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Optimizing timing of rhPSMA-7.3 (18F), for assessing site(s) of recurrent disease following radical prostatectomy

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Funding Sponsor:	*Blue Earth Diagnostics, Inc.* 25 Burlington Mall Road, Ste. 206 Burlington, MA 01803 (855) 298-6461
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Study Product Provider:	*Blue Earth Diagnostics, Inc.*
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- ## Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonization ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

• List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federal wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

BCR	Biochemical Recurrence
PET	Positon Emission Tomography
NYU	New York University
RP	Radical Prostatectomy
GGG	Gleason Grade Group
PSADT	PSA doubling time
BED	Blue Earth Diagnostics

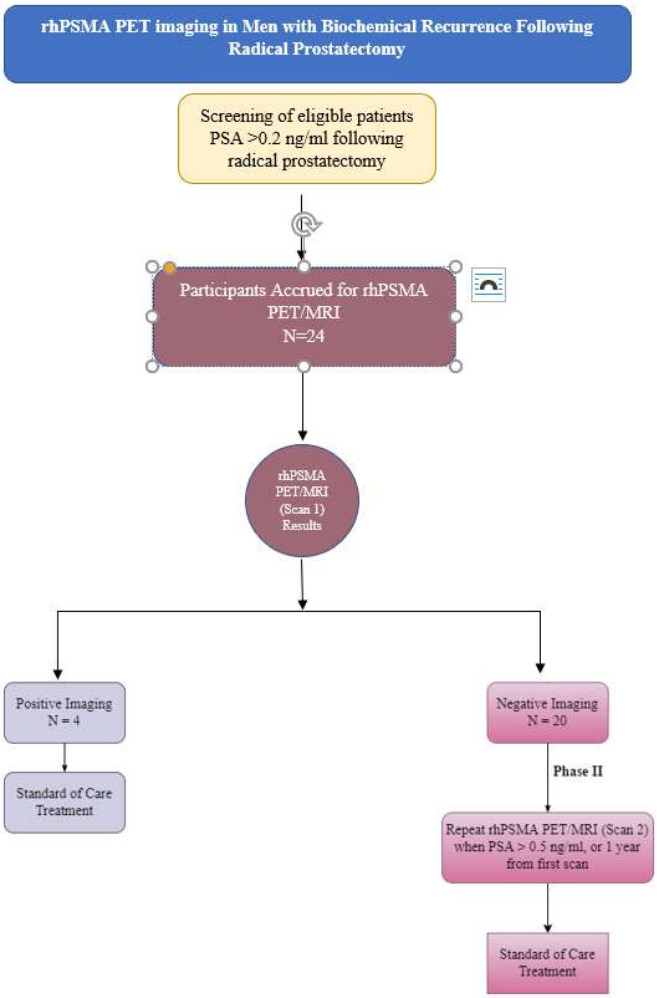
• Protocol Summary

Title	**Optimizing timing of rhPSMA-7.3 (18F), for assessing site(s) of recurrent disease following Radical Prostatectomy**
Short Title	*rhPSMA-7.3 (18F) study*
Brief Summary	All men following RP at NYU Langone Health undergo routine PSA testing in order to identify disease recurrence. By consensus, a BCR following RP occurs once the PSA > 0.2 ng/ml/ Biochemical recurrence often develops years prior to clinical evidence of disease recurrence. Early identification of the site(s) of disease recurrence enables early salvage intervention. Men will be eligible for the study at the point in time their post-prostatectomy PSA level first becomes >0.2 ng/ml. Only those subjects with rhPSMA-7.3 (18F) identifiable disease (local, nodal or systemic) will be offered salvage intervention per our standard of care. All subjects with a negative initial rhPSMA-7.3 (18F) scan will undergo a second scan when the PSA is > 0,5 ng/ml or one year after the initial PET study. The salvage interventions will be at the discretion of the investigator. The study will compare the diagnostic yield of the first and second rhPSMA-7.3 (18F) studies.
Objectives	***The primary study objective*** is to evaluate the optimal timing for rhPSMA-7.3 (18F) PET imaging for detecting site(s) of disease recurrence following RP. ***The secondary objective***: determine the disease characteristics that are associated with earliest Rh-PSMA detection of disease recurrence
Methodology	*Open Label*

