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 suspected prostate cancer recurrence based on elevated PSA following prior therapy

SPOTLIGHT

BED-PSMA-302

Phase: 3

EudraCT Number: 2019-003382-18

IND Number: 141,561

Revision Chronology:

Protocol Version 1, 31-Oct-2019

Protocol Version 2, 07-Jan-2020

Protocol Version 3, 01-Jul-2020

Protocol Version 4, 23-Oct-2020

Sponsor: Blue Earth Diagnostics

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organization, and members of the Research Ethics Committee, unless authorized to do so.

Blue Earth Diagnostics

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 suspected prostate cancer recurrence based on elevated PSA following prior therapy

Protocol Number:	BED-PSMA-302
Protocol Version / Date:	Protocol Version 4, 23-Oct-2020
Investigational Product:	rhPSMA-7.3 (^{18}F)
EudraCT Number:	2019-003382-18
IND Number:	141,561
Development Phase:	3
Sponsor:	Blue Earth Diagnostics **UK Office:** The Oxford Science Park, Magdalen Centre, Robert Robinson Avenue, Oxford, OX4 4GA, United Kingdom Telephone: +44 1865 784186 **IE Office:** 6th Floor, 2 Grand Canal Square, Dublin 2, Ireland. Telephone: +353 1 761 7403
Funding Organization:	Blue Earth Diagnostics Ltd
Coordinating Investigator:	[redacted]
Medical Monitor:	[redacted]
Coordinating Center:	[redacted]

Approval:

[redacted] 28-Oct-2020

Sponsor Signature (Name and Title) Date

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

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-302

Protocol 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 suspected prostate cancer recurrence based on elevated PSA following prior therapy

Protocol Version: 4 Protocol Date: 23-Oct-2020

_____ _____

Investigator Signature Date

_____

Print Name and Title

Site # _____

Site Name _____

Address _____

_____

_____

_____

Phone Number _____

CONTENTS

CONTENTS **4**
LIST OF TABLES **7**
LIST OF FIGURES **7**
LIST OF ABBREVIATIONS **8**
PROTOCOL SYNOPSIS **10**
1. BACKGROUND **17**
1.1 Overview of Non-clinical Studies 17
1.2 Overview of Clinical Studies 18
2 STUDY RATIONALE **18**
2.1 Risk-benefit Assessment 20
2.1.1 Benefits 20
2.1.2 Risks 20
3 STUDY OBJECTIVES **22**
3.1 Primary Objective 22
3.2 Secondary Objectives 22
3.3 Exploratory Objectives 22
4 STUDY DESIGN **23**
4.1 Study Overview 23
4.2 Key Assumptions 24
5 CRITERIA FOR EVALUATION **24**
5.1 Primary Efficacy Endpoints 24
5.2 Secondary Endpoints 24
5.3 Exploratory Efficacy Endpoints 25
5.4 Safety Evaluations 25
6 PATIENT SELECTION **25**
6.1 Study Population 25
6.2 Inclusion Criteria 25
6.3 Exclusion Criteria 26
7 CONCURRENT MEDICATIONS **26**
7.1 Prohibited Medications 26
8 STUDY TREATMENTS **27**
8.1 Method of Assigning Patients to Treatment Groups 27
8.2 Blinding 27
8.3 Formulation of Test and Control Products 27
8.3.1 Formulation of Test Product 27

8.3.2 Formulation of Control Product 27
8.3.3 Packaging and Labeling 27
8.4 Supply of IP at the Site 28
8.4.1 Dispensing 28
8.4.2 Administration Instructions 28
8.4.3 Storage 28
8.5 IP Accountability 29
8.6 Measures of Treatment Compliance 29
8.7 End of Trial 29
9 STUDY PROCEDURES AND GUIDELINES 29
9.1 Clinical Assessments 29
9.1.1 Concomitant Medications 29
9.1.2 Demographics 29
9.1.3 Medical History 29
9.1.4 Vital Signs 30
9.1.5 Conventional Imaging 30
9.1.6 Confirmatory Imaging 30
9.1.7 rhPSMA-7.3 (^{18}F) PET Scan 30
9.1.8 Image Interpretation 31
9.1.9 Biopsy/Surgery 31
9.2 SoT 31
9.2.1 Step 1: Histological SoT 32
9.2.2 Imaging as Standard of Truth (Steps 2 to 4) 32
9.2.3 Post-scan Treatment Options 35
9.2.4 Clinical Management 36
9.2.5 Adverse Events 36
9.3 Clinical Laboratory Measurements 36
10 EVALUATIONS BY VISIT 36
10.1 Visit 1 (Screening; Day -28 [Within 28 Days Before IP Administration]) 36
10.2 Visit 2 (Day 1; IP Administration) 37
10.3 Visit 1 and Visit 2 Combined (Day 1; IP Administration) 37
10.4 Visit 3 (up to 7 Days Post-visit 2; Follow-up Visit) 38
10.5 Follow-up Procedures (Within 45 Days Following IP Administration) 38
10.6 Secondary Follow-up Procedures (46 to 90 Days After IP Administration) 38
10.7 Early Withdrawal 38
11 IMAGING PROTOCOL 39
11.1 PET Scanner 39
11.2 rhPSMA-7.3 (^{18}F) Injection Administration 39
11.3 rhPSMA-7.3 (^{18}F) PET Acquisition 39
11.4 Image Transfer 39
11.5 rhPSMA-7.3 (^{18}F) Image Reads 39

12 ADVERSE EVENT REPORTING AND DOCUMENTATION 40
12.1 Adverse Events 40
12.1.1 Severity of Adverse Events 40
12.1.2 Relationship of Adverse Events to IP 41
12.2 Serious Adverse Events (SAEs) 41
12.2.1 Serious Adverse Event Reporting 42
12.3 Urgent Safety Measures 42
12.4 Medical Monitoring 42
13 DISCONTINUATION AND REPLACEMENT OF PATIENTS 42
13.1 Discontinuation of IP 42
13.2 Discontinuation/Withdrawal from the Study 42
13.3 Replacement of Patients 43
13.4 Lost to Follow-up 43
13.5 Study Discontinuation or Termination 44
14 PROTOCOL DEVIATIONS 44
15 DATA SAFETY MONITORING 44
16 STATISTICAL METHODS AND CONSIDERATIONS 44
16.1 Data Sets Analyzed 44
16.2 Accountability of Patients and Imaging 45
16.3 Demographic and Baseline Characteristics 45
16.4 Analysis of Primary Endpoints 45
16.5 Analysis of Secondary and Exploratory Endpoints 45
16.6 Analysis of Safety Endpoint(s) 46
16.7 Planned Interim Analysis 46
16.8 Sample Size and Randomization 46
16.8.1 Assumptions 46
16.8.2 Sample Size 46
17 DATA COLLECTION, RETENTION AND MONITORING 46
17.1 Data Collection Instruments 46
17.2 Data Management Procedures 47
17.3 Data Quality Control and Reporting 47
17.4 Archive of Data 47
17.5 Availability and Retention of Investigational Records 48
17.6 Monitoring and Auditing 48
17.7 Patient Confidentiality 48
18 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS 49
18.1 Institutional Review Boards and Independent Ethics Committees 49

18.2 Amendments 49
18.3 Patient Information and Consent 49
18.4 Post-trial Care 51
18.5 Publications 51
19 REFERENCES 51
APPENDIX 1: STUDY SCHEDULE 53

LIST OF TABLES

Table 1: Central Reading Plan 34
Table 2: CTCAE (V5) AE Severity Grading 40
Table 3: AE Severity Grading 41
Table 4: Relationship of AEs to IP 41

LIST OF FIGURES

Figure 1: Study Schema 15
Figure 2: Structure of rhPSMA-7.3 (^{18}F) 17
Figure 3: Standard of Truth Algorithm (to be Applied for Each PET-positive Region) 35

LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
BCR	Biochemical recurrence
CDR	Correct Detection Rate
CI	Confidence interval
COVID-19	Corona Virus Disease-19
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
eCRF	Electronic case report form
EAP	Efficacy Analysis Population
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
FP	False Positive
FSP	Full Safety Population
^{68}G	Gallium-68
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIFU	High-intensity focused ultrasound
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
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NaF	Sodium fluoride
PCa	Prostate cancer
PET	Positron emission tomography
PP	Per Protocol
PPV	Positive predictive value

PSA	Prostate-specific antigen
PSAdt	PSA doubling time
PSMA	Prostate-specific membrane antigen
rh	Radiohybrid
RP	Radical prostatectomy
RT	Radiation therapy
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCID	Severe combined immunodeficiency
SOP	Standard Operating Procedure
SoT	Standard of Truth
^{99m}Tc-HDP	^{99m} Technetium-hydroxydiphosphate
^{99m}Tc-MDP	^{99m} Technetium-methyldiphosphonate
TP	True Positive
TUM	Technical University of Munich
UK	United Kingdom
US	United States

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 suspected prostate cancer recurrence based on elevated PSA following prior therapy
Protocol Number	BED-PSMA-302
Phase	3
Sponsor	Blue Earth Diagnostics
Funding Organization	Blue Earth Diagnostics Ltd
Study Design	This is a prospective, Phase 3, multi-center, single-arm, single dose study designed to evaluate the safety and diagnostic performance of radiohybrid prostate-specific membrane antigen (rhPSMA)-7.3 (fluorine-18 [^{18}F]) positron emission tomography (PET) ligand for imaging in men with suspected biochemical recurrence (BCR) of prostate cancer (PCa) based on elevated prostate-specific antigen (PSA) following prior therapy. 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. Patients with a diagnosis of BCR of PCa being worked up for re-staging and eligible for potential salvage treatment will be consented and enrolled. After enrollment (either before or after conventional imaging if not already completed), patients will receive 8 mCi (296 MBq) ± 20% rhPSMA-7.3 (^{18}F), delivered as an intravenous (IV) bolus injection, followed by PET imaging. If feasible, the patient will undergo image-guided biopsy of a PET-positive lesion(s) suspicious for recurrence of PCa within 45 days following rhPSMA-7.3 (^{18}F) PET imaging. Note: due to the COVID-19 pandemic, this may be extended up to 60 days. If necessary, confirmatory imaging (for Standard of Truth [SoT]) will be performed within 45 days following rhPSMA-7.3 (^{18}F) PET imaging or attempted biopsy and, if necessary, additional follow-up confirmatory imaging may be performed up to 90 days after rhPSMA-7.3 (^{18}F) PET. Patients may receive salvage treatment following further consultation with their physician (outside of the scope of this study). The salvage treatment prescribed will be recorded. If treatment consists of a surgical resection, the histology obtained will be correlated with rhPSMA-7.3 (^{18}F) PET imaging (and will serve as the SoT for PET-positive lesions resected). Follow-up confirmatory imaging, as part of the SoT algorithm, should not delay the patient's treatment. Notes: due to the COVID-19 pandemic, biopsy and surgical procedures performed to obtain SoT histology and initial confirmatory imaging assessments (in patients not undergoing biopsy/resection) may be delayed up to Day 60 to ensure the safety (i.e., decreased potential exposure to severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) of enrolled patients. In patients with multiple PET-positive regions, confirmation of at least one PET-positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging. Safety (adverse events [AEs] and vital signs) will be monitored during the study.

