CLINICAL STUDY PROTOCOL

A phase 1, open-label study to assess safety, biodistribution, and internal radiation dosimetry of ^{18}F-rhPSMA-7.3 injection in healthy volunteers, and to assess safety and investigate the imaging characteristics in subjects with prostate cancer

Study Code:	BED-PSMA-101 (Sponsor), C632 (CRST)
EudraCT No:	2018-004703-39
Phase:	I
Sponsor:	Blue Earth Diagnostics Ireland Ltd.
Principal Investigator:	[redacted]
Protocol Version:	3.0
Protocol Date:	25 October 2019

The study will be conducted in accordance with GCP.

SIGNATURES

Principal Investigator: _____ Date: _____/_____/_____

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Biostatistician: _____ Date: _____/_____/_____

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Representative of the Sponsor _____ Date: _____/_____/_____

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SYNOPSIS

Title: A phase 1, open-label study to assess safety, biodistribution, and internal radiation dosimetry of ^{18}F-rhPSMA-7.3 injection in healthy volunteers, and to assess safety and investigate the imaging characteristics in subjects with prostate cancer
Sponsor: Blue Earth Diagnostics Ireland Ltd.
Funding organisation: Blue Earth Diagnostics Ltd.
Number of sites: 1
Background and Rationale: The investigational medicinal product (IMP) of this clinical trial, ^{18}F-rhPSMA-7.3 injection, is a promising PET ligand for the detection of prostate cancer (PCa). The ^{18}F-rhPSMA-7 isomer mixture and the ^{18}F-rhPSMA-7.3 stereoisomer have already been administered to humans under Section 13, Subsection 2b of the German *Medicinal Products Act*. Therefore, several hundred patients with PCa have been imaged clinically, which has helped to design the current study. PCa is the most prevalent cancer of men and the third leading cause of death in industrialized countries. PCa is most commonly diagnosed in men aged >65 years. In its early stages it is largely asymptomatic and tumours are detected by identification of increased levels of prostate specific antigen (PSA) in peripheral blood. If detected early and when the disease is organ confined, the 5-year survival rate is approaching 100 %. However, increased PSA concentrations are also detected in benign conditions and for this reason additional testing is required to confirm the presence of cancer. Elevated PSA levels with no other explanation will often trigger a transrectal ultrasound-guided biopsy, which is an uncomfortable and invasive procedure. As the false positive rate of PSA screening is high, many men without PCa are referred for biopsy following PSA screening. The biopsy procedure, which is often not targeted based on imaging, may fail to detect significant cancerous foci; thus, treatment may be delayed to the detriment of the patient. Recently, multi-parametric magnetic resonance imaging (mpMRI) has gained diagnostic relevance and provided a non-invasive aid to help guide biopsy strategy. The recently published EAU-ESTRO-SIOG Guidelines on PCa recommend mpMRI in patients with negative biopsy when other test results are suspicious. However, mpMRI has limitations which include false negative rates of at least 10 % for intraprostatic lesions and poor performance for detection of small pelvic lymph node metastases. In addition, the natural history of PCa remains unclear, and distinguishing men who have an indolent cancer from those with a more aggressive cancer remains a clinical and research priority. These diagnostic challenges drive the demand for individualised staging of PCa that is both sensitive and specific. Accurate staging of newly diagnosed PCa aids the selection of an appropriate treatment strategy. Pelvic lymph node dissection at the time of radical prostatectomy can be used to clear lymph node metastases, and increasing evidence is available to support the use of PSMA PET as a decision-making aid for whether or not to perform this more extensive surgery. Similarly, the diagnosis of metastatic disease that lies outside of the field of surgery or

radiotherapy allows patients and clinicians to make more informed decisions about appropriate treatment, including potential metastasis-directed therapy.

PSMA (prostate-specific membrane antigen) is a 100 kD transmembrane glycoprotein that is overexpressed in nearly all prostate cancers, and less ubiquitously also in some other cancers such as breast cancer. Peptidomimetic glu-ureido-based PSMA inhibitors were initially described in 2001 (Kozikowski *et al.,* 2001), and bind to a carboxypeptidase active site in the extracellular domain of PSMA. In the last 5 years, many centres around the world have imaged PCa patients using PSMA-targeted PET tracers. Whilst initial results have demonstrated very promising diagnostic performance, no PSMA-targeted PET imaging agent has so far been licensed or approved, and availability is restricted to use under physicians' own responsibility and research protocols. Increasingly, the limited production capacity of the radiometal ^{68}Ga represents a practical disadvantage when considering the high patient numbers that need to be imaged in this common disease. To overcome this, ^{18}F labelled PSMA ligands have also been developed. This phase 1 study aims to evaluate the safety, biodistribution, optimal administered radioactivity and imaging time post administration for PCa lesion visualisation of an ^{18}F labelled radiohybrid (rh) PSMA ligand.

Study design:
This is a phase 1, open-label study to assess the safety, biodistribution, and internal radiation dosimetry of ^{18}F-rhPSMA-7.3 injection in healthy volunteers, to assess its safety in patient volunteers with PCa and to obtain data to optimise the imaging protocol for future studies in subjects with PCa.

Primary objective:
To assess the safety of a single administration of ^{18}F-rhPSMA-7.3 in healthy subjects and subjects with PCa.

Secondary Objectives:

1. To determine the biodistribution of ^{18}F following intravenous (i.v.) administration of ^{18}F-rhPSMA-7.3 and hence calculate the internal radiation dosimetry and the effective dose (ED) in healthy volunteers.
2. To explore the optimisation of PET imaging with ^{18}F-rhPSMA-7.3 injection in visualizing tumours in subjects with biopsy-proven PCa.
3. To perform kinetic modelling on the distribution of ^{18}F-rhPSMA-7.3 in subjects with PCa.
4. To use the kinetic modelling data to optimise the imaging protocol for future studies in subjects with PCa.
5. To determine the *in vivo* stability of ^{18}F-rhPSMA-7.3 injection by determining proportion of radioactive parent compound present over time.

Number of subjects:
6 evaluable healthy volunteer subjects (3 males and 3 females) followed by 9 evaluable patients (3 in each patient cohort) with PCa at a single centre.

Subject selection criteria:

Healthy Volunteers (3 males, 3 females)

INCLUSION CRITERIA (Healthy Volunteers)

1. The subject is between 21 and 65 years old.
2. The subject is willing to abstain from sexual intercourse for 24 hours after IMP administration.
3. The male subject is willing to practice effective contraception for 3 months after IMP administration.

4. The female subject is post-menopausal or surgically sterile.
5. The subject is able and willing to provide signed, dated and timed informed consent to comply with study procedures, before any study-related procedure is performed.
6. The subject has normal or clinically acceptable medical history, physical examination, and vital signs findings during the screening period (up to 21 days before administration of study drug) as determined by the investigator.
7. The subject's ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits, they are considered to be clinically insignificant, as determined by the investigator.
8. The subject has negative test results for drugs of abuse and alcohol at screening and on the day of IMP administration/PET imaging.
9. The subject's body mass index is <30 kg/m^2 and body weight is <90 kg.

EXCLUSION CRITERIA (Healthy Volunteers)

1. The subject has been previously included in this study and has received any dose of the study medication.
2. The subject has received, or is scheduled to receive, another IMP from 3 months before to 1 week after administration of ^{18}F-rhPSMA-7.3.
3. The subject has received ionising radiation exposure from clinical trials or medical examinations or treatment (other than plain radiographs of the chest or bones, or comparable) in the last 12 months.
4. The subject is undergoing monitoring of occupational ionising radiation exposure.
5. The subject suffers from claustrophobia.
6. The subject has bilateral hip prostheses.
7. The subject has tested positive for hepatitis B, hepatitis C, or human immunodeficiency virus.
8. The subject has a history of alcohol or drug abuse within the previous 12 months, or is a habitual user of excessive amounts of alcohol (>21 units per week).

Patients with Prostate Cancer

INCLUSION CRITERIA **(All Cohorts)**

1. The subject is a male and is 18-80 years old.
2. The subject has histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
3. The subject is willing to abstain from sexual intercourse for 24 hours after IMP administration and to practice effective contraception for 3 months after IMP administration.
4. The subject is able and willing to provide signed, dated and timed informed consent to comply with study procedures, before any study-related procedure is performed.
5. The subject has clinically acceptable medical history, physical examination, and vital signs findings during the screening period, as determined by the investigator (up to 21 days before administration of study drug), apart from findings related to PCa.
6. The subject's ECG and clinical laboratory tests are within normal limits, apart from findings related to PCa, or if any are outside of normal limits, the out-of-range values are considered to be not clinically significant as determined by the investigator.

7. Eastern Cooperative Oncology Group [ECOG] performance status 0-2 (Appendix 2).

Cohort A specific inclusion criteria – High risk primary PCa

8. Unfavourable intermediate-risk or high-risk PCa as defined by NCCN Guidelines Version 2.2019 (clinical stage ≥T2b or PSA >10 ng/mL or Gleason score ≥ 4 + 3 = 7).
9. Scheduled for radical prostatectomy with or without pelvic lymph node dissection.

Cohort B specific inclusion criteria - Hormone sensitive metastatic PCa

10. Castration naïve metastatic PCa with a known number of metastases or a high likelihood of lymph node metastases and/or bone metastases.
11. Either clearly demonstrated disease by site standard of care imaging performed as part of the subject's routine clinical work-up within 12 weeks before enrolment or biochemical recurrence with a PSA < 15 ng/mL.

Cohort C specific inclusion criteria – Castration resistant metastatic disease

12. A quantifiable number or a high likelihood of metastases documented by standard of care imaging performed as part of the subject's routine clinical work-up within 12 weeks before enrolment or by biochemical progression (see 14a).
13. Ongoing androgen deprivation with luteinizing hormone-releasing hormone (LHRH) agonist/antagonist therapy or bilateral orchiectomy.
14. Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;
    a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50 % increases over the nadir, and a PSA > 2 ng/mL or,
    b. Radiological progression: The appearance of new lesions (either two or more new bone lesions on bone scan or soft tissue lesion(s) progression using RECIST (Response Evaluation Criteria in Solid Tumours)).

EXCLUSION CRITERIA **(All patient Cohorts)**

1. A biopsy has been obtained from the prostate within the 28 days before enrolment.
2. Patients with extensive metastatic disease (more than 20 lesions).
3. Patients with a second primary cancer or any other underlying disease which might confound interpretation of the study results.
4. The subject has had any major surgery within 2 months prior to screening.
5. The subject has bilateral hip prostheses.
6. The subject has received, or is scheduled to receive, ^{68}Ga-PSMA-11 or ^{18}F-PSMA-1007 from 1 month before to 1 week after administration of ^{18}F-rhPSMA-7.3, or any other IMP from 3 months before to 1 week after administration of ^{18}F-rhPSMA-7.3.
7. The subject has a history of alcohol or drug abuse within the previous 12 months, based on a review of medical records or other available evidence.
8. The subject has known hypersensitivity to ^{18}F-rhPSMA-7.3 injection or any of its constituents.
9. Subjects administered any high energy (>300 keV) gamma-emitting radioisotope within five physical half-lives, or any intravenous iodinated contrast medium within 24 hours, or any high density oral contrast medium (oral water contrast is acceptable) within 5 days prior to study drug administration.