Endpoint	***Primary Endpoint:*** Comparative diagnostic yield (focal, nodal or systemic disease recurrence) of rhPSMA-7.3 (18F) PET MRI in men with BCR following RP at two time points after PSA first becomes > 0.2ng/ml. ***Secondary Endpoint:*** Factors associated with positive rhPSMA-7.3 (18F) study.
Study Duration	*This current study will be conducted for approximately 24 months*
Participant Duration	*24 months is the time it will take for each individual participant to complete all participant visits.*
Population	*All men undergoing RP at NYU Langone Health will be eligible at the first time the PSA >0.2ng/ml.*
Study Sites	*Department of Urology at NYU Langone Health*
Number of participants	*Number of participants projected for the entire study 26*
Description of Study Agent/Procedure	*rhPSMA-7.3 (18F) is a 18F-labeled PET diagnostic agent FDA approved for the diagnosis of PCa. The molecular structure of the drug substance comprises a PSMA binding motif, a peptide spacer, an 18F-radiolabeled silicon fluoride acceptor moiety and a gallium chelator complex.*
Key Procedures	*rhPSMA-7.3 (18F) PET MRI imaging*

Statistical Analysis	Subjects who test positive at Scan #1 and undergo salvage treatment will carry forward as a positive second scan which enables us to use a McNemar's test to compare paired results between Scan 1 and 2. We consider a clinically significant detection rate for 30 percentage points between Scan 1 and 2. Assumptions: 1. 20% of our participants will have a positive Scan #1 o 100% of these 20% will have a presumed positive Scan #2 2. 80% of our participants will have a negative Scan #1 o 37.5% of these 80% will have a positive Scan #2 o 62.5% of these 80% will have a negative Scan #2 At a power of 80% and alpha of 5%, we would need a sample size of 19 to be adequately powered to show a clinically significant change in detection rates. Thus, a sample of 26 allows for some drop-out or failure to follow-up without compromising the study. With a sample size of 26, if we have no drop-outs, at a power of 80% and an alpha of 5%, we are adequately powered to detect a change from 20% positive between Scan 1 and 2.

Schematic of Study Design



1 Key Roles

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2 Introduction, Background Information and Scientific Rationale

2.1 *Background Information and Relevant Literature*

Approximately 20% of men undergoing radical prostatectomy (RP) will develop biochemical disease recurrence (BCR) defined as PSA > 0.2 ng/ml within 10 years of surgical intervention (Ref.1) The challenge is to determine if the site(s) of disease is local, nodal or systemic. Knowing the site(s) of disease influences salvage management. Historically, imaging studies used to identify sites of disease recurrence imaging CT or MRI and bone scintigraphy. Unfortunately, these studies lacked both sensitivity and specificity for identifying site(s) of metastasis at the time BCR first detected (Ref.2) PET MRI imaging using various commercially available ligands has been shown to be more sensitive than standard imaging for detecting site(s) of recurrent disease at lower levels of PSA. Following radical prostatectomy (Ref.3). Early identification of the sites of disease recurrence would inform whether to offer salvage radiation or androgen deprivation therapy. rhPSMA-7.3 (18F), is a new ligand being developed for detecting recurrent disease following RP (Ref.4) The lower limit of sensitivity for detecting disease recurrence following RP has not been elucidated. PET imaging is costly and a negative scan provides patient anxiety since treatment decisions are often deferred. The rationale for the present study is to define the sensitivity of rhPSMA-7.3 (18F), imaging at the earliest time point following development of BCR following RP. This objective will be explored by obtaining a rhPSMA-7.3 (18F), test soon at a BCR > 0.2ng/ml If the scan is non-diagnostic, no treatment will be offered and a second scan will be performed when the PSA is >0.5 ng/ml or one year after the detection of BCR.

