research participants. Patients (and the patient's legally acceptable representative) will have the opportunity to carefully review the written information and consent form, to discuss the study with their family or surrogates, and be given ample time to think about the study and ask questions before agreeing to participate.

Patients (and the patient's legally acceptable representative) must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Prior to the patient undergoing any study-specific procedures, the written informed consent form must be signed and personally dated by the patient, or their legally acceptable representative, and by the person who conducted the informed consent discussion. The informed consent process will also be documented in the source document (including the date/time consent was obtained).

If a patient is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The patient, or patient's legally acceptable representative, may orally consent to the patient's participation, if the patient, or patient's legally acceptable representative, is not capable of providing of signing and personally dating the consent form. Once the patient, or patient's legally acceptable representative, has provided consent, the witness should also sign and personally date the consent form. By signing the consent form the witness attests that the information sheet/consent form/any other written information was accurately explained to, and apparently understood by, the patient, or patient's legally acceptable representative, and that informed consent was freely given by the patient, or patient's legally acceptable representative.

The distribution of the signed information sheet/consent form will be as required by any applicable local regulations. Otherwise a copy of the signed informed consent document will be given to the patient and the original maintained with the patient's records.

The patient, or patient's legally acceptable representative, will be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information will be documented in the source documentation. The written patient information/consent form and any other written information provided to the patients should be revised whenever important new information becomes available that may be relevant to the patient's consent. Any revised written patient information and consent form should receive IRB/IEC approval/favorable opinion prior to use. The patient, or patient's legally acceptable representative, should sign and personally date any revised consent form and receive a copy (or original, if required by applicable regulations).

18.4 Post-trial Care

rhPSMA-7.3 (^{18}F) is a single-use diagnostic agent. Therefore, no additional care for trial participants is planned once their participation in the study has ended. All patients will receive standard of care treatment in line with their medical condition as determined by their physician.

18.5 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the US HIPAA 1996 and the EU GDPR 2018.

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APPENDIX 1. STUDY SCHEDULE

	VISIT 1 Screening (Day -28)*	VISIT 2 (Day 1)*	VISIT 3 Follow-up (Day 2-4)**	Follow-up Procedures (up to Day 45)***
Informed Consent	X			
Review of Inclusion/Exclusion Criteria	X			
Demographics	X			
Medical History	X[a]			
Focused Physical Examination	X		X	
Height	X			
Weight	X	X[b]		
Vital Signs (blood pressure, pulse, respiration rate, temperature)	X	X[c]		
12-lead ECG		X[d]	X	
Conventional Imaging	X[e]			
Hematology		X[f]	X	
Biochemistry		X[f]	X	
Coagulation		X[f]	X	
Record Adverse Events[g]	X	X	X	X
Concomitant Medication Review	X	X	X	
Administration of IP		X		
Drug Accountability		X		
Post-IP PET scan		X[h]		
Imaging findings/results for rhPSMA-7.3 (^{18}F)			X	

	VISIT 1 Screening (Day -28)*	VISIT 2 (Day 1)*	VISIT 3 Follow-up (Day 2-4)**	Follow-up Procedures (up to Day 45)***
Clinical review[i]			X	
Planned treatment/change in planned treatment[j,k]				X
Biopsy/surgery and/or additional imaging[j]				X

AE=adverse event; COVID-19=Corona Virus Disease-19; CT=computed tomography; EBRT=external beam radiation therapy; ECG=electrocardiogram; eCRF=electronic case report form; ^{18}F=fluorine-18; IP=investigational medicinal product; MRI=magnetic resonance imaging; PCa=prostate cancer; PET=positron emission tomography; PLND=pelvic lymph node dissection; rhPSMA=radiohybrid prostate-specific membrane antigen; RP=radical prostatectomy; SARS-CoV-2=severe acute respiratory syndrome coronavirus; SoT=Standard of Truth; ^{99m}Tc-HDP=^{99m}technetium-hydroxydiphosphonate; ^{99m}Tc-MDP=^{99m}technetium-methyldiphosphonate.

* Due to the COVID-19 pandemic, for patients who already have baseline conventional imaging, Visit 1 and Visit 2 may be combined (named "Visit 1 and Visit 2 combined") if judged by the investigator to be necessary to decrease potential exposure to SARS-CoV-2 for patients. For all patients enrolled through the Visit 1 and Visit 2 combined pathway, pre-screening via telephone contact with the patient is required prior to Day 1 to review the study eligibility criteria, obtain initial consent (remote consent is acceptable if permitted under local regulations and approvals), to promote study visit compliance and to ensure patient understanding of the combined study visit and planned IP administration, as well as ask about baseline conventional imaging that may already have been performed or needs to be scheduled. Full written informed consent will be taken on Day 1 (Visit 1 and Visit 2 combined). For sites with on-site manufacturing, the visits may be combined if mutually agreed by the Radiopharmacy and investigator even post-COVID-19 pandemic restrictions.

Alternatively, the time from Visit 1 (initial screening) to Visit 2 (rhPSMA-7.3 (^{18}F) PET scan) may be extended up to 45 days due to the COVID-19 pandemic.

** Visit 3 Follow-up should be performed within 1 to 3 days post-IP administration. At this visit, the patient must return to the clinic for safety follow-up including ECG, blood safety laboratory tests and focused physical examination. Clinical review of imaging results and discussion of further procedures/treatments with the patient should also take place at this visit, if feasible. In cases where the rhPSMA-7.3 (^{18}F) PET imaging results are not available at this 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 may be conducted by telephone at the clinician's discretion). Patients will remain in the study until the results of the histology or confirmatory imaging are obtained in order to satisfy the SoT.

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.

*** The patient should receive treatment within 45 days (may be extended up to 60 days due to the COVID-19 pandemic) post-IP administration, with treatment decision based on rhPSMA-7.3 (^{18}F) PET imaging and conventional imaging (see k below).

[a] To include medical history and concomitant disease record, including a history of PCa, diagnosis date and prior PCa treatments, as well as histological confirmation of adenocarcinoma of the prostate.

[b] Pre-IP administration.

[c] Vital signs to be recorded pre-IP administration and post-IP administration.

[d] To be performed pre-IP administration.

[e] If not already performed within 60 days prior to screening, conventional imaging will be performed as part of routine clinical practice, which may include bone scan (^{99m}Tc-HDP, ^{99m}Tc-MDP), abdominal/pelvic CT or MRI, and chest CT as per local practice). Note: Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are retrievable and reviewed by the participating institution. Note: baseline conventional imaging performed as part of routine clinical practice should be performed at least 24 hours prior to the investigational rhPSMA-7.3 (^{18}F) PET scan.

[f] Baseline blood safety laboratory tests, including hematology (full blood count), biochemistry (urea and electrolytes, liver function tests) and coagulation to be performed pre-IP administration.

[g] AEs will be monitored and recorded from the time of informed consent until the last study visit.

[h] For full details see the Study Imaging Manual.

[i] To discuss imaging results and further procedures/treatments with the patient (all patients).

[j] 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 RP, the patient may proceed to EBRT and the rationale for this change of management will be documented on the eCRF.
Patients in whom the rhPSMA-7.3 (^{18}F) PET shows M1 metastatic disease 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 treatment decision may be altered, based on the responsible physician's clinical judgement. This change will be documented on the eCRF.

[k] Any confirmatory procedure for suspected M1 disease, as described above, should be performed prior to initiation of treatment.