10. Subjects who have recently received an x-ray contrast agent (<24 hr for i.v. agents and <5 days for oral agents).
11. Subjects with a history of claustrophobia or panic attacks when in confined spaces.

Cohort A and B specific exclusion criteria

12. The subject is being treated or has been treated for PCa with chemotherapy or radiation therapy.
13. Patients currently receiving or with a prior history of hormonal treatment/androgen deprivation therapy including bilateral orchiectomy.

Cohort C specific exclusion criteria

14. Radiation therapy for treatment of any metastatic lesions in the field of view of the dynamic images.

Test product, administered activity and route of administration:
^{18}F-rhPSMA-7.3 Injection. Approximately 225 MBq (±10 %) for healthy volunteers, single i.v. injection (the total radiation effective dose will not exceed 10 mSv).

For subjects with PCa, the administered radioactive dose will be based upon the results of the preliminary dosimetry analysis on data from the healthy volunteer subjects. The total radiation effective dose will be 9.2 mSv); 300 MBq (±10 %) will be injected.

The total maximum dose for both healthy volunteers and patients will be less than 100 µg.

Control product, dose and route of administration:
Not applicable.

Trial design, duration of subject participation and duration of study:
A phase 1, open label, single administration, healthy volunteer and patient study for a PET imaging agent.

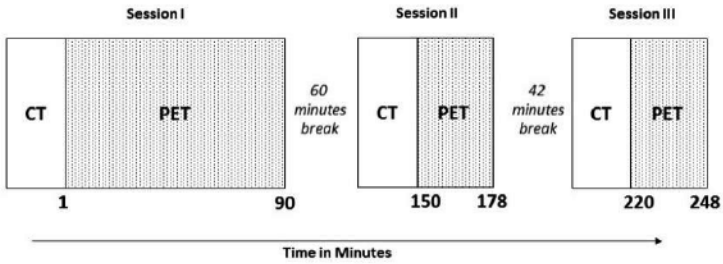
Each subject will receive a single administration of ^{18}F-rhPSMA-7.3 by i.v. injection which will be immediately followed by a PET-CT scan.

Standard of Truth (Cohort A only):
Histopathological diagnosis in patients undergoing radical prostatectomy. PSMA immunohistochemistry will be employed for exploratory analysis of Cohort A prostate specimens removed at surgery.

Duration of Subject participation:
Up to 52 days (screening period of up to 21 days, IMP administration visit, 24-hour follow-up visit and 30-day follow-up by telephone; additional visits will be scheduled as needed in case of AEs).

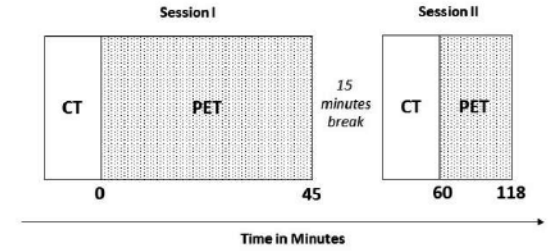
Image Acquisition

Healthy Volunteers



The healthy volunteers will undergo 3 CT attenuation-correction scans, each followed by whole-body (WB) PET acquisitions; the PET acquisitions will be obtained at scheduled time points up to 4 hours post injection (p.i.) for biodistribution and radiation dosimetry assessments.

Subjects with Prostate Cancer



The subjects with PCa will undergo two CT attenuation-correction scans and dynamic PET imaging of the pelvic region (Cohort A; BCR patients in Cohort B; patients with biochemical progression in Cohort C) or the body region(s) with one or more metastases defined as representative target lesions (metastatic patients in Cohort B and radiologically progressive patients in Cohort C) for 45 min, then 15 min break, and then two base of skull to proximal-thigh acquisitions up to 118 mins p.i.

Efficacy, Pharmacokinetic and Safety Variables:

Efficacy:

- Standardised uptake values (SUV) (e.g. SUV_{max}, SUV_{mean}, SUVR)
- Uptake irreversibility/reversibility
- Lesion detectability: comparison of SUV in detected lesion(s) against pathology grading.

Pharmacokinetics:

- Time-activity curves.
- ^{18}F radioactivity concentration assays in whole blood and plasma.
- % radioactive parent compound present over time, and proportions of possible radioactive metabolites, if found in measurable amounts in the radio-HPLC analysis.
- Radioactivity in urine.

Safety:

- AEs
- Clinical laboratory parameters (serum biochemistry including liver function tests, haematology, coagulation/clotting and urinalysis)
- Vital signs
- ECG (Electrocardiography)
- Physical examination findings
- Injection site monitoring.

Statistical Methods and Planned Analysis:

Healthy Volunteer Evaluability Criteria:

A healthy volunteer is considered as evaluable for efficacy when he/she completes scanning sessions I, II and III, and collection of venous blood and urine analysis (as described in the Study Imaging Manual) to be able to undertake a calculation of the subject's internal radiation dosimetry. As it is important that the study has the required number of evaluable healthy volunteers, these evaluability criteria will be applied, and if the healthy volunteer is not evaluable, an additional subject may be included in the study to substitute for the non-evaluable subject.

Patient Evaluability Criteria:

A patient is considered as evaluable for efficacy when he completes scanning sessions I and II and collection of venous blood and urine analysis (as described in the Study Imaging Manual) to be able to perform kinetic modelling; has at least one positive lesion on the ^{18}F-rhPSMA-7.3 scan, and for cohort A only: undergoes radical prostatectomy within 30 days of the ^{18}F-rhPSMA-7.3 scan. As it is important that each cohort has the required number of evaluable patients, these evaluability criteria will be applied and if the patient is not evaluable, an additional subject may be included in the study to substitute for the non-evaluable subject.

Efficacy Analysis:

In subjects with PCa, the lesion(s) detected on the PET images will be visually evaluated by the on-site investigator. Analysis, using SUV, will be used to compare lesions seen on the PET images with lesions from histopathology results, where available. This assessment of which lesion detected on the PET images matches the lesion for which histopathology results are available will be made by the on-site investigator. As far as possible, exploratory comparisons will be made regarding:

- Gleason Scores and degree of uptake of ^{18}F-rhPSMA-7.3 in primary prostate lesions
- Historical Gleason Score, PSA, PSA kinetics or other biomarkers and degree of uptake of ^{18}F-rhPSMA-7.3 in metastatic lesions.

Concentration and Pharmacokinetic Data:

An analysis of the % of radioactive parent compound present in blood samples collected over time will be performed. Other endpoints will be presented by descriptive statistics.

Radiation Dosimetry Data:

Quantitative measurements of ^{18}F radioactivity in volumes of interest (VOIs) from whole-body healthy volunteer images over target organs will be made at several time points p.i. Time activity curves will be generated and integrated to calculate the cumulated radioactivity in each organ. OLINDA/EXM (or similar software) provides a means of calculating the radiation absorbed doses associated with the internal distribution of a radioactive substance using the Medical Internal Radiation Dose (MIRD) schema and requires, as input, the normalised cumulated activities (also known as residence times) for source organs, tissues and contents. The normalised cumulated activity is the cumulated activity per unit administered activity. The cumulated activities are then used with the OLINDA/EXM software to calculate the ensemble of organ-absorbed doses to the MIRD target organs in an adult phantom from which the effective dose can be evaluated. A dynamic urinary bladder model is used and the internal radiation dosimetry is calculated for 1-hour and 3.5-hour urinary bladder voiding intervals. The effects of the

urinary bladder voiding interval upon the urinary bladder wall dose and the effective dose will also be evaluated. Descriptive statistics of absorbed doses to target organs and tissues specified in the MIRD schema will be tabulated.

Safety Analyses:
The number and percent of subjects with one or more AEs will be summarised for each group of subjects. Changes in serum biochemistry, haematology, coagulation, urinalysis, vital signs, ECG, injection site status, and physical examination findings will be summarised.

Primary Endpoints:

1. Safety is the primary endpoint of the study and it will be assessed from data on the occurrence of one or more treatment-emergent AEs from the time of i.v. administration of ^{18}F-rhPSMA-7.3 throughout the study period, and changes in serum biochemistry, haematology, coagulation, urinalysis, vital signs, ECG, injection site status, and physical examination findings.

Secondary Endpoints:

1. Dosimetry estimates and cumulated radioactivity exposure by source region and the entire body including analysis of radioactivity in whole blood, plasma and excreted urine in healthy volunteers.
2. Uptake of ^{18}F-rhPSMA-7.3 visualised by PET imaging compared to histopathology in subjects with PCa, if histopathology information is available.
3. Use of kinetic modelling data to investigate distribution of ^{18}F-rhPSMA-7.3 in subjects with PCa.
4. Use of kinetic modelling data to optimise the imaging protocol for future studies in subjects with PCa, by estimating *in vivo* ^{18}F radioactivity in PCa lesions.
5. Analysis of % of radioactive parent compound present in plasma over time in healthy volunteers and subjects with PCa. Relative proportions of radioactive tracer metabolites will be monitored, as well, if detected in significant amounts in the radio-HPLC analysis.

Safety Evaluations:
Safety will be assessed from data on the occurrence of adverse events (AEs) and changes in clinical laboratory tests, vital signs, injection-site status, and physical examination findings from the time of administration of ^{18}F-rhPSMA-7.3 injection throughout the study period.

Rationale for Number of Subjects:
Sufficient numbers of evaluable subjects have been planned to be included in the study in order to fulfil the study objectives, at the same time limiting the groups of healthy volunteer and patient volunteer subjects to the smallest informative numbers.

LIST OF ABBREVIATIONS USED IN THE PROTOCOL

ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the concentration by time curve
BMI	Body mass index
BP	Blood pressure
CA	Competent authority
Cmax	Maximum observed consentration
CT	Computed tomography
DM	Data management
EC	Ethics committee
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(electronic) Case report form
ED	Effective dose
^{18}F	Isotope of fluorine
GCP	Good Clinical Practise
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practise
GMP	Good Manufacturing Practise
HBsAg	Hepatitis B virus surface antigens
HCVAg	Hepatitis C virus antibodies
HIVAgAb	Human immunodefiency virus antibodies
HR	Heart rate
IC	Informed consent
ICF	Informed consent form
ISF	Investigator's study file
IMP	Investigational medicinal product
i.v.	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities

MBq	MegaBecquerel
mpMRI	Multi-parametric MRI
mSv	MilliSievert
OTC	Over-the-counter
p.i.	Post injection
PCa	Prostate cancer
PET	Positron Emission Tomography
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
µg	Microgram
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SUV	Stardardized Uptake Value
SUVR	Standardized Uptake Value Ratio
$t_{½}$	Elimination half-life
TMF	Trial Master File
TPC	Turku PET Centre
TRUS	Transrectal ultrasound

1 INTRODUCTION

1.1 Background

Prostate cancer

Prostate cancer (PCa) is one of the most common cancers in males. The incidence rates vary significantly in different parts of the world. In industrialised countries, PCa is the most prevalent malignancy of men and the third leading cause of cancer death (Jemal *et al*., 2011). Higher incidence and prevalence in affluent countries are probably related to the wider use of prostate-specific antigen (PSA) testing in screening for PCa (Kvåle *et al.,* 2007).