2.2 *Name and Description of the Investigational Agent*

rhPSMA-7.3 (18F) is a 18F-labeled PET diagnostic agent FDA approved for the diagnosis of PCa. The molecular structure of the drug substance comprises a PSMA binding motif, a peptide spacer, an 18F-radiolabeled silicon fluoride acceptor moiety and a gallium chelator complex.

2.2.1 Preclinical and Clinical Data to Date

As rhPSMA-7.3 (18F) represents approximately 39% of rhPSMA-7 (18F), initial clinical data from a retrospective study of 1189 patients who underwent rhPSMA-7 (18F) PET scans are relevant to the understanding of rhPSMA-7.3 (18F) (Study BED-PSMA-402). Based on these data, it was concluded that use of moderate activities >8 to 10 mCi (>297 to 370 MBq) at an early imaging time point (50 to 70 minutes) is likely preferable for rhPSMA-7 (18F) in general use. However, the most abundant diastereoisomer in the rhPSMA-7 (18F) mixture, rhPSMA-7.3 (18F), appears to have slightly higher tumor uptake compared to the other isomers. Although initial clinical use involved rhPSMA-7 (18F) diastereoisomeric mixture, rhPSMA-7.3 (18F) has been taken into future development as a single isomer (Studies BED-PSMA-403, BED-PSMA-101, BED-PSMA-301 and BED-PSMA-302) and the recommended activity may differ from the data generated on rhPSMA-7 (18F).

2.2.2 Dose Rationale (if applicable)

Defining the performance of rhPSMA-7.3 (18F) at different PSA levels thresholds is the primary objective of the present study.

2.3 Rationale

Optimal management of disease recurrence following RP requires identification of the site(s) of disease. PET MRI imaging is the most sensitive imaging modality for identifying site(s) of disease recurrence following RP. Elucidating the sensitivity of PET MRI imaging will inform the optimal time to initiate assessment for recurrent disease. Since BCR following RP is defined by a PSA >0.2 ng/ml, the first rhPSMA-7.3 PET MRI in the present study will be performed as soon as BCR is detected. If the rhPSMA-7.3 PET MRI fails to identify site(s) of disease recurrence then no treatment will be offered and a second scan will be performed when the PSA is > 0.5 ng/ml or one year after designation of BCR.

Our hypothesis is that the diagnostic yield when BCR is first designated by a PSA > 0.2 ng/ml is too low to justify routine testing. We anticipate a significantly higher diagnostic yield when the PSA is >0.5 ng/ml or one year after initial imaging.

2.4 *Potential Risks & Benefits*

2.4.1 Known Potential Risks

One minor risk is related to a single venipuncture to inject the rhPSMA-7.3 (18F). Participants undergoing 1 scan will be exposed to 4.7 mSv (0.47 rem) radiation. The participants who will undergo two scans will be exposed to approximately 9.4 mSv .0.94 rem) of radiation, equivalent to the amount of radiation received from the natural radiation background environment over a period of about 3 years. rhPSMA-7.3 (18F).

MRI associated risks:

- Magnetic resonance imaging or MRI scanning uses magnetism, radio waves, and a computer to produce images of body structure
- MRI scanning is painless and does not involve x-ray radiation.
- Patients with heart pacemakers, metal implants, or metal chips or clips in or around the eyes cannot be scanned with MRI because of the effect of the magnet.
- Claustrophobic sensation can occur with MRI scanning
- Privacy protection procedures are in place and good clinical practice guidelines are followed for the study to minimize risks associated with research procedures and participation.