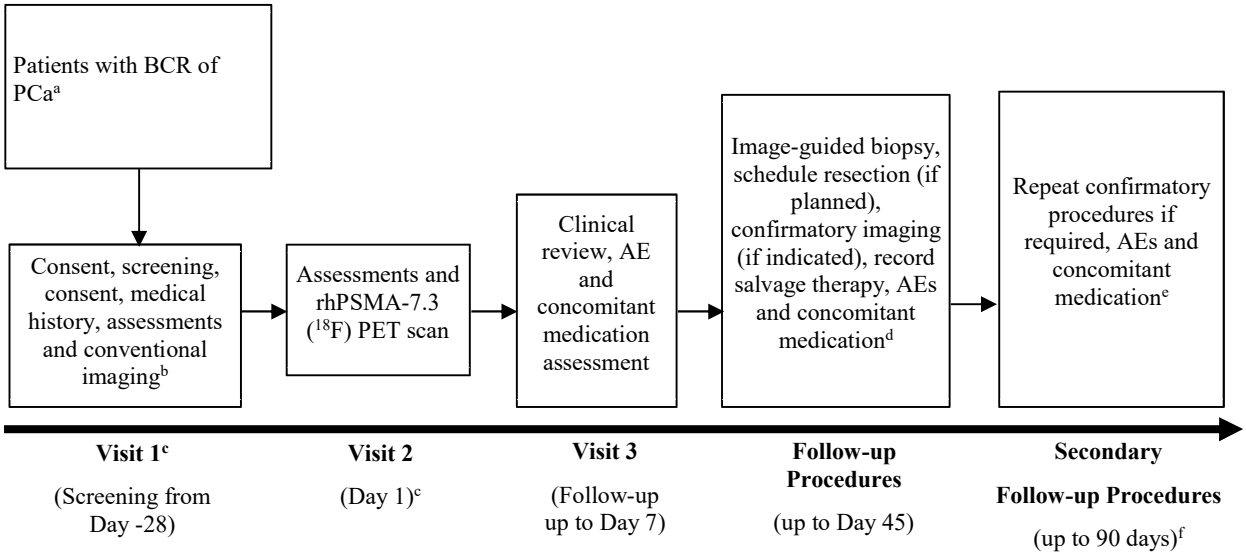
Study Rationale	The purpose of this study is to assess co-primary endpoints of patient level Correct Detection Rate (CDR) and region level positive predictive value (PPV) of rhPSMA-7.3 (^{18}F) PET for BCR of PCa using histopathology or imaging as a SoT. The CDR is defined as the percentage of all patients scanned who have at least one True Positive (TP) lesion (localized correspondence between rhPSMA-7.3 (^{18}F) PET imaging and the reference standard) regardless of any coexisting False Positive (FP) findings. When determining the region level PPV, all rhPSMA-7.3 (^{18}F) PET-positive regions will be categorized as TP or FP regions using histopathology or imaging. Regions will include the prostate bed, pelvic lymph nodes, and other (bone, extra-pelvic lymph nodes, viscera and other soft tissues); a region will be categorized as a TP region if at least one PET-positive lesion in the region is confirmed as a TP. For the primary analysis, pelvic lymph nodes will include the right and left external iliac, obturator, hypogastric (internal iliac), perirectal and presacral lymph node groups. 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. Most trials investigating diagnostic PSMA ligands have thus far focused on patients with prior negative conventional imaging. Going forward in routine clinical care, given the low sensitivities of these conventional imaging procedures, it is difficult to continue to support subjecting patients to two or three non-sensitive imaging procedures before the patient may receive a more sensitive one. rhPSMA-7.3 (^{18}F) injection is a PET ligand for the detection of PCa. rhPSMA-7.3 (^{18}F) has already been administered to patients at the Technical University of Munich (TUM). Based on the retrospectively determined high sensitivity of PSMA ligands, this study is designed to establish the diagnostic performance of rhPSMA-7.3 (^{18}F) PET irrespective of the findings of conventional imaging in order to support the use of rhPSMA-7.3 (^{18}F) as an imaging option during the initial workup of these patients.	
Primary Objective and Endpoint	Objective: To assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET for BCR of PCa using histopathology or imaging as a SoT.	Co-primary Endpoints: Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET as defined above in Study Rationale. For details of the null hypothesis, see STATISTICS: Primary Analysis Plan and Rationale for Number of Patients (below).
Secondary Objectives and Endpoints	Objectives: 1. To assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET in the subgroup of patients who have negative baseline conventional imaging.	Endpoints: 1. Patient level CDR and region level PPV in patients who have negative conventional imaging.

Secondary Objectives and Endpoints *(Cont.)*	2. To assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET separated into subgroups of patients with reference standard histopathology available and unavailable.	2. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET for recurrence in those patients with and without reference standard histopathology available.
	3. To assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET stratified by PSA level.	3. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET stratified by PSA level.
	4. To assess the CDR of rhPSMA-7.3 (^{18}F) PET on a region level.	4. CDR of rhPSMA-7.3 (^{18}F) PET in the following regions: local recurrence, pelvic lymph nodes, other.
	5. To assess the impact of rhPSMA-7.3 (^{18}F) PET imaging results on the intended clinical management of study participants using a clinician survey.	5. Percentage of patients in whom rhPSMA-7.3 (^{18}F) PET imaging results changed the intended patient management (major and other changes).
	6. To assess the inter- and intra-reader agreement of rhPSMA-7.3 (^{18}F) scan interpretation by the blinded independent readers.	6. Reader kappa statistics of rhPSMA-7.3 (^{18}F) scan interpretation by the blinded independent readers.
	7. To assess the safety of rhPSMA-7.3 (^{18}F) injection in patients.	7. Safety (AEs and vital signs) of rhPSMA-7.3 (^{18}F) injection in patients.
Exploratory Objectives and Endpoints	Objectives: 1. To assess the overall detection rate (without SoT confirmation) on a patient level and including detection rate subgroup analyses of patients: a) who have negative baseline conventional imaging, b) with reference standard histopathology available and unavailable, and also detection rate stratified by PSA level and assessed by region.	Endpoints: 1. Overall patient level detection rate (without SoT confirmation), including detection rate subgroup analyses of patients: a) who have negative baseline conventional imaging, b) with reference standard histopathology available and unavailable, and detection rate stratified by PSA level and assessed by region.
	2. To assess the patient level PPV in which a TP patient is defined as having at least one TP region, regardless of any coexisting FP regions.	2. Patient level PPV in which a TP patient is defined as having at least one TP region, regardless of any coexisting FP regions.

Exploratory Objectives and Endpoints *(Cont.)*	3. To assess the impact of rhPSMA-7.3 (^{18}F) PET on upstaging patients with BCR of PCa a) post-radical prostatectomy (RP) or b) post-radiation therapy (RT) compared to conventional imaging. 4. To assess patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET. 5. To assess patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET as a function of PSA, prior Gleason score, and PSA doubling time (PSAdt) in a) post-RP or b) post-RT patients.	3. The number of positive rhPSMA-7.3 (^{18}F) scans compared to conventional imaging in defined regions, leading to upstaging of the patient a) post-RP and b) post-RT. 4. Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET. 5. Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET as a function of PSA, prior Gleason score and PSAdt in a) post-RP and b) post-RT patients.
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: none.	
Study and Participant Duration	Study Duration: The total study duration from first site activation to data analysis is estimated to be 18 months. Participant Duration: Patients will be screened for inclusion into the study up to 28 days before rhPSMA-7.3 (^{18}F) PET imaging (up to 45 days due to the COVID-19 pandemic) and remain as a participant until histology or confirmatory imaging data has been obtained in order to satisfy the SoT assessment. The last visit will be the End of Study assessment which will take place within 45 days following administration of rhPSMA-7.3 (^{18}F) for patients requiring follow-up procedures (may be extended up to 60 days due to the COVID-19 pandemic) or for patients requiring additional confirmatory imaging procedure, up to 90 days after rhPSMA-7.3 (^{18}F) PET.	
Planned Interim Analyses	No formal hypothesis testing interim analysis will be performed. Once 60% of the planned 190 positive cases have information, the proportion of patients with a PSA <1 ng/mL will be assessed. If this proportion exceeds 60% then investigators will be informed to stop further enrolment of this cohort.	
STATISTICS: Primary Analysis Plan and Rationale for Number of Patients	The co-primary endpoints for the study are the patient level CDR and the region level PPV of rhPSMA-7.3 (^{18}F) PET. The joint hypothesis is as follows: H_0: CDR ≤36.5% or PPV ≤62.5% versus H_1: CDR >36.5% and PPV >62.5%. Both primary endpoints will be summarized as a percentage together with a two-sided exact 95% confidence interval (CI) for each reader. In addition, a one-sided exact binomial test p-value will be provided for each reader for each CDR. As this is a by-region endpoint patients may have one to three regions that may be included in the PPV assessment. The one-sided test based on clustered binary data will be used to evaluate the PPV hypothesis (Zhou,	