Detection of PCa is challenging, since it is often asymptomatic in its early stages, and locally advanced cancer often causes similar lower urinary tract symptoms as benign prostatic hyperplasia (Hamilton *et al*., 2004). Elevated circulating PSA levels may be caused by PCa but also, for example, benign prostatic hyperplasia and prostate inflammation can cause high circulating PSA levels (Carver *et al*., 2003, Malati *et al*., 2006). Transrectal ultrasound (TRUS) -guided biopsy is the standard procedure for histopathological diagnosis (Heidenreich *et al.,* 2008).

There are many harms associated with PSA screening and subsequent TRUS-guided biopsy. The major disadvantage of PSA screening is its lack of specificity, which leads to false positive results and overdiagnosis (Ilic *et al.,* 2013). Adverse effects of TRUS-guided biopsy include infection, pain, haematuria, haematochezia and haemoejaculate (Ilic *et al.,* 2013, Rosario *et al.,* 2012). In addition, the biopsy procedure may fail to detect cancer (Rabbani *et al*., 2008).

In recent years, multi-parametric MRI (mpMRI) has been increasingly used for the detection of PCa and to guide biopsies. mpMRI is able to detect significant PCa accurately, and it has the potential to reduce unnecessary biopsies (Bjurlin *et al.,* 2014, Nazim *et al*., 2018, Radtke *et al*., 2015). However, the false negative rate is high. Anterior lesions are more likely to be missed than intraprostatic lesions (Serrao *et al*., 2014).

Based on the challenges in diagnosing PCa, there is a medical need for a diagnostic tool that is both sensitive and specific.

PSMA PET tracers

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein with carboxypeptidase and folate hydrolase activity, produced by the prostatic epithelium. PSMA is expressed also in normal prostate tissue, but the expression increases significantly in PCa (Silver *et al*., 1997, Wright *et al*., 1995, Tsourlakis *et al*., 2015). Small-molecule PSMA inhibitors labelled with radiotracers have recently been used as PET ligands for the detection of PCa, and the initial results have been promising. Sensitivity and specificity of ^{68}Ga-PSMA PET imaging were evaluated by Perera *et al*. in 2016. In a per-lesion analysis, the specificity and sensitivity were 97 % and 80 %. In a per-patient analysis, the specificity and sensitivity

were both 86 % (Perera *et al*., 2016). However, a main practical drawback of ^{68}Ga-PSMA PET is the limited production capacity of gallium-68 generators. Because of the need for alternative tracers, ^{18}F labelled PSMA ligands have been developed (Cardinale *et al*., 2017).

^{18}F-PSMA ligands

Compared to ^{68}Ga, ^{18}F has some advantages which include a longer radiochemical half-life (110 vs. 68 min) and improved spatial resolution. The production capacity of ^{18}F is also larger, since high activities of ^{18}F can be produced inexpensively with on-site cyclotrons (Kesch *et al*., 2017).

^{18}F-DCFBC was one of the first ^{18}F-labelled PSMA ligands, and it demonstrated promising ability to detect metastatic PCa (Cho *et al*., 2012, Robu *et al*., 2018). However, its major disadvantage was slow clearance and high blood-pool radioactivity, which could interfere with the detection of lymph node metastases located close to major vessels (Cho *et al*., 2012). The second generation ^{18}F-labelled PSMA ligand ^{18}FDCFPyL showed lower blood-pool activity and higher tumour uptake, but it accumulated within the urinary bladder (Szabo *et al*., 2015).

Fluorine-18 labelled PSMA-1007 has recently been developed as a next-generation PSMA-targeted imaging agent (Cardinale *et al*., 2017). The PSMA-1007 precursor and nonradioactive reference compound can be produced by solid-phase chemistry. The radioligand ^{18}F-PSMA-1007 is synthesized by a 2-step procedure using the prosthetic group 6-^{18}F-fluoronicotinic acid 2,3,5,6-tetrafluorophenyl ester for coupling the PSMA-1007 precursor (Cardinale *et al*., 2017, Giesel *et al*., 2017).

In its preclinical evaluation, ^{18}F-PSMA-1007 has demonstrated promising binding and internalization properties *in vitro* and high and specific tumour uptake *in vivo* (Cardinale *et al*., 2017). In its clinical evaluation carried out until now, it has behaved comparably to other PSMA-targeted imaging agents. The effective dose of ^{18}F-PSMA-1007 is 4.4-5.5 mSv for 200-250 MBq, which is similar to many other PET agents. However, ^{18}F-PSMA-1007 has benefits which include reduced urinary excretion and high tumour-to-background ratios in comparison to other PSMA-targeting PET tracers. Hence, ^{18}F-PSMA-1007 seems to be a promising PET ligand for the detection of PCa (Giesel *et al*., 2017, Frederik *et al*., 2017).

The PET tracer used in this study is a ^{18}F labelled radiohybrid (rh) PSMA ligand (^{18}F-rhPSMA-7.3) that has been developed for the diagnosis and staging of PCa and other cancers manifesting increased expression of PSMA. The ligand, and its isomer mixture ^{18}F-rhPSMA-7, has already been administered to hundreds of patients under the German 'AMG 13 (2b)' regulation (please see the Investigator's Brochure (IB) for more information).

1.2 Rationale of the study

Based on the challenges in diagnosing PCa, there is a medical need for a diagnostic tool that is both sensitive and specific. ^{18}F-rhPSMA7.3 is a promising PET ligand for the detection of PCa. This study aims to evaluate the safety, biodistribution, optimal administered radioactivity

and imaging time post administration for lesion visualisation of an ^{18}F-labelled PET tracer, ^{18}F-rhPSMA7.3.

1.3 Risk benefit assessment

The subjects will be exposed to ionising radiation. For healthy volunteers, the administered radioactivity will be approximately 225 MBq (±10 %) and their radiation total effective dose will not exceed 10 mSv. For subjects with PCa, the administered radioactivity will be based upon the results of the preliminary dosimetry analysis on data from the healthy volunteer cohort, and will be 300 MBq (±10 %). The total radiation effective dose of the patients will be 9.2 mSv. The total maximum dose for both healthy volunteers and patients will be less than 100 µg.

There will be no medical benefit for the healthy volunteers from their participation. They will be compensated according to applicable regulation and practices. The study results will have no direct impact on the treatment of the study participants with PCa. Possible incidental findings observed in the healthy volunteers or in the participants with PCa will be discussed with the subjects and evaluated by the clinical investigators for clinical significance, employing all appropriate diagnostic measures.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary objective

The primary objective of the study is to assess the safety of a single i.v. administration of ^{18}F-rhPSMA-7.3 in healthy subjects and subjects with PCa.

2.2 Secondary objectives

The secondary objectives of the study are:

1. To determine the biodistribution of ^{18}F following i.v administration of ^{18}F-rhPSMA-7.3 and hence calculate the internal radiation dosimetry and the effective dose (ED) in healthy volunteers.
2. To explore the optimisation of PET imaging with ^{18}F-rhPSMA-7.3 injection in visualising tumours in subjects with biopsy-proven PCa.
3. To perform kinetic modelling on the distribution of ^{18}F-rhPSMA-7.3 in subjects with PCa.
4. To use the kinetic modelling data to optimise the imaging protocol for future studies in subjects with PCa.
5. To determine the *in vivo* stability of ^{18}F-rhPSMA-7.3 injection by determining proportion of radioactive parent compound present over time.

2.3 Primary endpoint

Safety is the primary endpoint of the study and it will be assessed from data on the occurrence of one or more treatment-emergent AEs from the time of i.v. administration of ^{18}F-rhPSMA-7.3 throughout the study period, and changes in serum biochemistry, haematology, coagulation, urinalysis, vital signs, ECG, injection site status, and physical examination findings.

2.4 Secondary endpoints

The secondary endpoints of the study are:

1. Dosimetry estimates and cumulated activity exposure by source region and the entire body including analysis of activity in whole blood, plasma and excreted urine in healthy volunteers.
2. Uptake of ^{18}F-rhPSMA-7.3 injection visualised by PET imaging compared to histopathology in subjects with PCa, if histopathology information is available.
3. Use of kinetic modelling data to investigate distribution of ^{18}F-rhPSMA7.3 in subjects with PCa.
4. Use of kinetic modelling data to optimise the imaging protocol for future studies in subjects with PCa, by estimating *in vivo* ^{18}F radioactivity in PCa lesions.
5. Analysis of % of radioactive parent compound present in plasma over time in healthy volunteers and subjects with PCa. Relative proportions of radioactive tracer metabolites will be monitored, as well, if detected in significant amounts in the radio-HPLC analysis.

3 STUDY DESIGN

3.1 Type and design of the study

This is a phase 1, open-label, single administration, healthy volunteer and patient study of a PET imaging agent performed at a single centre. The use of placebo, randomisation or blinding are not applicable in this study. Altogether 15 evaluable subjects are planned to participate in the trial: 6 healthy volunteer subjects (3 males and 3 females) and 9 patients with PCa (3 in each patient cohort). Additional subjects may be enrolled in order to end up with evaluable PET imaging data from 6 healthy volunteer subjects and 9 patients with PCa. Each subject will receive a single i.v. administration of ^{18}F-rhPSMA-7.3.

3.2 Randomisation and blinding

Not applicable in this study.

3.3 General study outline

The total duration of subject participation will be up to 52 days for each subject. The study consists of a screening period (up to 21 days), an IMP administration/PET imaging visit, a 24-hour post scan visit and a 30-day telephone contact. In case surgical prostatectomy is for

some reason delayed in Cohort A patients scheduled for surgery, the participation of such subjects may be extended by up to two days to cover the surgery.

Subjects who sign the informed consent form (ICF) will enter the screening period of the study. A screening visit will take place within 21 days prior to the IMP administration/PET scan visit.

After the screening period, each subject will receive a single administration of IMP. The healthy volunteers will have 3 CT attenuation-correction scans, each followed by multiple whole-body (WB) PET acquisitions.

The subjects with PCa will have two CT attenuation-correction scans and dynamic PET imaging of the pelvic region (Cohort A) or the area with one or more metastases defined as representative target lesions (Cohorts B and C) for 45 min, followed by a 15 min break, and then multiple base of skull to mid-thigh PET acquisitions of up to 118 min p.i. The investigator will determine what the representative target lesions are in order to ensure that in the Cohort B and C patients all types of metastases, i.e. lymph node metastases, bone metastases, and soft tissue metastases, are represented on the dynamic images.

All subjects will attend a safety follow-up visit 24 hours (+/- 6 hours) after IMP administration and will be contacted by telephone 30 days (+/- 2 days; this may be extended further in Cohort A patients if the prostatectomy is delayed) after IMP administration to determine whether any AEs have occurred. Additional study visits will be arranged as needed for AE management. Any AEs will be followed up until resolution or stabilisation.

The study outline is presented in Table 1 below.