2.4.2 Known Potential Benefits

Not all insurance providers will pay for the PET component of MRI imaging in order to detect disease recurrence following RP. The potential benefit to the patient is earlier identification of the site(s) of disease following RP which enables early intervention.

3 Objectives and Purpose

3.1 *Primary Objective*

The primary study objective is to evaluate the optimal timing for Rh-PSMA-7.3 PET imaging for detecting site(s) of disease recurrence following RP should be performed at a PSA of 0.2 ng/ml vs 0.5 ng/ml.

3.2 Secondary Objective

Determine the disease characteristics that are associated with Rh-PSMA-7.3 detection of disease recurrence.

4 Study Design and Endpoints

4.1 Description of Study Design

All men undergoing RP at NYU Langone Health undergo routine PSA testing in order to identify disease recurrence. By consensus, a BCR following RP occurs once the PSA.0.2ng/ml. Biochemical recurrence develops years prior to clinical evidence of disease recurrence. Early identification of the site (s) of disease recurrence enables early salvage intervention. Men will be eligible for the study when their post-prostatectomy PSA level is initially observed to be PSA >0.2ng/ml. Only those subjects with rhPSMA-7.3 (18F) identifiable disease will be offered salvage intervention per our standard of care. All subjects with a negative initial rhPSMA-7.3 (18F) scan will undergo a second scan when the PSA> 0.5 ng/ml or one year after the initial PET study. The salvage intervention will be at the discretion of the investigator. The study will compare the performance of rhPSMA-7.3 (18F) at different and specified time points. Gleason grade group, (GGG), pathological stage, margin status, PSA doubling time (PSADT) will be compared between those subjects with a positive vs negative rhPSMA-7.3 (18F) scan.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

Performance of rhPSMA-7.3 (18F) MRI in men with BCR following RP between scan 1 (onset of BCR) and scan 2 (PSA > 0.5 ng/ml or one year after scan 1).

4.2.2 Secondary Study Endpoints

The secondary endpoint is to elucidate those factors associated with a positive rhPSMA-7.3 (18F) scan.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

Eligible subjects will include all men between age 18 -100 years old,-that have had RP, at the first point in time the PSA > 0.2 ng/ml.

Reasons for Withdrawal or Termination.

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
-
- If subject is unable to tolerate the rhPSMA-7.3 (18F) PET /MRI scan.
-
- The subject's insurance company denies pre-authorization for payment of a post radical prostatectomy MRI which is standard of care.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Eligible subjects will include all men undergoing RP at the first point in time the PSA > 0.2 ng/ml.
- Consented to undergo rhPSMA-7.3 (18F) PET/MRI following the protocol requirements.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Any contraindication for MRI imaging.
- Prior allergic reaction to rhPSMA-7.3 (18F).
- Patient refuses rhPSMA-7.3 (18F) PET/MRI.

5.4 *Strategies for Recruitment and Retention*

Potential subjects will be identified from the co-investigators clinical practices at NYU Langone Health. The patients are being followed periodically for their PSA levels, and at the first point in time their PSA > 0.2 ng/ml they will be invited to participate in our study.
Men undergoing RP are routinely followed for biochemical recurrence as standard of care. The PI and co-investigators will identify potential candidates when the PSA initially is >0.2ng/ml. At this time point, it is also standard of care (SOC) to obtain an abdominal /pelvic and prostate MRI to identify site (s) of disease recurrence. The research PET scan will be performed in addition to the SOC MRI, at the same time.
Men following RP whose PSA increases > 0.2ng/ml will be eligible for the study. All men meeting this PSA threshold and interested participants will be invited to enroll in the clinical study. The research coordinator will explain the study to the participant and answer any questions that may arise during the discussion. All potential risks will be discussed with the participant. The rhPSMA-7.3 (18F) PET/MRI scan will be performed only after obtaining the participant's signature on the informed consent form.
We anticipate screening 3 patients a month who initially develop BCR following RP, of which two will enroll in the study. We anticipate enrolling 26 subjects over a twelve-month interval. The justification for the sample size is included in the statistical analysis section (Section 9).