	Obuchowski, and McClish (2002), pg. 104) to adjust the variance estimates in the analysis based on clustering of regions within a patient. For the study to be considered a success, the p-values for both endpoints must be statistically significant for at least two out of the three readers (same readers for both CDR and PPV). In the overall study population, the detection rate of rhPSMA-7.3 (^{18}F) PET is expected to be approximately 60%, the overall PPV is estimated to be 73.5%, and the overall CDR is anticipated to be 49% (point estimates). The lower bound of the CI for the region level PPV will be set at 62.5% and the overall CDR will have a lower bound of 36.5%. The study will aim to include approximately 40% of patients with a PSA level <1 ng/mL and approximately 60% of patients with a PSA level ≥1 ng/mL. Approximately 316 patients will be enrolled in this study. For the PPV endpoint, based on a one-sided 0.025 exact binomial test and assuming a true PPV of 73.5%, a sample size of 190 positive cases provides >88% power for the evaluation of region level PPV (H_0: PPV ≤62.5%). Assuming that 60% of all scans have a positive finding, a total of approximately 316 evaluable patients would be required to obtain 190 positive rhPSMA-7.3 (^{18}F) PET cases. Note that PPV region-based analysis is expected to provide more than 88% power based upon the number of positive regions per patient being >1, even adjusting for the correlation between the regions within a patient. Thus, 316 patients are planned to be enrolled in order to get at least 190 cases with disease detected with rhPSMA-7.3 (^{18}F) and an evaluable result. For the patient level CDR endpoint, based on a one-sided 0.025 exact binomial test and assuming a true CDR of 49%, a sample size of 316 cases provides >99% power for the evaluation of CDR (H_0: CDR ≤36.5%). Hence, a sample size of at least 316 patients is adequate based on the region level PPV endpoint and is expected to provide at least 90% power for the regional PPV analysis. 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 will be replaced. No more than 15% of patients enrolled will be replaced. 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.

Figure 1: Study Schema



ADT=androgen deprivation therapy; AE=adverse event; BCR=biochemical recurrence; COVID-19=Corona Virus Disease-19; EBRT=external beam radiation therapy; ^{18}F=fluorine-18; FP=False Positive; HIFU=high-intensity focused ultrasound; IP=investigational product; PCa=prostate cancer; PET=positron emission tomography; PPV=positive predictive value; PSA=prostate-specific antigen; PSMA=prostate-specific membrane antigen; rh=radiohybrid; RP=radical prostatectomy; RRT=radical radiotherapy; RT=radiation therapy; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; TP=True Positive.

a Patients will be male and aged >18 years, with a history of localized adenocarcinoma of the prostate with prior curative intent treatment and experiencing BCR of PCa potentially eligible for salvage therapy with curative intent, following prior treatment with one or more of the following a) RP, b) RP plus adjuvant RT, c) RP plus adjuvant ADT, d) EBRT or e) focal gland therapies (e.g. brachytherapy, HIFU). Note: at least 6 weeks must have elapsed after RP; if previously taking ADT, it should have been discontinued at least 16 weeks prior to screening; in the case of focal gland therapies (e.g. HIFU) and RT, the treatment will have occurred at least 1 year prior to screening. Patients will have an elevated PSA, clinically suspicious for biochemically recurrent disease (following RP: PSA >0.2 ng/mL that increases on serial determination; following RT (e.g. RRT or brachytherapy): nadir +2 ng/mL. Patients must be willing to undergo biopsy for histological confirmation of rhPSMA-7.3 (^{18}F) PET findings, where safe and feasible.

b Collect historical conventional imaging. Schedule patient for conventional imaging (to take place following Visit 1 and up to 2 weeks after Visit 2 [Optional Visit 2(a)]) if historical conventional imaging took place greater than 90 days before Visit 1. Note: conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are reviewed by the participating institution. Note: contrast-enhanced CT/MRI and radiopharmaceutical-based baseline conventional imaging (performed as per local standard of care) should be performed at least 24 hours apart from the investigational rhPSMA-7.3 (^{18}F) PET scan.

c Due to the COVID-19 pandemic, 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 and historic 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 Obtain image-guided biopsy of PET-positive lesion(s), if feasible. If surgical resection is planned, record date and make arrangements for obtaining histology results. If biopsy is not feasible, obtain confirmatory imaging, if indicated, as per algorithm. If necessary, schedule further confirmatory imaging, up to 90 days after rhPSMA-7.3 PET imaging. Record any salvage treatment. Record any AEs and change in concomitant medication.
Note: due to the COVID-19 pandemic, biopsy and surgical procedures to obtain SoT histology and initial confirmatory imaging assessments (in patients not undergoing biopsy/resection) may be delayed up to Day 60 to ensure the safety (i.e., decreased potential exposure to SARS-CoV-2) of enrolled patients.

e Obtain a second confirmatory image if necessary. Follow-up confirmatory imaging should not delay the patient's treatment. If surgical resection has been performed, correlate with rhPSMA-7.3 (^{18}F) PET imaging. Record any salvage treatment since IP administration. Record any AEs and change in concomitant medication.

f Up to 90 days after rhPSMA-7.3 (^{18}F) PET.

Notes:

* In patients with multiple PET-positive regions, confirmation of at least one PET-positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging in order to calculate the region level PPV for the efficacy analyses.

** In patients with multiple lesions in a specific region, the presence of one TP lesion determines truth for the region regardless of any concurrent FP findings in the same region. Therefore, multiple PET-positive lesions can be evaluated in a specific region in order to confirm at least one TP.

*** Due to the COVID-19 pandemic, investigators should carefully consider the timing of confirmatory imaging procedures (when histology is not available) and are encouraged to minimize patients' potential exposure to SARS-CoV-2 by combining follow-up visits for multiple confirmatory imaging scans, when feasible.

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).

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 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; 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) 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) at the Technical University of Munich (TUM), administered under the physician's personal responsibility (exempt from a manufacturing authorization as per Section 13, Subsection 2b of the German Medicinal Products Act). In a retrospective, non-interventional review of data from patients (N=558) with known or suspected PCa who underwent a clinically indicated rhPSMA-7.3 (^{18}F) PET/computed tomography (CT) or PET/magnetic resonance imaging (MRI) scans at TUM, diagnostic performance, biodistribution and safety data for rhPSMA-7.3 (^{18}F) were analyzed (Study BED-PSMA-403). 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.

A total of 558 patients, with known or suspected PCa, underwent a clinically indicated rhPSMA-7.3 (^{18}F) PET/CT or PET/MRI scan at TUM between 30 August 2018 and 15 February 2019. Based on the retrospective chart review, rhPSMA-7.3 (^{18}F) was well-tolerated, with no safety concerns identified. A total of 285 consecutive patients with biochemical recurrence (BCR) of PCa were analyzed. Overall, 225/285 (79%) had positive findings on rhPSMA-7.3 (^{18}F) PET imaging. The detection rates were 58%, 83%, and 97% for patients with prostate-specific antigen (PSA) levels of <1 ng/mL, 1 to <2 ng/mL, and ≥2 ng/mL, respectively.

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

PCa is the most prevalent cancer in men in the developed world and the third leading cause of death (Jemal 2011). It is most commonly diagnosed in men aged 65 years and over and

diagnosis is often made following the detection of elevated PSA and/or an abnormal digital rectal examination, with confirmation of this diagnosis by prostate biopsy. PSA is used as a tumor marker and serum levels of PSA positively correlated with the risk of metastatic disease or subsequent disease recurrence or progression.

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. 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 agent.

rhPSMA-7.3 (^{18}F) injection, is a PET ligand for the detection of PCa. The rhPSMA-7.3 (^{18}F) stereoisomer has already been administered to patients at the TUM (see Section 1.2). Several hundred patients with PCa have been imaged clinically, 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).

As described in Section 1.2, the detection rate of rhPSMA-7.3 (^{18}F) varies depending on the PSA level at scanning. The findings at TUM are consistent with the recently published paper (Fendler 2019), describing the use of gallium-68 (^{68}Ga)-PSMA-11 in 635 patients with BCR irrespective of the results of other imaging. They reported an overall detection rate of 75%, but stratifying for PSA levels, the detection rates were 45%, 84%, 86%, and 97% for patients with PSA levels of <1 ng/mL, 1 to <2 ng/mL, 2 to <5 ng/mL and ≥5 ng/mL, respectively.

One of the major disadvantages of the (mostly retrospective) studies to date is the lack of confirmation of the finding on the PSMA PET scan. Although the detection rates (defined as the number of positive scans/all included patients) are reported, it is not known if every positive scan is a True Positive (TP) scan. Ideally, both the positive predictive value (PPV) and the *Correct* Detection Rate (CDR) of PET findings should be known. The CDR is defined as the percentage of all patients scanned who have at least one **TP** lesion (localized correspondence between rhPSMA-7.3 (^{18}F) PET imaging and the reference standard) regardless of any coexisting False Positive (FP) findings. Unfortunately, in the Fendler (2019) study, confirmation of the positive scans was only obtained in 217 out of 635 patients. Therefore, the PPV and CDR cannot be determined for the entire study population.

Based on data from the retrospective chart review, data from the Fendler (2019) study, and from a comprehensive review of the literature, the influence of the PSA level at the time of scanning on detection rate and diagnostic performance cannot be underestimated.