Table 1 General study outline

	Screening (Day -21 to 0)	IMP administration visit (Day 1)[a]	24-hour follow-up visit (Day 2)[b]	30-day follow-up[c]
Informed consent	x			
Entry criteria	x			
Demography data	x			
Medical History	x			
Physical examination	x	x		
12 lead ECG	x	x	x	
Continuous ECG monitoring (lead II)		x		
Body weight	x	x		
Height	x			
Vital signs (supine BP and HR, body temperature, respiration rate)[d]	x	x	x	
Clinical laboratory tests	x[e]	x[f]	x[f]	
Urine analysis (stick test)	x	x	x	
Fertility status for female subjects	x			
Pregnancy test for female subjects		x		
Drug abuse test	x	x		
Alcohol breath test	x	x		
IMP administration		x		
PET-CT imaging		x		
Urine for ^{18}F radioactivity counting		x		
Venous blood for ^{18}F radioactivity counting and % radioactive parent analysis		x		
Injection site monitoring		x	x	
Concomitant medications	x	x	x	x
AEs and SAEs	x	x	x	x

a Please refer to Tables 2 and 3 for time points of activities to be performed during IMP administration visit.
b Visit will be performed 24 h (+/- 6 hours) after IMP administration.
c Subjects will be contacted by telephone at 30 days (+/- 2 days) after IMP administration and will be asked a non-leading question to determine whether any AEs have occurred. Extra study visits will be arranged as needed for AE management.
d Before vital signs are measured, the subject should be resting for at least 5 minutes.
e Please refer to Section 7.1.2 for laboratory safety assessments to be performed during the screening visit.
f The safety laboratory parameter set. Please refer to Section 7.3.2.

4 STUDY SUBJECTS

4.1 Source population

The subjects participating in this study will be males or females who fulfil all of the inclusion criteria and none of the exclusion criteria.

4.2 Number of study subjects

Fifteen (15) evaluable subjects will be included in the study: 6 healthy volunteer subjects (3 males, 3 females); 3 patients with high risk PCa, 3 patients with hormone sensitive metastatic PCa, and 3 patients with castration-resistant metastatic PCa. If an included subject's results are non–evaluable, an additional subject may be included in the study to substitute for this.

4.3 Inclusion criteria - Healthy Volunteers

1. The subject is between 21 and 65 years old.
2. The subject is willing to abstain from sexual intercourse for 24 hours after IMP administration.
3. The male subject is willing to practice effective contraception for 3 months after IMP administration.
4. The female subject is post-menopausal or surgically sterile.
5. The subject is able and willing to provide signed, dated and timed informed consent to comply with study procedures, before any study-related procedure is performed.
6. The subject has normal or clinically acceptable medical history, physical examination, and vital signs findings during the screening period (up to 21 days before administration of study drug), as determined by the investigator.
7. The subject's ECG and clinical laboratory test results are within normal limits, or if any are outside of normal limits, they are considered to be clinically insignificant as determined by the investigator.
8. The subject has negative test results for drugs of abuse and alcohol at screening and on the day of IMP administration/PET imaging.
9. The subject's body mass index is <30 kg/m^2 and body weight is <90 kg.

4.4 Exclusion criteria - Healthy Volunteers

1. The subject has been previously included in this study and has received any dose of the study medication.
2. The subject has received, or is scheduled to receive, another investigational medicinal product (IMP) from 3 months before to 1 week after administration of ^{18}F-rhPSMA-7.3.
3. The subject has received ionising radiation exposure from clinical trials or medical examinations or treatment (other than plain radiographs of the chest or bones, or comparable) in the last 12 months.
4. The subject is undergoing monitoring of occupational ionising radiation exposure.
5. The subject suffers from claustrophobia.
6. The subject has bilateral hip prostheses.

7. The subject has tested positive for hepatitis B, hepatitis C, or human immunodeficiency virus.
8. The subject has a history of alcohol or drug abuse within the previous 12 months, or is a habitual user of excessive amounts of alcohol (>21 units per week).

4.5 Inclusion criteria - Patients with Prostate Cancer

All Cohorts

1. The subject is a male and is 18-80 years old.
2. The subject has histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
3. The subject is willing to abstain from sexual intercourse for 24 hours after IMP administration and to practice effective contraception for 3 months after IMP administration.
4. The subject is able and willing to provide signed, dated and timed informed consent to comply with study procedures, before any study-related procedure is performed.
5. The subject has clinically acceptable medical history, physical examination, and vital signs findings during the screening period, as determined by the investigator (up to 21 days before administration of study drug), apart from findings related to PCa.
6. The subject's ECG and clinical laboratory tests are within normal limits, apart from findings related to PCa, or if any are outside of normal limits, the out-of-range values are considered to be not clinically significant as determined by the investigator.
7. Eastern Cooperative Oncology Group [ECOG] performance status 0-2 (Appendix 2).

Cohort A specific inclusion criteria – High risk primary PCa

8. Unfavourable intermediate-risk or high-risk PCa defined by NCCN Guidelines Version 2.2019 (clinical stage ≥T2b or PSA >10 ng/mL or Gleason score ≥ 4 + 3 = 7).
9. Scheduled for radical prostatectomy with or without pelvic lymph node dissection.

Cohort B specific inclusion criteria - Hormone sensitive metastatic PCa

10. Castration-naïve metastatic PCa with a known number of metastases or a high likelihood of lymph node metastases and/or bone metastases.
11. Either clearly demonstrated disease by site standard of care imaging performed as part of the subject's routine clinical work-up within 12 weeks before enrolment or biochemical recurrence with a PSA < 15 ng/mL.

Cohort C specific inclusion criteria– Castration resistant metastatic disease

12. A quantifiable number or a high likelihood of metastases, either documented by standard of care imaging performed as part of the subject's routine clinical work-up within 12 weeks before enrolment or by biochemical progression (see 14a).
13. Ongoing androgen deprivation with luteinizing hormone-releasing hormone (LHRH) agonist/antagonist therapy or bilateral orchiectomy.
14. Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;
    a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50 % increases over the nadir, and a PSA > 2 ng/mL or,

b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or soft tissue lesion(s) progression using RECIST (Response Evaluation Criteria in Solid Tumours).

4.6 Exclusion criteria - Patients with Prostate Cancer

All Patient Cohorts

1. A biopsy has been obtained from the prostate within the 28 days before enrolment.
2. Patients with extensive metastatic disease (more than 20 lesions).
3. Patients with a second primary cancer or any other underlying disease which might confound interpretation of the study results.
4. The subject has had any major surgery within 2 months prior to screening.
5. The subject has bilateral hip prostheses.
6. The subject has received, or is scheduled to receive, ^{68}Ga-PSMA-11 or ^{18}F-PSMA-1007 from 1 month before to 1 week after administration of ^{18}F-rhPSMA-7.3, or any other IMP from 3 months before to 1 week after administration of ^{18}F-rhPSMA-7.3.
7. The subject has a history of alcohol or drug abuse within the previous 12 months, based on a review of medical records or other available evidence.
8. The subject has known hypersensitivity to ^{18}F-rhPSMA-7.3 injection or any of its constituents.
9. Subjects administered any high energy (>300 keV) gamma-emitting radioisotope within five physical half-lives, or any i.v. iodinated contrast medium within 24 hours, or any high density oral contrast medium (oral water contrast is acceptable) within 5 days, prior to study drug administration.
10. Subjects who have recently received an x-ray contrast agent (<24 hr for i.v. agents and <5 days for oral agents).
11. Subjects with a history of claustrophobia or panic attacks when in confined spaces.

Cohort A and B specific exclusion criteria

12. The subject is being treated or has been treated for PCa with chemotherapy or radiation therapy.
13. Patients currently receiving or with a prior history of hormonal treatment/androgen deprivation therapy including bilateral orchiectomy.

Cohort C specific exclusion criteria

14. Radiation therapy for treatment of any metastatic lesions in the field of view of the dynamic images.

4.7 Recruitment

CRST has a data bank of healthy volunteers, which will be screened for suitable candidates. In addition, volunteers may be recruited by advertising in newspapers, via mailing lists, internet pages and bulletin boards. Interested persons are advised to call or contact by e-mail the person responsible for subject recruitment. Subjects with PCa are recruited from the clinics of Urology and Oncology of Turku University Hospital.

At first, the study is briefly described to the subject candidate in layman's language. The candidate is told that the information gained in this discussion is collected on a study-specific interview form. The name, date of birth and contact information of the candidate are recorded on the interview form. Next, the main inclusion and exclusion criteria are checked. If an exclusion criterion is fulfilled, this is immediately told to the candidate, and the interview is ended with possible health-related instructions. If the candidate might be suitable for the study, the procedures for providing the study ICF are discussed, and the next steps in the recruitment procedure are agreed upon. Upon the subject candidate's agreement, a screening visit may be booked. The ICF is sent to the candidate by post, e-mail or another method. A subject can only be enrolled into the study after a sufficient consideration period.

4.8 Instructions concerning lifestyle and concomitant treatments

1. Alcohol intake is prohibited during 48 hours before the IMP administration/PET scan visit.
2. The subjects will have to fast for at least 4 hours before the screening visit and the IMP administration/PET scan.
3. Subjects should be well-hydrated before the IMP administration (e.g. oral intake of 500 mL of water during a 2 hour period prior to IMP administration).
4. Strenuous physical exercise is not allowed in the 48 hours before the screening and IMP administration/PET scan visits, and until 24 hours after IMP administration.
5. For instructions regarding prior and concomitant treatments, please see Section 5.4.
6. Subjects will be instructed to report all prior and concomitant medications and possible AEs to the study personnel.

4.9 Withdrawal and replacement of subjects

The Investigator may withdraw a subject from the study at any time based on the Investigator's clinical judgement. A subject will be withdrawn from the trial prematurely if an AE jeopardising her/his well-being occurs, or if the discontinuation is otherwise in the best interest of the subject. A subject will also be withdrawn from the study if she/he fails to comply with the trial protocol.

A subject has the right to withdraw her/his consent without the need to justify the decision. However, every effort should be made to find out the reason for the withdrawal.

All information collected from a withdrawn subject, including the reason for withdrawal, will be included in the study file for use as study data and for purposes of verification.

Once withdrawn, a subject cannot re-enter the study unless the withdrawal was due to scheduling reasons and the subject did not receive the IMP. It will be decided case-by-case, in joint agreement between the Investigator and the Sponsor, whether a discontinued subject will be replaced or not.

4.10 Evaluability criteria and additional subjects

Healthy Volunteer Evaluability Criteria:

As it is important that the study has the required number of evaluable healthy volunteers, the following criteria will be applied, and if the healthy volunteer is not evaluable for efficacy, an additional subject may be included in the study to substitute for the non-evaluable subject:

- Completion of scanning sessions I, II and III and collection of venous blood and urine analysis (as described in the Study Imaging Manual) to be able to undertake a calculation of the subject's internal radiation dosimetry.

Patient Evaluability Criteria:

As it is important that each cohort has the required number of evaluable patients, the following criteria will be applied and if the patient is not evaluable for efficacy, an additional subject may be included in the study to substitute for the non-evaluable subject:

- Completion of scanning sessions I and II and collection of venous blood and urine analysis (as described in the Study Imaging Manual) to be able to perform kinetic modelling.
- At least one positive lesion on the ^{18}F-rhPSMA-7.3 scan.
- Cohort A only: Radical prostatectomy performed within 30 days of the ^{18}F-rhPSMA-7.3 scan. In case of a delay of the planned surgery by up to 2 days beyond this 30-day window, a subject may still be considered evaluable.