5.5 Duration of Study Participation

We anticipate the 26 subjects to be enrolled within one year of study initiation. The first rhPSMA-7.3 (18F) imaging study will be obtained within a month of enrollment. The second rhPSMA-7.3 (18F) imaging study will be performed within a year of the initial study. The total duration of the study should be 24 months.

5.6 Total Number of Participants and Sites

All participating subjects will be drawn by patients actively followed by the PI and co-investigators at NYU Langone Urology Faculty Group Practice.

This is a single site study. Recruitment will end when 26 participants are enrolled. It is expected that approximately 26 participants will be enrolled to produce 19 evaluable participants.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination, and Handling of Participant Withdrawals or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

If subject is unable to tolerate the rhPSMA-7.3 (18F) PET /MRI study

The subject's insurance company denies pre-authorization for payment of MRI and diagnostic biopsy.

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the funding sponsor Blue Earth Diagnostic Ltd., and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

rhPSMA-7.3 (18F) is a 18F-labeled PET diagnostic agent FDA approved for the diagnosis of PCa. The molecular structure of the drug substance comprises a PSMA binding motif, a peptide spacer, an 18F-radiolabeled silicon fluoride acceptor moiety and a gallium chelator complex. The significant over-expression of PSMA in the majority of PCa cells makes it an excellent target for imaging in PCa. Expression of PSMA is higher in more advanced stages of PCa and correlates with Gleason score and PSA concentrations (Ref.5). This increased expression of PSMA is less evident in prostatic hyperplasia (Ref.6). rhPSMA-7.3 (18F) is a sterile, aqueous solution for intravenous administration.

6.1.1 Acquisition

The study agent, rhPSMA-7.3 (18F) will be provided by Blue Earth Diagnostics Ltd. It will be shipped directly to the Isotope Radiology department at NYU Langone Health, where it will be administered to the research subject.

6.1.2 Formulation, Appearance, Packaging, Labeling, Product Storage, and Stability

From the end of synthesis, the shelf-life of rhPSMA-7.3 (18F) injection is 6 hours for the formulation used in Phase 1, and 10 hours for the formulation used in the ongoing Phase 3 studies. The product must not be used beyond these limits. rhPSMA-7.3 (18F) injection should be stored at room temperature in a shielded container. All non-radioactive containers (shielding, transport cans) must be returned to the manufacturing site. Containers that are radioactive or that contained radioactive products must be disposed of at either the study site or another designated facility, with prior approval from the sponsor, after the study and after overall drug accountability has been completed by the sponsor or its representative.
Waste must be disposed of according to Federal, State, and local regulations for radioactive material. Precautions for the safe handling of radioactive materials should be observed.

6.1.3 Dosing and Administration

The mean effective dose for men per unit-administered activity was 0.0138 mSv/MBq using a 1-hour voiding interval and 0.0141 mSv/MBq using a 3.5-hour voiding interval. Biodistribution data derived from the healthy volunteers in Study BED-PSMA-101 suggest 8 – 10 mCi (296 – 370 MBq) would result in an image of diagnostic quality.

6.1.4 Route of Administration, and Duration of Therapy

rhPSMA-7.3 (18F) will be administered intravenously. And it is a single dose injection.

7 Study Procedures and Schedule

7.1 *Study Procedures/Evaluations*

7.1.1 Study Specific Procedures

- Identification of eligible subjects by the PI and Co-PI's
- Explanation of study objectives and design
- Informed consent
- Comparing the diagnostic yield for detection of site (s) of disease recurrence following RP using an investigational rhPSMA-7.3 MRI at two designated time points
- Assessing any adverse effects of the RhPSMA ligand

7.1.2 Standard of Care Study Procedures

All decisions related to management of prostate cancer and its recurrence will be standard of care

7.2 Study Schedule

7.2.1 Screening and Enrollment

All men at the first time point the BCR is observed following RP (PSA)0.2ng/ml) are eligible for enrollment in the study.
The study coordinator will discuss all aspects of the protocol with the eligible subjects.
Obtaining informed consent.
Schedule rhPSMA-7.3 (18F) for participants who sign informed consent.