In studies in patients with a PSA level ≥1 ng/mL, detection rates can range from 64% to over 90% (Perera 2019), with an average of 85%. In this multi-center US study of rhPSMA-7.3 (^{18}F) (without the selection bias of many of the studies referenced by Perera [2019]), an estimated overall detection rate of ≥75% is reasonable for patients with a PSA level ≥1 ng/mL. Fendler (2019) reported PPVs of 92% (composite Standard of Truth [SoT]) and 84% (histopathologic SoT) in patients with median PSA levels of 3.5 and 3.9 ng/mL, respectively. It is expected, with a composite SoT including both histopathology (when available) and ^{18}F-fluciclovine PET imaging (in cases without histopathology) to achieve a PPV of approximately 80% in this subpopulation.

However, in patients with a PSA level >0.2 to <1 ng/mL, PSMA scans can show detection rates between 46% and 63% (Perera 2019), with an average of 56%. A detection rate of 57% was reported by Fendler (2019) in patients with a PSA level of 0.5 to <1 ng/mL; this fell to 38% for patients with a PSA level <0.5 ng/mL. Therefore, an estimated overall detection rate of ≥45% is reasonable for patients with a PSA level >0.2 to <1 ng/mL. Confirming that lesions seen on PSMA PET imaging are TP will be challenging in this subgroup, since these lesions may be small, prone to biopsy error, and not yet visible on other diagnostic imaging techniques. In patients with PSA levels <1 ng/mL and histopathologic data, the PPV is likely to be well below the 92% reported by Fendler (2019) for a group of patients with a median PSA level of 3.9 ng/mL. Additionally, no patients in this subgroup will have an intact prostate amenable to biopsy and we might expect only ~50% concordance between one example imaging reference standard test - ^{18}F-fluciclovine - and PSMA PET-positive patients (Calais 2019). Therefore, the PPV (using histopathology or conventional/confirmatory imaging as the SoT) is expected to be low, at approximately 65%. It is important to note that PSMA PET may be a more sensitive way of demonstrating disease in men with recurrent PCa, as compared to conventional imaging-based SoT (Perera 2016). Importantly, the overall PPV will also likely be decreased by patients with multiple PSMA PET-positive regions given histological confirmation of multiple lesions in the same patient is highly unlikely.

Most trials investigating diagnostic PSMA ligands have thus far focused on those patients with prior negative conventional imaging. Going forward in routine clinical care, given the low sensitivities of these conventional imaging procedures, it is difficult to continue to support subjecting patients to two or three non-sensitive imaging procedures before the patient may receive a more sensitive one. Based on the retrospectively determined high sensitivity of PSMA ligands (Afshar-Oromieh 2015; Eiber 2015; Afshar-Oromieh 2017), this study is designed to establish the performance of rhPSMA-7.3 (^{18}F) PET irrespective of the findings of conventional imaging in order to support the use of rhPSMA-7.3 (^{18}F) as an imaging option during the initial workup of these patients. This study will do so acknowledging the limitations of obtaining proof of true-positivity of the PSMA-positive lesions given the difficulties of obtaining histopathology in all patients and the relative insensitivity of other imaging modalities. Therefore, CDR and PPV are set at reasonable threshold levels, accounting for the limitations of the SoT and considering the significant influence of the PSA level on the scan's performance.

2.1 Risk-benefit Assessment

2.1.1 Benefits

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.

rhPSMA-7.3 (^{18}F) is currently being formally evaluated by Blue Earth Diagnostics Ltd. 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 biodistribution and internal radiation dosimetry of ^{18}F following the IV administration of rhPSMA-7.3 (^{18}F) injection have been assessed in a cohort of six healthy adult volunteers (three male and three female; aged 25 to 64 years; all White). Subjects were scanned at intervals for up to 4 hours post-injection, with radioactivity in blood, urine, and organs of interest measured at each timepoint. The mean administered dose of radioactivity was 220 MBq. ^{18}F excretion into urine was 7.7% of the administered activity at 111 minutes post-injection. The three organs or tissues with the highest mean initial uptake of ^{18}F were liver, heart content, and cortical bone. The critical organs (i.e. those with the highest absorbed dose per unit administered activity) were the adrenals (0.1835 mGy/MBq), the kidneys (0.1722 mGy/MBq) and the submandibular glands (0.1479 mGy/MBq). The mean effective dose per unit administered activity was 13.8 µSv/MBq with a 1-hour voiding interval and 14.1 µSv/MBq with a 3.5-hour voiding interval. Based on these data, an injection of 8 mCi (296 MBq) would result in a favorable radiation effective dose of less than 5 mSv.

No serious adverse events (SAEs) were reported and no adverse events (AEs) led to subject withdrawal from the study. A total of five AEs were reported in two subjects (gastroenteritis, focal liver lesion, headache, and dizziness for one subject and headache for a second subject). All events, except one case of headache, were considered unrelated to study treatment and all events, except the case of focal liver lesion, resolved or recovered.

In the current study, 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.

If rhPSMA-7.3 (^{18}F) PET shows one or more sites of recurrence and if clinically feasible, the most accessible lesions(s) will be biopsied under radiological guidance.

A CT-guided biopsy may be required in these patients; mean effective doses of between 4.3 to 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 CT or PET (see Section 9.1.6). 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 (NaF) PET 8.9 mSv (Beheshti, 2015); Axumin (^{18}F-Fluciclovine) PET 8 mSv (Axumin USPI; Axumin SmPC).

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

As described in Section 1.2, 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, including 285 patients with BCR of PCa after radical prostatectomy (RP) and radiation therapy (RT)/brachytherapy. Although 35 out of 146 patients with documents in their electronic medical records within 30 days after rhPSMA-7.3 (^{18}F) injection had AEs or SAEs, there were no reports of adverse reactions or serious adverse reactions attributed to injection of rhPSMA-7.3 (^{18}F) (Study BED-PSMA-403).

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the study is to assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET for BCR of PCa using histopathology or imaging as a SoT. The CDR is defined as the percentage of all patients scanned who have at least one TP lesion (localized correspondence between rhPSMA-7.3 (^{18}F) PET imaging and the reference standard) regardless of any coexisting FP findings. When determining the region level PPV, all rhPSMA-7.3 (^{18}F) PET-positive regions will be categorized as TP or FP regions using histopathology or imaging.

3.2 Secondary Objectives

The secondary objectives of the study are to:

1. Assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET in the subgroup of patients who have negative baseline conventional imaging.
2. Assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET separated into subgroups of patients with reference standard histopathology available and unavailable.
3. Assess the patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET stratified by PSA level.
4. Assess the CDR of rhPSMA-7.3 (^{18}F) PET on a region level.
5. Assess the impact of rhPSMA-7.3 (^{18}F) results on the intended clinical management of study participants using a clinician survey.
6. Assess the inter- and intra-reader agreement of rhPSMA-7.3 (^{18}F) scan interpretation by the blinded independent readers.
7. Assess the safety of rhPSMA-7.3 (^{18}F) injection in patients.

3.3 Exploratory Objectives

The exploratory objectives of the study are to:

1. Assess the overall detection rate (without SoT confirmation) on a patient level and including detection rate subgroup analyses of patients: a) who have negative baseline conventional imaging, b) with reference standard histopathology available and unavailable, and also detection rate stratified by PSA level and assessed by region.
2. Assess the patient level PPV in which a TP patient is defined as having at least one TP region, regardless of any coexisting FP regions.
3. Assess the impact of rhPSMA-7.3 (^{18}F) PET on upstaging patients with BCR of PCa a) post-RP or b) post-RT compared to conventional imaging.
4. Assess patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET.
5. Assess patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET as a function of PSA, prior Gleason score, and PSA doubling time (PSAdt) in a) post-RP or b) post-RT patients.

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 imaging in men with suspected BCR of PCa based on elevated PSA following prior therapy.

Given the different performance of PSMA ligands in patients with PSA levels <1 ng/mL versus ≥1 ng/mL, the patient population will be weighted to prevent overrepresentation of patients with a PSA <1 ng/mL. The proportion of patients with a PSA <1 ng/mL will be maximized at approximately 40%, consistent with the study population studied by Fendler (2019). Once 60% of the planned 190 positive cases have information, the proportion of patients with a PSA <1 ng/mL will be assessed. If this proportion exceeds 60% then investigators will be informed to stop further enrolment of this cohort (see Section 16.7).

Patients with a diagnosis of BCR of PCa being worked up for re-staging and eligible for potential salvage treatment will be consented and enrolled. 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 rhPSMA-7.3 (^{18}F) PET imaging 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. Participation in this study does not replace conventional imaging required for staging as per local guidelines/standard of care. If not already completed within 90 days before Visit 1, standard of care conventional imaging will be performed following Visit 1 and up to 2 weeks after Visit 2 (Optional Visit 2(a)). Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are reviewed by the participating institution. Patients will be asked to provide historical imaging if available and if performed as part of their PCa care and follow-up. After enrollment (either before or after conventional imaging if not already completed), patients will receive an administered activity of 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, followed by PET imaging.

Note: Due to the COVID-19 pandemic, 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.

If feasible, the patient will undergo image-guided biopsy of a PET-positive lesion(s) suspicious for recurrence of PCa within 45 days following rhPSMA-7.3 (^{18}F) PET imaging (see Section 9.1.9).

If necessary, confirmatory imaging (for SoT) will be performed within 45 days following rhPSMA-7.3 (^{18}F) PET imaging or attempted biopsy according to the algorithm in Figure 3. If necessary, additional confirmatory imaging may be performed up to 90 days after rhPSMA-7.3 (^{18}F) PET. Note: in patients with multiple PET-positive regions, confirmation of at least one PET-positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging. Patients may receive salvage treatment following further consultation with their physician (outside the scope of this study). The salvage treatment prescribed will be recorded. If treatment consists of a surgical resection, the histology obtained will be correlated with rhPSMA-7.3 (^{18}F) PET imaging. Follow-up confirmatory imaging utilized as part of the SoT assessment should not delay the patient's treatment.