4.11 Standard of Truth (Cohort A only)

Histopathological diagnosis in patients undergoing radical prostatectomy. PSMA immunohistochemistry will be employed for exploratory analysis of Cohort A prostate specimens removed at surgery. Details of the planned histopathological analysis and the PSMA immunochemistry procedure are given in a separate Histopathology and Immunohistochemistry Manual prepared for this study.

5 TREATMENTS

5.1 Investigational treatment

The test product in this trial is an ^{18}F labelled PSMA ligand (^{18}F-rhPSMA-7.3) for i.v. administration, under development as a PET imaging tracer for the diagnosis and staging of PCa and possibly also other cancers manifesting increased expression of the target, PSMA, such as breast cancer. The IMP will be produced on-site at Turku PET Centre (TPC) according to the Scintomics platform ^{18}F-rhPSMA-7.3 manual and TPC's SOPs.

Manufacturing, packaging and labelling of ^{18}F-rhPSMA-7.3 will be performed in compliance with good manufacturing practice (GMP) regulations.

Each subject will receive a single ^{18}F-rhPSMA-7.3 injection. For healthy volunteer subjects, the administered radioactivity will be approximately 225 MBq (± 10 %). Their total radiation effective dose will not exceed 10 mSv. For subjects with PCa, the administered radioactive dose will be based on the results of the preliminary dosimetry analysis of the data obtained from the healthy volunteer subjects. Their total radiation effective dose will be 9.2 mSv; 300 MBq (± 10 %) may be injected. The total maximum dose for both healthy volunteers and patients will be less than 100 µg.

5.2 Reference treatment

Not applicable in this study.

5.3 Handling of the study product

Manufacturing, packaging and labelling of ^{18}F-rhPSMA-7.3 will comply with GMP regulations and standard practices at and SOPs of TPC.

5.4 Prior and concomitant treatments

Prior medication refers to medication taken before the IMP administration. Medications used within 4 weeks prior to IMP administration should be recorded.

Concomitant medication is defined as any medication received by a subject after administration of the IMP until the end of the subject's participation in the study (30 days after IMP administration, end-of-study telephone contact).

5.5 Procedures for monitoring subject compliance

IMP administration will be performed by the study personnel. The study team member administering the IMP will ascertain and document that the IMP was administered according to the protocol. The compliance is assumed to be 100 %.

TPC will keep accurate written records of the production, quality control and administration of ^{18}F-rhPSMA-7.3.

6 VISIT SCHEDULE

6.1 Screening

The screening period will begin up to 21 days before IMP administration. Each potential study subject will receive written and verbal information on the study and will have an opportunity to ask questions. If a subject decides to participate in the trial, written infomed consent will be obtained before any study-related procedures are performed. A copy of the signed ICF will be provided to the subject.

At screening, a medical history interview will be conducted and a physical examination will be performed. Based on the subject's consent given in the ICF, any existing relevant medical records of the subject will be reviewed and copies thereof will be filed in the subject's source data file. Blood and urine samples will be collected for screening laboratory tests. Demographic data, body weight and height, 12-lead ECG and vital signs will also be recorded.

For a detailed description on the information to be collected during the screening period, please refer to Section 7.1.

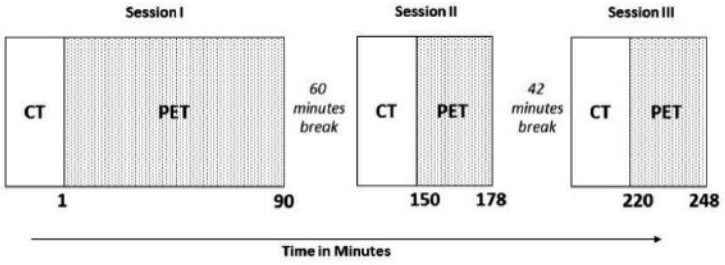
A subject will be entered into the study only if all inclusion criteria and none of the exclusion criteria are met. All screening assessment results must be available before the decision to enrol a subject. Once the decision to enrol a subject has been made, a PET scan will be scheduled. Participation in the study should not delay the planned treatment of a subject with PCa.

6.2 Study periods

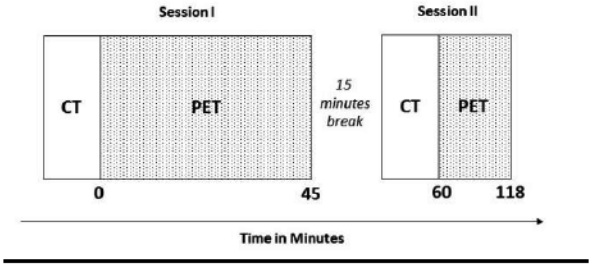
Day 1

Before administration of the IMP administration/PET scan, a brief physical examination is performed, 12-lead ECG and vital signs (body temperature, respiration rate, supine systolic and diastolic BP and HR) and body weight are recorded, and blood and urine samples are collected for clinical laboratory tests. In addition, subjects will be asked about possible AEs which have occurred since consent was obtained and about new medications or changes to concomitant medications. AEs will also be monitored throughout the visit. The results of the physical examination, ECG, vital signs, AEs etc. must be reviewed for eligibility before the subject proceeds for the IMP administration and PET scanning. Healthy volunteers already suffering an AE on the day of the scan will be withdrawn or their IMP administration/PET scan visit will be postponed. Each subject will receive IMP as a single i.v. administration of ^{18}F-rhPSMA-7.3.

After IMP administration, the healthy volunteer subjects will undergo a series of three CT attenuation-correction scans, each followed by multiple whole-body PET acquisitions. The minimum scanning data to be acquired for each healthy volunteer subject is the initial 1 to 90-min serial whole-body scan, 150 to 178-min mid-scan and the 220 to 248-min late scan, as illustrated in the figure below.



The subjects with PCa will undergo two CT attenuation-correction scans and dynamic PET imaging of the pelvic region (Cohort A; BCR patients in Cohort B; patients with biochemical progression in Cohort C) or the body region with one or more metastases defined as representative target lesions (metastatic patients in Cohort B and radiologically progressive patients in Cohort C) for 45 min, then 15 min break, and then multiple base of skull to mid-thigh PET acquisitions up to 118 min p.i. (see the figure below). The investigator will determine what the representative target lesions are in order to ensure that in the Cohort B and C patients all types of metastases, i.e. lymph node metastases, bone metastases, and soft tissue metastases, are represented on the dynamic images.



Once the scan aquisition is completed, the subject will be monitored for vital signs, ECG and AEs until at least 4 hr after IMP administration.

All procedures during the IMP administration day are presented in Table 2 (healthy volunteer subjects) and Table 3 (subjects with PCa).

Table 2 Healthy Volunteer Schedule of Events: PET Imaging visit

	Baseline (-120 to -5	-5 min	IMP administration	+2 min	+5 min	+10 min	+15 min	+30 min	+60 min	+90min	+180 min	+250 min
Physical examination	x											x
12 lead ECG	x	x								x	x	x
Continuous ECG monitoring (lead II)												
Body weight	x											
Vital signs (supine BP and HR, body temperature, respiration rate)[a]	x	x		x	x	x	x	x	x	x	x	x
Clinical laboratory tests	x[b]									x[b]	x[b]	x[b]
Urine analysis (stick test)	x											x
Pregnancy test for female subjects	x											
Drug abuse test	x											
Alcohol breath test	x											
IMP administration			x									
PET-CT imaging[c]												
Urine for ^{18}F radioactivity counting[d]												
Venous blood for ^{18}F radioactivity counting and % radioactive parent and metabolite analysis[e]												
Injection site monitoring												
AEs and SAEs	x											
Concomitant medications												

NOTE: Shaded areas depict continuous monitoring.
a Before vital signs are measured, the subject should be resting for at least 5 minutes.
b The safety laboratory parameter set. Please refer to Section 7.3.2.
c Total healthy volunteer PET acquisition time is 248 minutes (~4 hours). Please refer to Imaging Manual to see entire acquisition protocol with specific scanning time points.
d Urine will be collected in the following fractions as calculated from the time of ^{18}F-rhPSMA-7.3 administration: until -5 min, -5 to 95 min, 95 to 185 min, and 185 to 255 min. The collection times are approximations and will depend on actual voiding times.
e Blood samples will be taken at the following time-points as measured from the time of ^{18}F-rhPSMA-7.3 administration: 30 sec, 60 sec, 90 sec, 4 min 30 sec, 5 min, 6 min, 7 min, 8 min, 15 min, 31 min, 47 min, 75 min, 120 min, 180 min, and 250 min after injection. Additional bood samples for radioactive metabolite analyses are taken at 5, 8, 15, 31 and 47 min after injection.

Table 3 Prostate Cancer Patients Schedule of Events: PET Imaging visit

	Baseline (-120 min to -5 min)	-5 min	IMP administration	+5 min	+10 min	+15 min	+30 min	+45 min	+120 min	+180 min	+240 min
Physical examination	x										x
12 lead ECG	x	x						x	x	x	x
Continuous ECG monitoring (lead II)											
Body weight	x										
Vital signs (supine BP and HR, body temperature, respiration rate)[a]	x	x		x	x	x	x	x	x	x	x
Clinical laboratory tests	x[b]							x[b]		x[b]	x[b]
Urine analysis (stick test)	x										x
Drug abuse test	x										
Alcohol breath test	x										
IMP administration			x								
PET-CT imaging[c]											
Urine for ^{18}F radioactivity counting[d]											
Venous blood for ^{18}F radioactivity counting and % radioactive parent and metabolite analysis[e]											
Injection site monitoring											
AEs and SAEs											
Concomitant medications											

NOTE: Shaded areas depict continuous monitoring.
a Before vital signs are measured, the subject should be resting for at least 5 minutes.
b The safety laboratory parameter set. Please refer to Section 7.3.2.
c Total PCa patient PET acquisition time is 118 minutes (~2 hours). Please refer to Imaging Manual to see entire acquisition protocol with specific scanning time points.
d Urine will be collected in the following fractions as calculated from the time of ^{18}F-rhPSMA-7.3 administration: until -5 min, -5 to 50 min, 50 to 125 min, and 125 to 240 min. The collection times are approximations and will depend on actual voiding times.
e Blood samples will be taken at the following time-points as measured from the time of ^{18}F-rhPSMA-7.3 administration: 20 sec, 40 sec, 60 sec, 80 sec, 100 sec, 120 sec, 140 sec, 160 sec, 180 sec, 4 min, 5 min, 7.5 min, 10 min, 15 min, 20 min, 30 min, 40 min, 50 min, 59 min and 120 min after the injection. Additional bood samples for radioactive metabolite analyses are taken at at 5, 10, 20, 30, 40, and 50 min after injection.

6.3 Follow-up period

Day 2:

All subjects will visit the site 24 hours (+/- 6 hours) (Visit 2) after IMP administration for safety laboratory assessments, recording of 12-lead ECG and to collect information on concomitant medications and AEs.

30 Day Follow-up:

All subjects will be contacted by telephone at 30 days (+/- 2 days) after IMP administration to determine whether any AEs have occurred and to collect information on changes in concomitant medications. Additional study visits will be scheduled if needed for AE management. Any AEs will be followed up until resolution or stabilisation. In case of unanticipated delays in the planned surgical prostatectomy of the Cohort A PCa patients, the follow-up period of such subjects may be extended by up to 2 days to cover the surgery, and/or additional subjects may be enrolled into Cohort A in order to ensure that there are three evaluable subjects in Cohort A (see section 4.10 for criteria of evaluability).