7.2.2 Enrollment/Baseline

Enrollment/Baseline Visit Vital sign measurement before and after injection of the radiotracer is performed.
The rhPSMA-7.3 (18F) PET imaging scan #1 is performed.
Assessment of any possible AE, related with the rhPSMA-7.3 (18F) administration.
Men with positive scans undergo salvage treatment, as per standard of care.

7.2.3 Final Study Visit

Vital sign measurement before and after injection of the radiotracer is performed.
Conduct the second rhPSMA-7.3 (18F) PET imaging scan for subjects with negative rhPSMA-7.3 (18F) PET/MRI in the first scan.

The second scan will be one year from the first scan, or when the PSA > 0.5 ng/ml.

Assessment of any possible AE, related with the rhPSMA-7.3 (18F). Subjects will complete an AE form after completing the rhPSMA-7.3 (18F) scan.

8 Assessment of Safety, Adverse Events, Serious Adverse Events

8.1 Classification of an Adverse Event, and Expectedness

The Principal Investigator and/or co-investigators will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.2 Reporting Procedures – Notifying the IRB .

8.2.1 Adverse Event (AE) Reporting

The risks associated with this study are low and infrequent, Herbert Lepor, M.D. the PI for the study, will be responsible for monitoring the safety of the study. The subjects will be instructed to report any side effect of the rhPSMA-7.3 (18F) in the Adverse Events form that will be provided to them on the day of the rhPSMA-7.3 (18F) PET MRI scan. The research coordinator will be the contact person who will receive the AE information.

8.2.2 Serious Adverse Event (SAE) Reporting

The risks associated with this study are low and infrequent, Herbert Lepor, M.D. the PI for the study, will be responsible for monitoring the safety of the study. The subjects will be instructed to report any side effect of the rhPSMA-7.3 (18F) in the AE form that will be provided to them on the day of the rhPSMA-7.3 (18F) PET MRI scan. The research coordinator will be the contact person who will receive the AES information. In addition to reporting of Serious Adverse Events (SAEs) to the responsible IRB/IEC and Health Authority, Principal Investigator or designee will inform Blue Earth Diagnostics (BED) of all SAEs in connection with the Study that occur following receipt of rhPSMA-7.3, whether or not related to Product.

PI or designee shall notify BED within twenty four (24) hours of knowledge of any SAEs. SAE reports to BED must be recorded and faxed or scanned and emailed to:

Bracco Diagnostics Inc. Drug Safety Unit
E mail: Drugsafetyus@BlueEarthDx.com
Fax: +1-609-514-2522

To the extent permitted by federal law, additional and further requested information (follow-up or corrections to the original case) will be detailed and faxed/emailed to the same address and will include the following minimum information: The name and contact information of the reporter, the name of the study drug(s), a description of the reported SAE, with the patient identified by one or more of the following (patient initials/code, patient number age, sex), an investigator assessment of study drug causality, and any additional data customarily accompanying such reports which would aid the review and causality assessment of the case including but not limited to the date of onset, severity, the time from administration of study drug(s) to start of the event, the duration and outcome of the event, any possible etiology for the event, and the final diagnosis or syndrome, if known.

8.2.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

As BED continues to develop this compound, we recommend that the safety monitoring period can be suitably within 24 hours of injection, while acknowledging it is the sponsor's decision.

83 Reporting Procedures – Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as INDsafety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:
  - suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

8.4 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. Safety oversight will be under the direction of the PI. He will complete a DSM report about the safety and efficacy data semiannually.