Note: due to the COVID-19 pandemic, biopsy and surgical procedures performed to obtain SoT histology and initial confirmatory imaging assessments (in patients not undergoing biopsy/resection) may be delayed up to Day 60 to ensure the safety (i.e., decreased potential exposure to severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) of enrolled patients.

Safety (AEs and vital signs) will be monitored during the study.

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

4.2 Key Assumptions

Consistent with the data described in Section 2, the detection rate of rhPSMA-7.3 (^{18}F) PET in patients with a PSA level ≥1 ng/mL is expected to be at least 75%. The anticipated PPV in this population is expected to be approximately 80%. Therefore, the expected CDR in this subpopulation is (75% × 80% =) 60%.

However, in the subpopulation with a PSA level <1 ng/mL, the detection rate is expected to be approximately 45%. The PPV is expected to be lower too (approximately 65%), since it will be more difficult to obtain proof of the lesions detected (as outlined in Section 2). Therefore, the CDR in this subpopulation is estimated to be low at (45% × 65% =) 29%.

It is planned to include approximately 40% of patients with a PSA level <1 ng/mL and approximately 60% with a PSA level ≥1 ng/mL. Therefore, it is anticipated that the study will demonstrate an overall detection rate of approximately 60%, an overall PPV of at least 73.5% (taking into account multiple positive regions is anticipated in a proportion of patients), and, hence, an overall CDR of 49% (point estimates).

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoints

The co-primary endpoints for the study are the (1) patient level CDR defined as the percentage of all patients scanned who have at least one TP lesion (localized correspondence between rhPSMA-7.3 (^{18}F) PET imaging and the reference standard) regardless of any coexisting FP findings and (2) region level PPV (defined as TP/{TP+FP}) of rhPSMA-7.3 (^{18}F) PET. Histopathology (preferred method) or imaging will be utilized as the SoT (see Section 9.2). A lesion that is deemed positive for PCa based on rhPSMA-7.3 (^{18}F) PET will be assessed using the algorithm described in Figure 3.

5.2 Secondary Endpoints

The secondary endpoints for this study will be:

1. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET in the subgroup of patients who have negative baseline conventional imaging.
2. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET for recurrence in those patients with and without reference standard histopathology available.
3. Patient level CDR and region level PPV of rhPSMA-7.3 (^{18}F) PET stratified by PSA level.
4. CDR of rhPSMA-7.3 (^{18}F) PET in the following regions: local recurrence, pelvic lymph nodes, other.

5. Percentage of patients in whom rhPSMA-7.3 (^{18}F) PET imaging results changed the intended patient management (major and other changes).
6. Reader kappa statistics of rhPSMA-7.3 (^{18}F) scan interpretation by the blinded independent readers.
7. Safety (AEs and vital signs) of rhPSMA-7.3 (^{18}F) injection in patients.

5.3 Exploratory Efficacy Endpoints

The exploratory endpoints for this study will be:

1. The overall patient level detection rate (without SoT confirmation), including detection rate subgroup analyses of patients: a) who have negative baseline conventional imaging, b) with reference standard histopathology available and unavailable, and detection rate stratified by PSA level and assessed by region.
2. Patient level PPV in which a TP patient is defined as having at least one TP region, regardless of any coexisting FP regions.
3. The number of positive rhPSMA-7.3 (^{18}F) scans compared to conventional imaging in defined regions, leading to upstaging of the patient a) post-RP; b) post-RT.
4. Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET.
5. Patient and regional level detection rates of rhPSMA-7.3 (^{18}F) PET as a function of PSA, prior Gleason score and PSAdt in a) post-RP; b) post-RT patients.

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.

6 PATIENT SELECTION

6.1 Study Population

Patients with BCR of PCa who meet all of the inclusion and none of the exclusion criteria will be eligible for participation in this study.

6.2 Inclusion 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. Patient with a history of localized adenocarcinoma of the prostate with prior curative intent treatment, experiencing BCR of PCa potentially eligible for salvage therapy with curative intent, following prior treatment with one or more of the following: a) RP, b) RP plus adjuvant RT, c) RP plus adjuvant androgen deprivation therapy (ADT), d) external beam radiation therapy or e) focal gland therapies (e.g. brachytherapy, high-intensity focused ultrasound [HIFU]).

- At least 6 weeks must have elapsed after RP.
- If previously taking ADT, it should have been discontinued at least 16 weeks prior to screening.
- In the case of focal gland therapies (e.g. HIFU) and RT, the treatment will have occurred at least 1 year prior to screening.

4. An elevated PSA, clinically suspicious for biochemically recurrent disease, that meets one of the following conditions:
   - Following RP with or without adjuvant or salvage therapy: PSA ≥0.2 ng/mL followed by a subsequent confirmatory PSA value ≥0.2 ng/mL.
   - Following RT (e.g. radical radiotherapy or brachytherapy) as the primary treatment: nadir +2 ng/mL.
   - Following focal gland therapy (e.g. HIFU) as the primary treatment: nadir +2 ng/mL.
5. Patient willing to undergo biopsy for histological confirmation of rhPSMA-7.3 (^{18}F) PET findings, where safe and feasible.

6.3 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 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

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

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 targeted or systemic therapy should not occur until after definitive pathology (if feasible) is obtained satisfying the 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

The local sites will not be blinded and the patients will not be randomized to study treatment. All rhPSMA-7.3 (^{18}F) PET images from all study sites will be submitted for a randomized, blinded image evaluation.

The rhPSMA-7.3 (^{18}F) images will be randomized and read by three blinded, independent central PET readers who have received specific training on rhPSMA-7.3 (^{18}F) and are also blinded to results of conventional imaging.

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) or 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 Investigational Drug 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 imaging are available in order to satisfy the SoT.

Any treatment for PCa will be in accordance with local PCa management policy and procedures.

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, body mass index, as permitted by local regulations) will be recorded at screening. Weight will also be recorded pre-rhPSMA-7.3 (^{18}F) PET.

9.1.3 Medical History

Relevant medical history, including history of current disease, concomitant disease record, information regarding underlying diseases and family history of cancer will be recorded at

screening. A history of localized adenocarcinoma of the prostate with prior curative intent treatment must be confirmed at screening.

9.1.4 Vital Signs

Vital signs (body temperature, blood pressure, pulse and respiration rates) will be performed after resting for 5 minutes at screening and pre- and post-rhPSMA-7.3 (^{18}F) PET.

Any clinically significant changes in vital sign measurements should be reported as an AE.

9.1.5 Conventional Imaging

9.1.5.1 Baseline Conventional Imaging

Participation in this study does not replace conventional imaging required for staging as per local guidelines/standard of care. Conventional imaging may include: planar and/or single-photon emission CT bone scan (^{99m}technetium-hydroxydiphosphate [^{99m}Tc-HDP], ^{99m}technetium-methyldiphosphonate [^{99m}Tc-MDP] per institution preference), abdominal/pelvic CT or MRI, chest CT per institution preference, or PET with (^{18}F-NaF or Axumin). Conventional imaging that has been performed within 90 days prior to enrollment at non-participating institutions will be accepted provided the scans are reviewed by the participating institution.

If not already completed within 90 days before enrollment, conventional imaging will be performed at the study site, between Visit 1 and up to 2 weeks following the rhPSMA-7.3 PET scan according to site standard of care.

Note: contrast-enhanced CT/MRI and radiopharmaceutical-based baseline conventional imaging (performed as per local standard of care) should be performed at least 24 hours apart from the investigational rhPSMA-7.3 (^{18}F) PET scan.

9.1.5.2 Historical Conventional Imaging

Historical conventional imaging, acquired more than 90 days before Visit 1, if available and if performed as part of the patient's PCa staging and treatment in the prior ~24 months, can be used to establish SoT where a biopsy cannot be obtained.

Patients will be asked to provide these pre-existing images, if these were done at another institution. If done at the study site, these images will be made available by the study site.

9.1.6 Confirmatory Imaging

In cases where historical conventional imaging is not available or inconclusive for comparison to baseline imaging, rhPSMA-7.3 (^{18}F) directed (for confirmation of lesion location only) follow-up confirmatory imaging of the site(s), will be acquired at the discretion of the local investigator(s), with reference to the Study Imaging Manual. Examples of confirmatory imaging modalities include specific body region MRI (including functional or multi-parametric MRI), CT, Axumin, NaF, etc (see Sections 9.2.2.2 and 9.2.2.3).

9.1.7 rhPSMA-7.3 (^{18}F) PET Scan

After enrollment (either before or after conventional imaging; see Section 9.1.5), 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.

9.1.8 Image Interpretation

For biopsy/SoT confirmation guidance:

- Due to logistical and medical liability considerations, results of the image interpretation by local site readers must be used when patients are triaged for invasive biopsy procedures. rhPSMA-7.3 (^{18}F) PET imaging will be interpreted by on-site readers who have received specific training on rhPSMA-7.3 (^{18}F).

For determination of the primary endpoint:

- rhPSMA-7.3 (^{18}F) PET images will be blinded, randomized, and read by three trained independent central PET readers who have received specific training on rhPSMA-7.3 (^{18}F) scans and are blinded to results of conventional/confirmatory imaging.

9.1.9 Biopsy/Surgery

If rhPSMA-7.3 (^{18}F) PET shows one or more sites of recurrence, the most accessible and feasible* (as judged by the local investigator) lesion(s) will be biopsied under radiological guidance. In patients with multiple rhPSMA-7.3 PET-positive regions, attempt should be made, where safe and medically feasible, to obtain histopathology on the most accessible and feasible lesion(s) in each region (prostate bed, pelvic lymph nodes, and other [bone, extra-pelvic lymph nodes, viscera and other soft tissues]).

*Note: in addition to patient safety, assessment of feasibility may include location, but also lesion size, where a minimum size may be needed to avoid excessive sampling error on biopsy; soft tissue lesions will be preferred over bone lesions due to the higher likelihood of non-diagnostic bone biopsies (Didolkar 2013; Yang 2010).