7 ASSESSMENTS

7.1 Screening data

Information to be recorded during the screening period includes demographic and other baseline information and results of screening laboratory determinations.

7.1.1 Demographic and other baseline information

Information to be recorded during the screening visit includes:

- subject's name, personal identity number, address; telephone number and e-mail address; none of this information is to be recorded on the CRF; personal identity number is collected due to laboratory logistics, on subject's permission given in the ICF;
- gender;
- race and ethnicity;
- height, weight, vital signs (supine BP and HR after 5 min rest, body temperature, respiration rate);
- 12-lead ECG;
- results of the physical examination (all main body systems according to site practice);
- habits (for the use of nicotine, alcohol, illicit drugs);
- information on previous diseases and current medical conditions;
- information on previous medications; all treatments used (including prescription medications, OTC medications, herbal remedies, trace elements and vitamins) within 4 weeks before the screening visit will be recorded;
- information on previous participation in clinical trials including PET trials or exposure to significant doses of ionizing radiation;
- blood and urine samples are collected for screening laboratory determinations;
- result of alcohol breath test and urine test for drugs of abuse;
- female reproductive status, information on menopause or surgical sterilisation and result of serum β-hCG pregnancy test;

- name and information of the subject's next-of-kin (not on CRF; this information will be removed from the subject's source data at end-of-study).

7.1.2 Screening laboratory determinations

All subjects will undergo blood and urine testing during the screening period. A study-specific Laboratory Manual will be available before study start. Screening laboratory tests include:

Haematology:
Haemoglobin
Haematocrit
Erythrocytes
Leucocytes
Mean corpuscular volume (MCV)
Mean corpuscular haemoglobin (MCH)
Platelets
Neutrophils
Eosinophils
Basophils
Lymphocytes
Monocytes

Chemistry:
Alkaline phosphatase
Alanine aminotransferase
Aspartate aminotransferase
Gamma-glutamyl transferase
Albumin
Total protein
Total and conjugated bilirubin
Creatinine
Blood urea nitrogen (BUN)
Chloride
Potassium
Sodium
C-reactive protein
Prostate specific antigen (PSA)
Follicle Stimulating Hormone (FSH) and serum β-hCG pregnancy test (female volunteers only)

Serology:
HIVAgAb
HBsAg
HCVAg

Clotting status:
Partial Thromboplastin time (PTT)
Activated partial thromboplastin time (aPTT)

Urine analysis:

- Stick test: pH, erythrocytes, leukocytes, nitrite, protein, glucose, ketones; microscopy and bacterial culture will be performed if indicated by the stick test results;
- Urine test for drugs of abuse: tetrahydrocannabinol, amphetamine, morphine and related opioids, benzodiazepines, methamphetamine, ecstasy, buprenorphine, tramadol, methadone, fentanyl, oxycodone.

Alcohol breath test: Alcotest 6510 test system

7.2 Assessment of efficacy

7.2.1 Standardised Uptake Values (SUV_{max}, SUV_{mean}, SUVR)

- SUV (standardised uptake value) is a ratio of tissue radioactivity concentration and administered dose of radioactivity divided by body weight:
- SUV = activity (Bq/g)/[injected activity (Bq))/body weight (g)]
- SUV_{max} is the maximum standardized uptake value.
- SUV_{mean} is the mean standardized uptake value.
- SUVR is a ratio of SUV in a detected lesion and SUV of a reference tissue, such as blood.

Data will be presented graphically to evaluate the optimal imaging time post-injection.

7.2.2 Uptake irreversibility/reversibility

Kinetics of ^{18}F-rhPSMA-7.3 uptake in PCa lesions is compared to the availability of parent ^{18}F-rhPSMA-7.3 in plasma by plotting SUVR of lesion and parent ^{18}F-rhPSMA-7.3 in plasma, and by irreversible and reversible multiple-time graphical analyses (Patlak and Logan plots) (Logan, 2000).

7.2.3 Lesion detectability

Comparison of SUV in detected lesion(s) against pathology grading. Details of the planned histopathological analysis and the PSMA immunochemistry procedure are given in a separate Histopathology and Immunohistochemistry Manual prepared for this study.

7.3 Assessment of safety

7.3.1 Clinical safety assessments

A standard physical examination will be performed by the Investigator at the screening visit, and brief physical examinations will be performed before IMP administration and at discharge

from the site. The following organ systems will be checked: head, eyes, ears, nose, throat, cardiovascular, respiratory, musculoskeletal, gastrointestinal, hepatic, psyche, endocrine, dermatologic and lymph nodes.

A 12-lead ECG will be recorded at the screening visit. During the IMP administration visit, 12-lead ECG will be recorded at baseline (between -120 to -15 min), 5 min pre-injection and at 90, 180 and 250 min after IMP administration (healthy volunteer subjects) or at the baseline, 5 min pre-injection, 45 min, 120 min, 180 min and 240 min after IMP administration (subjects with PCa). Continuous 2-lead ECG monitoring will be performed from 5 min pre-injection until the end of the PET scan visit.

Vital signs (body temperature, respiration rate, supine systolic and diastolic BP and HR) will be measured after 5 min rest at the screening visit. During the IMP administration visit, vital signs will be measured at baseline, 5 min pre-injection and 2, 5, 10, 15, 30, 60, 90, 180 and 250 min post-injection (healthy volunteer subjects) or at baseline, 5 min pre-dose and 5, 10, 15, 30, 45 120, 180 and 240 min post-injection (subjects with PCa). The injection site will also be monitored for signs of any adverse effects.

At 24 (± 6) hr after IMP administration, AEs, concomitant medications, 12 lead ECG and vital signs (body temperature, respiration rate, supine systolic and diastolic BP and HR) will be recorded and blood and urine samples will be collected for safety evaluations. The injection site will be examined and any bruising or erythema will be recorded as an AE.

Additional safety data (physical examination findings, 12-lead ECG and vital signs, or any laboratory or other assessments considered to be clinically relevant) will be collected at 24 hours post-dose or at any later time point at an unscheduled visits in the event of a safety signal being abnormal during the post-administration safety recordings or in the event of an AE.

7.3.2 Laboratory safety assessments

Please refer to Section 7.1.2 for laboratory safety assessments to be performed during the screening visit.

Day 1:

A urine pregnancy test (female subjects only), drug abuse test and breath alcohol test will be repeated before IMP administration.

During the IMP administration visit, sampling for the safety laboratory parameter set will be performed at baseline and at 90, 180 and 250 min post-injection (healthy volunteers) or at baseline, 45, 180 and 240 min post-injection (subjects with PCa). The safety laboratory parameter set will include all laboratory assessments described in Section 7.1.2, except for PSA, FSH, serum βhCG and the serology assessments.

Urine analysis will be performed at baseline and at 250 min post-injection (healthy volunteers) or at 240 min post-injection (subjects with PCa).

Day 2:

At the 24 hour follow-up visit, the safety laboratory parameter set will be repeated and will include all laboratory assessments described in Section 7.1.2, except for PSA, FSH, serum βhCG and the serology assessments.

The urine analysis will also be repeated.

Additional follow-up:

Additional laboratory safety assessments may be performed later as needed in the event of an AE or a safety variable being clinically significantly abnormal in the post-administration safety samples.

7.3.3 Adverse events

AEs will be collected throughout the study from informed consent onwards. During the study visits, the subjects are monitored for AEs and they are asked about AEs with non-leading questions. They are asked to report AEs immediately when they appear outside of the visit schedule. Outside of the visits, the subjects are to contact the study personnel in case of a significant AE, particularly in case of possibly IMP-related AEs. In case of minor AEs, the subjects are to report them on their next visit to the study site or during the scheduled telephone contacts. In case of any illness, the subjects are instructed to seek regular medical care and to inform the study site about their condition and possible changes in their medication as soon as possible.

Definitions of adverse events (AE) and serious adverse events (SAE) and the documentation and reporting of them within this study follow GCP, EU and Finnish national guidance.

Adverse Events

An AE is defined as any untoward medical occurrence experienced by a subject, whether or not considered related to IMP administration by the Investigator. For the current study, all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.0 or later) by the data management (DM) provider in co-operation with CRST.

AEs are:

- Unfavourable changes in general condition.
- Subjective or objective signs/symptoms.
- Concomitant diseases or accidents.
- Clinically relevant adverse changes in laboratory parameters observed in a subject in the course of a clinical study.

AEs comprise all disturbances of general health status, subjective and objective disease symptoms (including significant, clinically relevant laboratory abnormalities), concomitant diseases, and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with IMP administration.

All AEs, whether volunteered, elicited, or noted on physical examination, will be recorded throughout the study, i.e., from the screening visit until the end of the subject's participation. AEs that occur prior to IMP administration will be reported separately from treatment-emergent AEs, which will be of particular interest.

When an AE occurs, the first decision will be to determine its severity and relationship to the IMP.

The severity of AEs will be categorised as follows:
- Mild = Experience is minor and does not cause significant discomfort to subject or change in activities of daily living (ADL) compared to subject baseline; subject is aware of symptoms but symptoms are easily tolerated.
- Moderate = Experience is an inconvenience or concern to the subject and causes interference with ADL compared to subject baseline but the subject is able to continue with ADL.
- Severe = Experience significantly interferes with ADL and the subject is incapacitated and/or unable to continue with ADL compared to subject's baseline.

The relationship of an AE to IMP administration will be categorised as follows:
- Related; when there is a reasonable possibility of a causal relationship between IMP administration and an AE (i.e. adverse drug reaction, ADR)
- Not related; when an AE does not follow a reasonable temporal sequence from IMP administration or when an AE can be reasonably explained by other factors including underlying disease, concomitant drugs or concurrent treatment.
- Not applicable: IMP not administered or AE is prior to IMP administration.

The Investigator or his delegate marks on the AE-CRF all AEs, indicating the Investigator's assessment of a causal relationship to IMP administration using the categories above.

As far as possible, each AE will also be described by its duration (start and end date and time), the actions taken, and, as relevant, the outcome.

Serious Adverse Events

A Serious Adverse Event (SAE) is any AE occurring during the study that results in any of the following outcomes:

- Death.
- A life-threatening AE that placed the subject, in the view of the Investigator, at immediate risk of death.
- Inpatient hospitalisation or prolongation of existing hospitalisation.
- A persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- Important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

In the present study, inpatient hospitalisation for the treatment of PCa will not be considered an SAE, unless the hospitalisation is considered by the Investigator to be causally related to IMP administration or other study procedures or is prolonged compared with what would be anticipated in that subject, i.e. not in agreement with the patient's scheduled treatment protocol. Likewise, other planned procedures already known and anticipated at the time of enrolment will not be considered SAEs unless similarly complicated or prolonged.

An important medical event that may not result in death, be life-threatening, or require hospitalisation may be considered an SAE when, based upon appropriate medical judgment, it may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this SAE definition.

Minimum criteria for SAE reporting are: The event or outcome meets the SAE definition, the event happens to an identifiable subject, and the event is reported by an identifiable and qualified reporter (usually an Investigator or other qualified study centre personnel).