In cases where a patient will undergo a lymph node dissection or other surgical procedure (resection of the PET-positive lesion(s)) as part of their standard of care, a biopsy prior to the surgical procedure is not required. The histology obtained following surgery will serve as the SoT. The removed surgical samples will be carefully correlated to rhPSMA-7.3 (^{18}F) PET and the conventional imaging technique(s).

In cases where a biopsy is not feasible or refused by the patient, then specific imaging may be used, to confirm positivity of the finding on rhPSMA-7.3 (^{18}F) PET (see below Steps 2 to 4; Sections 9.2.2.1, 9.2.2.2 and 9.2.2.3). Histopathology remains the preferred SoT.

9.2 SoT

One of the following will determine SoT: If a positive lesion on PET is confirmed by one of the Steps (1 to 4) listed below, the lesion will be considered TP. When determining the CDR on a patient level, a patient will be categorized as a TP if there is at least one TP lesion confirmed in one body region (prostate bed, pelvic lymph nodes, or other extra-pelvic sites [bone, viscera, lymph nodes and soft tissues]) on rhPSMA-7.3 (^{18}F) PET. For the primary analysis, pelvic lymph nodes will include the right and left external iliac, obturator, hypogastric (internal iliac), perirectal and presacral lymph node groups.

Notes:

a. In patients with multiple PET-positive regions, confirmation of at least one PET-positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging in order to calculate the region level PPV for the efficacy analyses.

b. In patients with multiple lesions in a specific region, the presence of one TP lesion determines truth for the region regardless of any concurrent FP findings in the same region.

Therefore, multiple PET-positive lesions can be evaluated in a specific region in order to confirm at least one TP.

9.2.1 Step 1: Histological SoT

Histological confirmation, whenever possible:

a) Of PET-positive lesion.

b) Of surgically removed sample.

c) Re-biopsy (in case of inconclusive histology) or biopsy of a second lesion will be allowed.

If histology is not available or determined non-diagnostic (and re-biopsy not possible) then proceed with imaging confirmation as described below (Steps 2 to 4). If biopsy histology is negative, then images acquired during the procedure will be reviewed by local readers to ensure the targeted tissue was sampled. If local readers determine the biopsy placement was correct, then the biopsy results will stand. If local readers determine the targeted tissue was missed during the biopsy procedure, then either a re-biopsy will be performed or the following steps will also be undertaken to verify rhPSMA-7.3 (^{18}F) images.

9.2.2 Imaging as Standard of Truth (Steps 2 to 4)

Imaging as SoT should include a longitudinal assessment of all available conventional and confirmatory imaging scans. Any change over time at the PET-positive site (upon review of all available imaging) suggestive of the presence of cancer is accepted as the SoT. A change suggesting the disappearance of disease at the PET-positive site following treatment will also be accepted as the SoT (objective criteria defined in the study Independent Review Charter).

9.2.2.1 Step 2: Historical and Baseline Conventional Imaging SoT

If historical conventional imaging (as defined in Section 9.1.5.2) had been acquired prior to acquisition of the baseline conventional imaging as part of the patient's PCa management, then these images can be used along with baseline to establish the SoT.

Where historical conventional imaging (e.g. CT, MRI, bone scan, PET) is available that could be relevant to confirmation of an identified rhPSMA-7.3 (^{18}F) PET-positive lesion then as many prior imaging series as practical (from approximately the last 2 years) should be made available to the central reviewers.

In cases where historical imaging and baseline conventional imaging are deemed sufficient (by local site reader) for SoT determination, then this will be acceptable, and follow-up confirmatory imaging (Steps 3 and 4) will not be needed.

9.2.2.2 Step 3: Confirmatory Imaging SoT (up to 45 Days Post-rhPSMA-7.3 (^{18}F) PET)

In cases where historical conventional imaging is not available or inconclusive for comparison to baseline imaging, rhPSMA-7.3 (^{18}F) directed (for confirmation of lesion location only) follow-up confirmatory imaging of the site(s), will be acquired. Confirmatory imaging will be acquired at the discretion of the local investigator(s), with reference to the Study Imaging Manual.

9.2.2.3 Step 4: Additional Confirmatory Imaging SoT (up to 90 Days Post-rhPSMA-7.3 (^{18}F) PET)

If in the opinion of the local investigator(s) the above imaging Steps 2 or 3 do not allow SoT verification, then a final follow-up, rhPSMA-7.3 (^{18}F) PET directed (for confirmation of lesion location only) confirmatory imaging scan can be obtained up to 90 days post rhPSMA-7.3 (^{18}F) PET.

Reading of conventional and confirmatory imaging to determine the next steps in the confirmation process will be performed locally.

Both the rhPSMA-7.3 (^{18}F) PET scans and all available conventional and confirmatory imaging scans acquired under Steps 2 to 4 above will be read centrally for the primary endpoint assessment, according to Table 1 and Figure 3 below. 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 post-RP with PLND and adjuvant pelvic RT 5 years before; PSA rising to 1.2 ng/mL prior to rhPSMA scan; PSAdt 9 months). Readers will be blinded to all other information. Further details are given in the study Independent Review Charter.

rhPSMA-7.3 (^{18}F) positive target lesions will be categorized as positive, negative or indeterminate by consensus central read of all available imaging when histological confirmation is not available. Indeterminate classifications will be categorized as False Positives for the primary analysis. Further details are given in the study Independent Review Charter.

If a positive lesion on rhPSMA-7.3 (^{18}F) PET suspicious for PCa recurrence is confirmed by SoT, the lesion will be considered a TP. For the primary efficacy analysis, a region will be categorized as a TP if there is at least one TP lesion confirmed in that body region (prostate bed, pelvic lymph nodes, or other extra-pelvic sites) on rhPSMA-7.3 (^{18}F) PET. For the primary analysis, pelvic lymph nodes will include the right and left external iliac, obturator, hypogastric (internal iliac), perirectal and presacral lymph node groups.

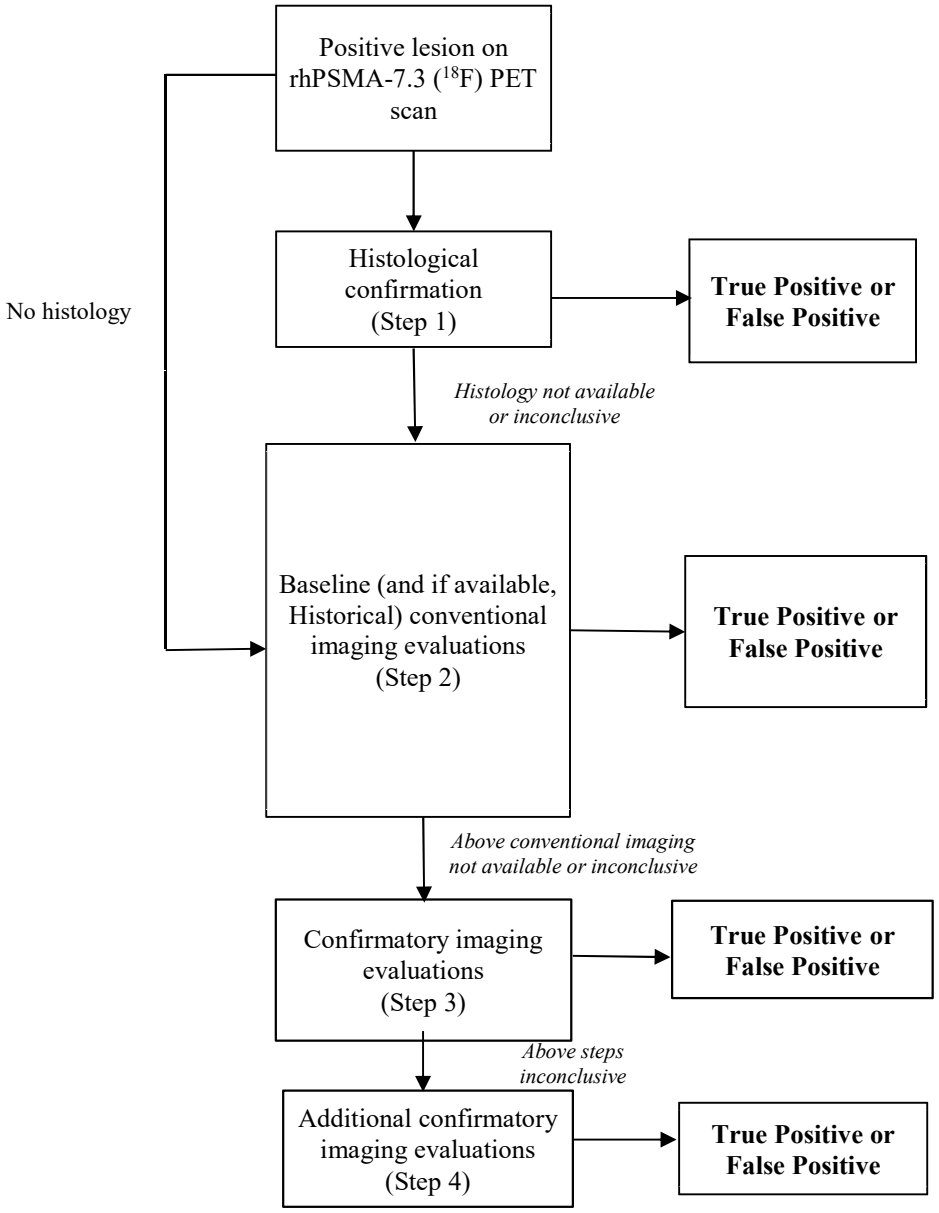
If all above SoT techniques fail to positively confirm the PET-positive lesion(s), the rhPSMA-7.3 (^{18}F) PET lesion will be deemed FP.