SAEs must be reported within 24 hours of the Investigator or study staff becoming aware of an SAE, regardless of the time that may have elapsed since the time the event occurred and regardless of the causal relationship of IMP to the event. An initial SAE report will be submitted by the Investigator to the pharmacovigilance (PV) provider, and follow-up reports will be provided later as needed. Follow-up reports to an SAE should be prepared when any relevant changes in the condition of the study subject occur after the initial report or if any new relevant information on the SAE becomes available. SAEs should be followed up until resolved or until the event is considered chronic and/or stable outcome.

The PV provider in this study is PharSafer Associates Ltd. The contact information for SAE reporting is located in the ISF.

Suspected Unexpected Serious Adverse Reactions

An unexpected adverse drug reaction is any serious adverse drug reaction (ADR), the nature or severity of which is not consistent with the approved Reference Safety Information contained within the current Investigator's Brochure (IB) of ^{18}F-rhPSMA-7.3. Suspected unexpected serious ADRs (SUSARs) are subject to expedited reporting to the CA. The PV provider reports all authority-reportable AEs to the Sponsor and the CA.

7.4 Assessment of pharmacokinetics

7.4.1 Blood sampling

Blood samples for ^{18}F radioactivity counting and % radioactive parent/metabolite analysis will be taken from peripheral venous blood.

Healthy Volunteers
Blood samples should be collected at the following time-points as calculated from the time of ^{18}F-rhPSMA-7.3 administration: 30 sec, 60 sec, 90 sec, 4 min 30 sec, 5 min, 6 min, 7 min, 8 min, 15 min, 31 min, 47 min, 75 min, 120 min, 180 min, and 250 min after injection. Sample volume is 2 ml except at the 5, 8, 15, 31, and 47 min time points when an extra 5 ml sample is collected for radioactive metabolite analysis.

PCa Patients
Blood samples should be taken at the following time points as calculated from the time of ^{18}F-rhPSMA-7.3 administration: 20 sec, 40 sec, 60 sec, 80 sec, 100 sec, 120 sec, 140 sec, 160 sec, 180 sec, 4 min, 5 min, 7.5 min, 10 min, 15 min, 20 min, 30 min, 40 min, 50 min, 59 min, and 120 min after the injection. Sample volume is 2 ml except at the 5, 10, 20, 30, 40, and 50 min time points when an extra 5 ml sample is collected for radioactive metabolite analysis.

7.4.2 Urine sampling

Urine samples should be collected in timed fractions before the tracer injection, during the scanning break(s) and after the scan. Urine samples should be collected in the following fractions as calculated from the time of ^{18}F-rhPSMA-7.3 administration: until -5 min, -5 to 95 min, 95 to 185 min and 185 to 255 min (healthy volunteers) or until -5 min, -5 to 50 min, 50 to 125 min and 125 to 240 min (patients with PCa). The collection times are approximations and will depend on actual voiding times.

7.4.3 Sample analyses

Radioactivity measurements will be performed for blood and urine samples collected from the study subjects after IMP administration. The analytics will be performed according to standard practises of TPC.

7.4.4 Pharmacokinetic parameters

- Metabolite-corrected tracer AUC(0-t_{last}), C_{max} and t_{max} of total ^{18}F-radioactivity in whole blood and plasma
- Total ^{18}F-radioactivity in urine
- Fractions (%) of radioactive compounds (parent and metabolites) in plasma.

8 STATISTICS AND DATA MANAGEMENT

8.1 Estimation of sample size

Sufficient numbers of evaluable subjects have been planned to be included in the study in order to fulfil the study objectives, at the same time limiting the groups of healthy volunteer and patient volunteer subjects to the smallest informative numbers.

Altogether 15 evaluable subjects will be included in the study: 6 evaluable healthy volunteer subjects (3 males, 3 females) and 9 evaluable subjects with PCa (3 in each patient cohort). A patient is considered evaluable if at least one positive lesion on the ^{18}F-rhPSMA-7.3 scan is seen (see Section 4.10).

8.2 Statistical methods

A summary of the statistical methods is given below.

8.2.1 Statistical Analysis Plan

Detailed statistical analysis information will be provided in a separate Statistical Analysis Plan (SAP), to be approved and signed before the database lock.

8.2.2 Statistical hypotheses

No formal statistical hypotheses are stated. This study is exploratory in nature.

8.2.3 Data sets to be analyzed

The safety analysis set (SAF) will include all subjects who received any administration of the IMP.

Evaluable Analysis set (EAS) will include subjects who met all inclusion and exclusion criteria, received IMP, underwent PET/CT scans and met the scan evaluability criteria set out in section 4.10.

Statistical analyses for the primary and secondary endpoints (besides safety) will be performed using EAS. Safety will be assessed using the safety analysis set (SAF).

8.2.4 General statistical considerations

The study is explorative in nature. An analysis of the percent of radioactive parent compound present in blood over time will be performed. Other endpoints will be presented using descriptive statistics.

In general, all data collected will be presented with summary statistics and given in subject data listings. Summary statistics will include at least number of subjects, mean, standard deviation, median, minimum and maximum for continuous data, and frequency and percentage for categorical data. Tables with summary statistics will be divided by group and visit where applicable. Subject data listings will be sorted by treatment, subject and timing of assessments.

For PK assessments, geometric means and CVs will also be presented, where appropriate.

Details of the planned histopathological analysis and the PSMA immunochemistry procedure are given in a separate Histopathology and Immunohistochemistry Manual prepared for this study. The detailed results of such analysis will not be entered into the eCRF, and will be reported separately for each Cohort A subject in a Histopathology and Immunohistochemistry Report to be prepared by the study pathologist and to be included as an Appendix in the Clinical Study Report. The histopathology and immunohistochemistry analysis results that are to be entered into the eCRF are detailed below in section 8.2.6.

8.2.5 Demographic and baseline characteristics

The demographic and baseline characteristics of the subjects will be presented using descriptive summary statistics.

8.2.6 Analysis of efficacy variables

In subjects with PCa, the lesion(s) detected on the PET images will be visually evaluated by the on-site investigator. A semi-quantitative analysis, using standardised uptake values (SUV), will be derived. SUV is a ratio of tissue radioactivity concentration and administered dose of radioactivity divided by body weight:

- SUV = activity (Bq/g)/[injected radioactivity (Bq))/body weight (g)]
- SUV_{max} is the maximum standardized uptake value.
- SUV_{mean} is the mean standardized uptake value.
- SUVR is a ratio of SUV in a detected lesion and SUV of a reference tissue, such as blood.

The variables will be presented using summary statistics.

Analysis, using SUV, will be used to compare lesions seen on the PET images with lesions from histopathology results, where available. This assessment of which lesion detected on the PET images matches the lesion for which histopathology results are available will be made by the on-site investigator. As far as possible, exploratory comparisons will be made regarding:

- Gleason Scores and degree of uptake of ^{18}F-rhPSMA-7.3 in primary prostate lesions
- Historical Gleason Score, PSA, PSA kinetics or other biomarkers and degree of uptake of ^{18}F-rhPSMA-7.3 in metastatic lesions.

Kinetic modelling of the dynamic imaging data in patients will be used to determine the optimal imaging protocol for future studies.

The detailed results of the histopathology and immunohistochemistry analysis of the prostate specimens of the Cohort A subjects will not be entered into the eCRF, but will be reported separately for each Cohort A subject in a Histopathology and Immunohistochemistry Report to be prepared by the study pathologist and to be included as an Appendix in the Clinical Study Report. The immunohistochemistry analysis results that are to be entered into the eCRF include the following:

- Number of carcinoma lesions and their diameter
- Gleason grade/score
  - Primary, secondary and tertiary if applicable
  - Overall and for each separate carcinoma lesion separately

  Perineural invasion (yes/no)
- Extraprostatic extension (yes/no)
- T-class (pTNM)
- Surgical margin positivity (yes/no, location)
- Seminal vesicle invasion (yes/no)
- Lymph node status (# of metastatic/benign lymph nodes reported for each location with dissected lymph nodes)

Gleason grade will be assigned to all lesions (excluding possible lymph node metastases) as combinations of primary, secondary, and tertiary Gleason grade.

The immunohistochemical staining results will be reported and entered into the eCRF according to the visual intensity of carcinoma cells as follows: score 0 (negative staining), 1 (low intensity), 2 (moderate intensity), and 3 (high intensity). For each carcinoma lesion, the overall (average) staining intensity and the highest (maximum) intensity will be reported based on the expected localization of PSMA at the apical plasma membrane and in the cytoplasm. In the case of intrafocal heterogeneity, the percentage of differently stained tumour cells will be estimated and reported (e.g. 50 % moderate, 50 % high).

8.2.7 Analysis of safety variables

Physical Examination results

Physical examination results will be categorically summarised as the number and percentage of subjects according to body system and type, subject group and assessment day.

Vital signs

For blood pressure and pulse rate, descriptive statistics of actual values and of change from baseline will be used to summarise by subject group and assessment day.

ECG (12-Lead) at rest

ECG variables will be summarised according to actual values and change from baseline using summary statistics and will be presented by subject group and assessment time point.

Safety laboratory values

All haematology, clinical chemistry and coagulation laboratory tests will be summarised using descriptive statistics for actual values and change from baseline and presented by subject group and assessment time point.

Adverse events

All AEs will be summarised according to time of appearance (screening period and post-administration (=TEAE) AEs separately), following classification of the verbatim terms according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The number and percentage of subjects for all classified events will be presented according to System organ class (SOC) and Preferred term (PT) by subject group and overall.

Separate summaries will be presented for all AEs by subject and also for all AEs according to Seriousness, Severity and Relationship.

8.2.8 Analysis of radiation dosimetry data

Quantitative measurements of ^{18}F radioactivity in volumes of interest (VOIs) from whole-body healthy volunteer images over target organs will be made at several time points p.i. Time activity curves will be generated and integrated to calculate the cumulated radioactivity in each organ. OLINDA/EXM provides a means of calculating the radiation absorbed doses associated with the internal distribution of a radioactive substance using the Medical Internal Radiation Dose (MIRD) schema and requires, as input, the normalised cumulated activities (also known as residence times) for source organs, tissues and contents. The normalised cumulated activity is the cumulated activity per unit of administered radioactivity. The cumulated activities are then used with the OLINDA/EXM software to calculate the ensemble of organ-absorbed doses to the MIRD target organs in an adult phantom from which the effective dose can be evaluated. A dynamic urinary bladder model is used and the internal radiation dosimetry is calculated for 1-hour and 3.5-hour urinary bladder voiding intervals. The effects of the voiding interval upon the urinary bladder wall dose and the effective dose will also be evaluated. Descriptive statistics of absorbed doses to target organs and tissues specified in the MIRD schema will be tabulated.

8.2.9 Analysis of pharmacokinetic variables

^{18}F radioactivity concentrations will be determined in whole blood, plasma and urine. The concentrations will be presented using descriptive summary statistics. Time-activity curves will be generated and summarised.

8.3 Data management

The data management routines include procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, QC of the database, and documentation of the performed activities including information on discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the study protocol.

Data validation/data cleaning procedures are designed to assure the validity and accuracy of the trial data. These procedures consist of computerised online edit checks identifying e.g. data values that are outside of allowed ranges and SAS-programmed offline checks on data exports. All study-specific and standard data validation programming will be tested in a separate testing environment prior to use on production data.