Table 1: Central Reading Plan

Imaging	Modalities	Image Interpretation	# readers	Read Criteria
rhPSMA-7.3	rhPSMA-7.3 PET	Blinded, independent, central reads	3	Further details are given in the Study Independent Review Charter
Conventional (Baseline and Historical) and Confirmatory Imaging as SoT	Conventional: Pelvic CT or MRI, bone scan, chest CT, Axumin. Confirmatory: Examples include specific body region MRI (including functional or multi-parametric MRI), CT, Axumin, NaF PET, etc.	rhPSMA-7.3 directed image re-reads. A brief summary of clinical information will be available to the readers (e.g. 67 year old male post-RP with PLND and adjuvant pelvic RT 5 years before; PSA rising to 1.2 ng/mL prior to rhPSMA scan; PSAdt 9 months). Readers will be blinded to all other information.	3 via consensus	Longitudinal assessment of all available conventional and confirmatory imaging scans per standard of care / society guidelines. Further details are given in the study Independent Review Charter. Specifically allowing, for example: a) sub-cm changes in LN size on CT during progression/therapy response to be indicative of cancer or b) small bone CT scleroses to be indicative of cancer

CT=computed tomography; ^{18}F=fluorine-18; LN=lymph node; MRI=magnetic resonance imaging; NaF=sodium fluoride; PET=positron emission tomography; PLND=pelvic lymph node dissection; PSA=prostate-specific antigen; PSAdt=prostate-specific antigen doubling time; rhPSMA=radiohybrid prostate-specific membrane antigen; RP=radical prostatectomy; RT=radiation therapy.

Figure 3: Standard of Truth Algorithm (to be Applied for Each PET-positive Region)



^{18}F=fluorine-18; FP=False Positive; PET=positron emission tomography; PPV=positive predictive value; rhPSMA=radiohybrid prostate-specific membrane antigen; TP=True Positive.

Notes:

a) In patients with multiple PET-positive regions, confirmation of at least one PET-positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging in order to calculate the region level PPV for the efficacy analyses.

b) In patients with multiple lesions in a specific region, the presence of one TP lesion determines truth for the region regardless of any concurrent FP findings in the same region. Therefore, multiple PET-positive lesions can be evaluated in a specific region in order to confirm at least one TP.

9.2.3 Post-scan Treatment Options

Patients may receive salvage treatment following further consultation with their physician (outside the scope of this study). The salvage treatment prescribed will be recorded. If treatment consists of a surgical resection, the histology obtained will be correlated with rhPSMA-7.3 (^{18}F) PET imaging. Follow-up confirmatory imaging should not delay the patient's treatment.

9.2.4 Clinical Management

The impact of the rhPSMA-7.3 (^{18}F) PET imaging results on patients' intended clinical management will be assessed by means of both a pre-PSMA PET scan (completed prior to rhPSMA-7.3 (^{18}F) imaging) and post-PSMA PET scan clinical utility questionnaire, in which the investigator will record any changes to the patients' intended management plan based on the rhPSMA-7.3 (^{18}F) PET scan.

9.2.5 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 rhPSMA-7.3 (^{18}F) PET and that persists at the final visit will be followed until resolution or stabilization of these events is recorded.

9.3 Clinical Laboratory Measurements

Not applicable.

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 confirmation of a history of localized adenocarcinoma of the prostate with prior curative intent treatment.
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. Schedule patient for conventional imaging (to take place following Visit 1 and up to 2 weeks after Visit 2) if historical conventional imaging took place greater than 90 days before Visit 1.

   Notes:

   a. Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are reviewed by the participating institution.

   b. Contrast-enhanced CT/MRI and radiopharmaceutical-based baseline conventional imaging (performed as per local standard of care) should be performed at least 24 hours apart from the investigational rhPSMA-7.3 (^{18}F) PET scan.

10. Schedule patient for Visit 2 within 28 days of consent.

    Note: Due to the COVID-19 pandemic, 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. Ask about and record any AEs since screening (omit if Visit 1 and Visit 2 are combined; see Section 10.3).
5. IP administration (IV bolus rhPSMA-7.3 [^{18}F] injection).
6. PET scan as described in the Study Imaging Manual.
7. Record any AEs occurring during the scan process.
8. Perform and record post-IP administration vital signs.
9. Schedule patient for Visit 3 within 7 days post-IP administration.

   Optional Visit 2(a): If not already performed, obtain baseline conventional imaging up to 2 weeks following IP administration. Any conventional imaging performed up to 90 days prior to Visit 1 and up to and including Visit 2(a) will be considered baseline conventional imaging.

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

Due to the COVID-19 pandemic, 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.

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 and historic conventional imaging that may already have been performed or needs to be scheduled (note above requirement regarding standard of care baseline conventional imaging).

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.

Optional Visit 2(a): should still be arranged if required when combining Visit 1 and Visit 2. Any conventional imaging performed up to 90 days prior to screening and up to and including 2 weeks post-combined Visit 1 and Visit 2 will be considered baseline conventional imaging.

10.4 Visit 3 (up to 7 Days Post-visit 2; Follow-up Visit)

1. Perform clinical review (AE collection and discussion of rhPSMA-7.3 [^{18}F] PET imaging results).
2. Record any AEs and changes in concomitant medication since Visit 2.

   Note: Visit 3 may be performed by an appropriately licensed and credentialed clinician and can be conducted by telephone per the site investigator's discretion.

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

1. Obtain image-guided biopsy of PET-positive lesion(s), if feasible.
2. If surgical resection is planned, record date and make arrangements for obtaining histology results.
3. Ensure available Historical and Baseline Conventional Imaging has been performed and reviewed by Site Investigator.
4. Obtain confirmatory imaging, if indicated, as per algorithm.
5. Record treatment performed for patient's PCa recurrence.
6. Record any AEs and change in concomitant medication.

   Note: due to the COVID-19 pandemic, biopsy and surgical procedures performed to obtain SoT histology and initial confirmatory imaging assessments (in patients not undergoing biopsy/resection) may be delayed up to Day 60 to ensure the safety (i.e., decreased potential exposure to SARS-CoV-2) of enrolled patients.

10.6 Secondary Follow-up Procedures (46 to 90 Days After IP Administration)

1. Obtain additional confirmatory imaging if necessary, up to 90 days after rhPSMA-7.3 PET imaging. Follow-up confirmatory imaging should not delay the patient's treatment.
2. If surgical resection has been performed, correlate pathology findings with rhPSMA-7.3 (^{18}F) PET imaging.
3. Record any salvage treatment since IP administration.
4. Record any AEs and change in concomitant medication.

   Note: due to the COVID-19 pandemic, investigators should carefully consider the timing of confirmatory imaging procedures (when histology is not available) and are encouraged to minimize patients' potential exposure to SARS-CoV-2 by combining follow-up visits for multiple confirmatory imaging scans, when feasible.

10.7 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.

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 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 (aka Technical Operations Manual).

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

A venous cannula will be inserted and the patient will receive an administered activity of 8 mCi (296 MBq) ± 20% 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-7.3 (^{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-7.3 (^{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. AEs will be recorded in the patient eCRF. AEs 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 2).

Table 2: 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 3 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 3: 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 4.

Table 4: 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 with certainty to have no 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: drugsafetyus@blueearthdx.com

For study sites in Europe: drugsafety@blueearthdx.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

Jingke Yang MD, PhD (Parexel) should be contacted directly at the following numbers to report medical concerns or questions regarding safety.

Phone: +1 978 313 3834 or +1 909 317 4177

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 316 evaluable patients 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 from the study and replaced. No more than 15% of patients enrolled will be replaced. A patient is considered to be evaluable if he complies with all study procedures, including the SoT algorithm (if the PET scan is positive) as provided in Figure 3.

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) before any follow-up procedures are obtained 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 assessments (histology, imaging) 7 days after their appointment was due and is unable to be contacted by the study site staff.

In order to decrease the extent of missing data for patients completing the rhPSMA-7.3 (^{18}F) PET but lacking SoT assessments, the following actions must be taken if a participant fails to complete 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 emails 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 6.2 and 6.3).
- 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 and with PET scan and sufficient data leading to a clear classification following the SoT algorithm.

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

All safety analyses will be performed using the FSP. The primary analysis of CDR and PPV will be based on the EAP.

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 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 and family history of cancer) at screening will be also be summarized.

16.4 Analysis of Primary Endpoints

The co-primary endpoints for the study are the patient level CDR and the region level PPV of rhPSMA-7.3 (^{18}F) PET. The joint hypothesis, based on the assumptions as outlined in Section 16.8, is as follows:

H_0: CDR $\leq$36.5% or PPV $\leq$62.5% versus H_1: CDR >36.5% and PPV >62.5%

Both primary endpoints will be summarized as a percentage together with a two-sided exact 95% confidence interval (CI) for each reader. In addition, a one-sided exact binomial test p-value will be provided for each reader for each CDR. As this is a by-region endpoint, patients may have one to three regions that may be included in the PPV assessment. The one-sided test based on clustered binary data will be used to evaluate the PPV hypothesis (Zhou, Obuchowski, and McClish, (2002), pg 104) to adjust the variance estimates in the analysis based on clustering of regions within a patient. For the study to be considered a success, the p-values for both endpoints must be statistically significant for at least two out of the three readers (same readers for both CDR and PPV).

16.5 Analysis of Secondary and Exploratory Endpoints

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 vital signs results, the change from baseline results will also be summarized.

16.7 Planned Interim Analysis

No formal hypothesis testing interim analysis will be performed.

Once 60% of the planned 190 positive cases have information, the proportion of patients with a PSA <1 ng/mL will be assessed. If this proportion exceeds 60% then investigators will be informed to stop further enrolment of this cohort.

16.8 Sample Size and Randomization

16.8.1 Assumptions

As discussed in Section 4.2, in the overall study population, the detection rate of rhPSMA-7.3 (^{18}F) PET is expected to be approximately 60%, the overall PPV is estimated to be 73.5% and the overall CDR is anticipated to be 49% (point estimates). The lower bound of the CI for the region level PPV will be set at 62.5% and the overall CDR will have a lower bound of 36.5%. The study will aim to include approximately 40% of patients with a PSA level <1 ng/mL and approximately 60% of patients with a PSA level ≥1 ng/mL.

16.8.2 Sample Size

Approximately 316 patients will be enrolled in this study. For the PPV endpoint, based on a one-sided 0.025 exact binomial test and assuming a true PPV of 73.5%, a sample size of 190 positive cases provides >88% power for the evaluation of region level PPV (H_0: PPV ≤62.5%). Assuming that 60% of all scans have a positive finding, a total of approximately 316 evaluable patients would be required to obtain 190 positive rhPSMA-7.3 (^{18}F) PET cases. Note that the PPV region-based analysis is expected to provide more than 88% power based upon the number of positive regions per patient being >1, even adjusting for the correlation between the regions within a patient. Thus, 316 patients are planned to be enrolled in order to get at least 190 cases with disease detected with rhPSMA-7.3 (^{18}F) and an evaluable result.

For the patient level CDR endpoint, based on a one-sided 0.025 exact binomial test and assuming a true CDR of 49%, a sample size of 316 cases provides >99% power for the evaluation of CDR (H_0: CDR ≤36.5%).

Hence, a sample size of at least 316 patients is adequate based on the region level PPV endpoint and is expected to provide at least 90% power for the regional PPV analysis.

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 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 United Kingdom (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 the final report), 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 Procedure (SOP; SOP-GEN-005, Management of Corporate and GxP Archive.

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.

19 REFERENCES

Afshar-Oromieh A, Avtzi E, Giesel FL, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging 2015;42(2):197-209.

Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging 2017;44(8):1258-68.

Beheshti M, Mottaghy FM, Paycha F, et al. (18)F-NaF PET/CT: EANM procedure guidelines for bone imaging. Eur J Nucl Med Mol Imaging 2015;42(11):1767-77.

Calais J, Ceci F, Eiber M, et al. ^{18}F-fluciclovine PET-CT and ^{68}Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 2019;20(9):1286-94.

Didolkar MM, Anderson ME, Hochman MG, et al. Image guided core needle biopsy of musculoskeletal lesions: are nondiagnostic results clinically useful? Clin Orthop Relat Res 2013;471(11):3601-9.

rhPSMA-7.3 (^{18}F) Investigator's Brochure. Version 2, 13 September 2019. Blue Earth Diagnostics.

Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid ^{68}Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med 2015;56(5): 668-74.

Fendler WP, Calais J, Eiber M, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: A prospective single-arm clinical trial. JAMA Oncology 2019;5(6):856-63.

Guberina N, Forsting M, Ringelstein A, et al. Radiation exposure during CT-guided biopsies: recent CT machines provide markedly lower doses. Eur Radiol 2018;28(9):3929-35.

ICH-GCP E6 (R2). Integrated addendum to ICH E6(R1): guideline for Good Clinical Practice. November 2016. Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf [Accessed 16 August 2019].

ICRP publication 56, part 2: Age-dependent doses to members of the public from intake of radionuclides. Oxford: Pergamon; 1992.

Israeli RS, Powell CT, Corr JG, et al. Expression of the prostate-specific membrane antigen. Cancer Res 1994;54(7):1807-11.

Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61(2):69-90.

Kozikowski AP, Nan F, Conti P, et al. Design of remarkably simple, yet potent urea-based inhibitors of glutamate carboxypeptidase II (NAALADase). J Med Chem 2001;44(3):298-301.

McCollough CH, Bushberg JT, Fletcher JG, et al. Answers to common questions about the use and safety of CT scans. Mayo Clin Proc 2015;90(10):1380-92.

Osborne JR, Akhtar NH, Vallabhajosula S, et al. Prostate-specific membrane antigen-based imaging. Urol Oncol 2013;31(2):144-54.

Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive ^{68}Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70(6):926-37.

Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer—Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol 2019. pii: S0302-2838(19)30095-8.

Rowe SP, Pienta KJ, Pomper MG, et al. PSMA-RADS Version 1.0: A step towards standardizing the interpretation and reporting of PSMA–targeted PET imaging studies. Eur Urol 2018; 73(4):485-87.

Silver DA, Pellicer I, Fair WR, et al. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res 1997;3(1):81-5.

Study BED-PSMA-403: Study Report. Version 1, 12 September 2019. Blue Earth Diagnostics.

Yang J, Frassica FJ, Fayad L, et al. Analysis of nondiagnostic results after image-guided needle biopsies of musculoskeletal lesions. Clin Orthop Relat Res 2010;468(11):3103-11.

Zhou XH, Obuchowski NA and McClish, DK. Statistical Methods in Diagnostic Medicine. Wiley, New York, 2002 pp 104-6.

APPENDIX 1: STUDY SCHEDULE

				FOLLOW-UP PROCEDURES	
	VISIT 1 SCREENING (DAY -28)	**VISIT 2 (Day 1)***	**VISIT 3 FOLLOW-UP (up to Day 7)****	**UP TO DAY 45*****	**UP TO 90 DAYS**
Informed Consent	**X**				
Review of Inclusion/Exclusion Criteria	**X**				
Demographics	**X**				
Medical History	**X**[a]				
Height (at screening only)	**X**				
Weight	**X**	**X**			
Collect Historical Conventional Imaging[b]	**X**				
Acquire Conventional Imaging[b], Between Visit 1 and up to 2 weeks after Visit 2	**X (IF NOT YET OBTAINED)**	**X**			
Record Adverse Events	**X**	**X**	**X**	**X**	**X**
Concomitant Medication Review	**X**	**X**	**X**	**X**	**X**
Vital Signs (blood pressure, pulse, respiration rate, temperature)	**X**	**X**[c]			
Administration of IP		**X**			
Drug Accountability		**X**			
Post-IP PET Scan		**X**[d]			
Clinical Review			**X**		
Image-guided Biopsy Report[e]				**X**	
Surgery (with histology report)				**X**	

				FOLLOW-UP PROCEDURES	
	VISIT 1 SCREENING (DAY -28)	VISIT 2 (Day 1)*	VISIT 3 FOLLOW-UP (up to Day 7)**	UP TO DAY 45***	UP TO 90 DAYS
Record Salvage Therapy[f]				X	
Follow-up Confirmatory Imaging[g]				X	
Additional Follow-up Confirmatory Imaging [h]					X

COVID-19=Corona Virus Disease-19; CT=computed tomography; ^{18}F=fluorine-18; FP=False Positive; IP=investigational product; MRI=magnetic resonance imaging; NaF=sodium fluoride; PCa=prostate cancer; PET=positron emission tomography; PPV=positive predictive value; rhPSMA=radiohybrid prostate-specific membrane antigen; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SoT=Standard of Truth; SPECT=single-photon emission computed tomography; ^{99m}Tc-HDP=^{99m}technetium-hydroxydiphosphonate; ^{99m}Tc-MDP=^{99m}technetium-methyldiphosphonate; TP=True Positive.

* Due to the COVID-19 pandemic, 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 and historic 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 7 days post-IP administration and may be performed by an appropriately licensed and credentialed clinician and can be conducted by telephone per the site investigator's discretion.

*** If feasible, the patient will undergo image-guided biopsy of a PET-positive lesion(s) suspicious for recurrence of PCa within 45 days following rhPSMA-7.3 (^{18}F) PET imaging (may be extended up to Day 60 due to the COVID-19 pandemic). If biopsy is not feasible, confirmatory imaging should be performed, if indicated, as per algorithm.

a To include medical history and concomitant disease record, including a history of PCa, diagnosis date and prior PCa treatments, as well as confirmation of a history of localized adenocarcinoma of the prostate with prior curative intent treatment.

b Conventional imaging may include: planar and/or SPECT bone scan (^{99m}Tc-HDP, ^{99m}Tc-MDP per institution preference), abdominal/pelvic CT or MRI, chest CT per institution preference, or PET with ^{18}F-NaF or Axumin. Conventional imaging that has been performed at non-participating institutions will be accepted provided the scans are reviewed by the participating institution. If not already completed up to 90 days before inclusion, conventional imaging will be performed at the study site according to site standard of care (to take place following Visit 1 and up to 2 weeks after Visit 2). Historical imaging if available and if performed as part of the patient's PCa care (including approximately the past 2 years) can be used to establish SoT where a biopsy cannot be obtained. Patients will be asked to provide these pre-existing images if these were done at another institution. If done at the study site, these images will be made available by the study site.

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

d For full details see the Study Imaging Manual.

e If feasible, patients will undergo image-guided biopsy of a PET-positive lesion(s) suspicious for recurrence of PCa within 45 days following of rhPSMA-7.3 (^{18}F) PET imaging (may be extended up to Day 60 due to the COVID-19 pandemic).

f Patients may receive salvage treatment following further consultation with their physician (outside of the scope of this study). The salvage treatment prescribed will be recorded.

g If biopsy is not feasible, rhPSMA-7.3 (^{18}F) directed (for confirmation of lesion location only) follow-up confirmatory imaging of the site(s), with one or more recommended modalities, will be acquired at the discretion of the local investigator(s). Note: this time period may be extended up to Day 60 due to the COVID-19 pandemic.

h Follow-up confirmatory imaging may be performed, as necessary, up to 90 days after rhPSMA-7.3 PET.

Notes:

- Due to the COVID-19 pandemic, investigators should carefully consider the timing of confirmatory imaging procedures (when histology is not available) and are encouraged to minimize patients' potential exposure to SARS-CoV-2 by combining follow-up visits for multiple confirmatory imaging scans, when feasible.
- In patients with multiple PET-positive regions, confirmation of at least one PET-positive lesion in each region is required either by biopsy/surgical resection or confirmatory imaging in order to calculate the region level PPV for the efficacy analyses.
- In patients with multiple lesions in a specific region, the presence of one TP lesion determines truth for the region regardless of any concurrent FP findings in the same region. Therefore, multiple PET-positive lesions can be evaluated in a specific region in order to confirm at least one TP.