Detailed information on data management will be given in a study-specific Data Management Plan (DMP) to be approved and signed prior to study start.

8.4 Web-based eCRF

Study data will be entered into a 21 CFR Part 11-compliant eCRF system (Viedoc™) provided by PCG Solutions AB. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study data will be entered directly from the source documents.

Authorised site personnel designated by the Investigator will complete data collection and data entry. Appropriate training and security measures will be completed with the Investigator and all authorised trial site personnel prior to study start.

8.5 Data entry into the eCRF

All text-type data should be entered in English. The eCRF should be completed as soon as possible during or after the subject's visit. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or assigned clinical staff should record such information in the eCRF. The Investigator will be required to electronically sign off the clinical data. This will be performed by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature.

8.6 The query process

The Study Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source documents to ensure that there are no discrepancies. All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data into the eCRFs. Once study data have been saved,

corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

If corrections are needed, the responsible Monitor or the data manager will raise a query in the eCRF. An appropriate member of the site staff will answer the queries in the eCRF. This will be audit trailed electronically within the eCRF.

8.7 Audit trail

All changes to the eCRF will be fully recorded in a protected audit trail. A reason for the change will be required.

8.8 Medical coding

Medical coding will be performed by trained DM vendor personnel in collaboration and agreement with the Investigator. AEs and medical/surgical history verbatim terms are coded using the Medical Dictionary of Regulatory Activities (MedDRA; latest version available when the setup of the eCRF starts). Prior and concomitant medications will be coded according to the WHO Anatomic Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database lock.

8.9 Database lock

When all data have been entered and discrepancies solved, a clean file will be declared, and the database will be locked.

The trial database and edit checks will be defined according to the study protocol and study-specific Data Management and Data Validation Plans. eCRFs (Viedoc, version 4.38 or later) will be used to collect the data.

8.10 Software

OLINDA/EXM software will be used in calculating radiation absorbed doses to target organs. Viedoc version 4.38 will be used for eCRF. SAS 9.4 will be used in statistical analysis of the clinical data.

9 QUALITY CONTROL AND QUALITY ASSURANCE

During the clinical execution of the trial, the SOPs of CRST and TPC will be followed, unless otherwise agreed between the parties. For data management and statistics, the SOPs of the DM provider will be followed. The principles of GCP will be followed throughout the study.

The analyses of haematology, clinical chemistry and serology will be performed at TYKSLAB, the accredited clinical laboratory of Turku University Hospital. The ^{18}F radioactivity concentration assays in whole blood, plasma and urine are performed by TPC according to its SOPs. Laboratory quality certificates will be available.

The study will be monitored by CRST and BED as agreed between the parties. The monitor(s) will be allowed to monitor the study as frequently as necessary to ensure that the data recording and protocol adherence are satisfactory. The CRFs and related source data will be reviewed in detail.

The quality assurance personnel of CRST, TPC and the Sponsor may conduct audits in any phase of the study. The study may also be inspected by the independent EC and CAs.

A curriculum vitae in English will be obtained from all Investigators who sign the protocol and from other relevant study staff.

10 ETHICAL CONSIDERATIONS

This study will follow the relevant regulations and guidance for biomedical research involving human subjects, such as the Declaration of Helsinki, GCP, and national and EU legislation. Special emphasis will be put on the well-being of the study subjects.

Prior to initiation of the study, the study protocol, the ICF, the Data Filing system (according to GDPR) and the text of any advertisements used for the recruitment of study subjects will be submitted to and approved by an independent EC. Additionally, the EC will be notified of any study materials to be given to the subjects (e.g. study subject diary, participant card). The study will be authorised by the CA (the Finnish Medicines Agency, Fimea) before its commencement.

The study subject candidates will be provided both verbal and written information on the study, its risks and benefits. Subjects are encouraged to ask questions on the study. After having had enough time to consider their participation, they may sign the ICF after a consent discussion, in the presence of the Investigator or his designee. No study procedure will be implemented prior to obtaining written informed consent. A copy of the signed ICF will be given to the subject. The Investigator keeps each subject's signed ICF on file.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the Investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

The subjects are asked to report all AEs to the study personnel and they are given phone numbers of the Investigator and study staff whom they are instructed to call if they observe AEs, or in other urgent study-related issues.

Substantial changes to the final approved study protocol will be implemented only with the EC's favourable opinion of a written protocol amendment, except when the change in study conduct is necessary to eliminate immediate hazards to the study subjects. The CA will also be notified before implementation of a substantial protocol amendment. When the change involves only logistics or administration, it is considered non-substantial, and does not need to be submitted to the EC or the CA for approval prior to implementation.

An end of trial notification will be submitted within 90 days and the Clinical Study Report within 12 months of the end of study. The Investigator will notify the EC and the Sponsor will notify the CA. The end of the study is defined as the date of final database lock for data analysis.

11 DATA HANDLING AND RECORD KEEPING

11.1 Case report forms

Generated subject data will be recorded on eCRFs provided for this study by the DM provider. CRST will prepare source data forms that include the eCRF data points and that will be used to collect source data. Source data forms will be collected and retained in the ISF. The ISF will be archived by CRST in a GCP-compliant manner for as long as mandated by any applicable regulations.

Only authorised persons, as agreed at the study initiation meeting, are allowed to make entries on eCRFs. Agreed study team members can make corrective entries on the eCRFs if the Investigator has not yet signed the eCRF. After signing, only the Investigator is allowed to make corrections.

11.2 Source data

Study-specific source data forms will be prepared by CRST before study initiation. Access to the source data revealing the identity of the study subjects is only to study personnel. The generated source data are stored within the ISF at CRST, and are to be archived by CRST according to CRST's SOPs.

TPC will collect, store and handle source data related to IMP handling and dosing, PET/CT imaging and blood and urine radioactivity analysis according to its standard practices, defined

in TPC's SOPs. The imaging-related raw data and the results of the blood and urine radioactivity measurements will not be transcribed into the eCRFs.

The detailed results of the histopathology and immunohistochemistry analysis of the prostate specimens of the Cohort A subjects will be reported separately for each Cohort A subject in a Histopathology and Immunohistochemistry Report to be prepared by the study pathologists and to be included as an Appendix in the Clinical Study Report. These individual pathologist's reports are considered as source data. The histopathology and immunohistochemistry analysis results that are to be entered into the eCRF are listed in section 8.2.6 above. Copies of the pathologists' reports will be entered into the patient records of the Cohort A patients held by Turku University Hospital.

The results of the laboratory blood and urine safety determinations are stored as print-outs within the ISF at CRST and also in electronic form in the patient records of TYKSLAB, Hospital District of Southwest Finland, the personnel of which is bound to professional secrecy. The coded 12-lead ECG print-outs are stored within the ISF at CRST.

The contact information of the subject's next-of-kin will be destroyed before the ISF is archived. Archiving will be performed according to the SOPs of CRST, after database lock.

11.3 Deviations

In case the study monitor, the Investigator, a study nurse or other authorised person involved in the study observes a protocol deviation or discrepancy, he/she should describe the issue as clearly as possible in a written memorandum. In addition to the date and signature of the author, the Investigator, and possibly the monitor and/or authorised Sponsor's representative will also sign the memorandum. Deviations concerning a single subject will be described on the corresponding source document and eCRF. A Deviation Log will be maintained by CRST.

11.4 Amendments

Minor changes (e.g., concerning logistics or administration) to the clinical study protocol will be written in a non-substantial amendment provided the change has no effect on the safety of the subjects or on the scientific value of the study. The Investigator will inform the Sponsor of such minor changes. All other changes to the clinical study protocol will be described in a substantial amendment, which will be submitted for approval by the EC and CA before adopting the changes. Amendments to the clinical study protocol are prepared as agreed by the parties involved in the study.

12 STUDY SCHEDULE

The study is planned to be completed in the year 2019. The end of the study is defined as the date of final database lock for data analysis.

13 CRITERIA FOR PREMATURE STUDY TERMINATION

The study may be discontinued at the clinical site at the discretion of the Principal Investigator and the Sponsor based e.g. on the occurrence of the following:

- ADRs unknown to date in respect to their nature, severity, and duration or the unexpected incidence of known ADRs.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of subjects.
- Cancellation of product development.
- Significant deviations from the protocol.

CRST, acting on behalf of the Sponsor, will inform the EC and the CA if the study is terminated prematurely. The Sponsor reserves the right to prematurely terminate the study for valid scientific or administrative reasons. The Investigator will proceed to appropriate actions concerning the study subjects in the case of premature termination of the study.

14 FINANCING AND INSURANCE

Financial matters are covered by agreements between CRST and the Sponsor, and between any other relevant parties of the study. The Sponsor has procured an insurance policy covering damages caused by the IMP. The insurance statement will be provided in the ISF and TMF. In case of any injury caused by an incident that is related to the study procedures but is not causally related to the IMP, study subjects will be covered by the insurance policies of CRST and TPC.

15 STUDY REPORT AND PUBLISHING

A final Clinical Study Report will be prepared, as agreed between the parties, after the study has been completed or prematurely terminated. The Sponsor may submit the report to another party. The EC and CA are notified about the study completion according to laws and regulations and as agreed between the parties. The study report will be approved by the PI and the Sponsor. The Sponsor remains the exclusive owner of the study data defined in the protocol. The study results will be submitted for publication in a scientific journal. The authorship of such publication(s) will be determined according to ICMJE recommendations. No publication will be submitted for publication without prior approval of the Sponsor.

16 ARCHIVING

The ISF (including e.g. source data, subject screening and identification logs, original signed ICFs, copies of CRFs, and drug accountability records) will be archived by CRST in a secure, GCP-compliant manner to enable possible follow-up assessments or audits by the Sponsor, or inspections by the independent Ethics Committee or regulatory authorities. The ISF is archived for at least 25 years after the end of the study, unless specified otherwise in a written agreement between the Sponsor and CRST. Turku University Hospital will maintain the patient records of the PCa patients included in this study according to standard hospital practices and national legislation.

Information collected during the course of this study will be stored by the Sponsor and used in the development of ^{18}F-rhPSMA-7.3, and thereafter for as long as the information is relevant for patient care. Its use includes the transfer of data to regulatory authorities of the

European Union or its member states, the USA or other non-EU countries for the purpose of obtaining, maintaining and processing marketing authorisations. All personal information is handled confidentially and according to current laws and regulations.

The Sponsor will archive the TMF according to current laws and regulations.

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APPENDICES

Appendix 1. Signed consent of the Investigator
Appendix 2. ECOG performance status

Appendix 1

SIGNED CONSENT OF THE INVESTIGATOR

Sponsor: Blue Earth Diagnostics Ltd.

Study number: BED-PSMA-101 (Sponsor), C632 (CRST)

Study title: A phase 1, open-label study to assess safety, biodistribution, and internal radiation dosimetry of 18F-rhPSMA-7.3 injection in healthy volunteers, and to assess safety and investigate the imaging characteristics in subjects with prostate cancer

Study centre: Clinical Research Services Turku - CRST Ltd.

Name of the investigator: Mika Scheinin

I have read the protocol *(version 3.0 / 18Oct-2019)* and agree to its terms.

Date and location: _____

Signature: _____

ECOG PERFORMANCE STATUS

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.