9 Statistical Considerations, Hypothesis, and Sample Size

The primary study objective is to evaluate whether the first Rh-PSMA-7.3 PET imaging study for detecting site(s) of disease recurrence following RP should be performed at a PSA of 0.2 ng/ml vs 0.5 ng/ml.

Subjects who test positive at scan # 1, and undergo salvage treatment will carry forward as a positive second scan which enables us to use a McNemar's test to compare paired results between scan 1 and 2.

We consider a clinically significant detection increase to represent of 30 percentage points between scan 1 and 2 , from 20% positive at PSA 0.2 ng/ml to 50% positive at PSA 0.5 ng/ml:
Assumptions:

- 20% of our participants will have a positive scan 1
- 100% of these 20% will have a presumed positive scan 2.
- 80% of our participants will have a negative at scan 1.
- 37.5% of these 80% will switch to positive scan 2.
- 62.5% of these 80% will remain negative a scan 2.

At a power of 80% and alpha of 5%, we would need a sample size of 19 to be adequately powered to show a clinically significant change in detection rates. Thus, a sample of 26 would allow for some drop-out or failure to follow-up without compromising the study. With a sample size of 26, if we have no drop-outs, at a power of 80% and an alpha of 5%, we are adequately powered to detect a change from 20% positive between scan 1 and 2.

10 Source Documents and Access to Source Data/Documents

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

12 Ethics/Protection of Human Subjects

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

12.3 Informed Consent Process

Consent process will take place in the consult rooms, complete privacy will be provided. Consent forms describing in detail the study agent (rhPSMA-7.3 (18F)), study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. All the eligible and interested participants will be given an informed consent form to read before being scheduled for an rhPSMA-7.3 (18F) PET MRI scan. The research coordinator will explain the study to the participant and answer any questions that may arise during the discussion. All potential risks will be discussed with the participant. The rhPSMA-7.3 (18F) PET MRI scan will be performed only after obtaining the participant's signature on the informed consent form.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, , consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

12.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, will retain the ability to use all information collected prior to the revocation of subject authorization .Participant confidentiality will be strictly held in trust by the participating investigators, the research team.

13 Data Handling and Record Keeping

All the data that is collected for each participant will be included in the subject's research file. The files will be kept at a secure location. Only the members of the research team will have access to the research files. TrialMaster is the software that will be used for all data collection. The electronic data will be secured with a password which will be known only to the members of the research team.

13.1 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

13.2 Protocol Deviations

Protocol deviations or violations (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:

- One or more participants were placed at increased risk of harm.
- The event has the potential to occur again.
- The deviation was necessary to protect a subject from immediate harm.

Protocol deviations will be reported to the IRB no later than 5 working days after the event is discovered.

13.3 Publication and Data Sharing Policy

The publication of an abstract, article or paper in a journal or an electronic repository, or its presentation at a conference or seminar; and in clause 8 to Publish and words to a similar effect are to be construed accordingly.

14 Study Finances

14.1 Funding Source

Blue Earth Diagnostic Inc. is the company that manufactures rhPSMA-7.3 (18F). They will donate the rhPSMA-7.3 (18F). The rhPSMA-7.3 (18F) PET MRI adds approximately one hour to the imaging time.

14.2 Costs to the Participant

The standard of care includes a repeat PSA and MRI post radical prostatectomy. The patient will be responsible for the standard of care costs if these costs are denied by their insurance carrier. Pre-authorization will be obtained prior to performing the repeat MRI after radical prostatectomy.

14.3 *Participant Reimbursements or Payments*

Participants will not be reimbursed or get any payment for their participation in this study.

15 Study Administration

15.1 Study Leadership

The PI for the study will be Herbert Lepor, MD who is Professor and Chair of Urology at NYU Grossman School of Medicine. Drs Samir Taneja, William Huang, James Wysock, and Wei Phin Tan all who are fellowship trained in urologic oncology, will serve as co-PI. They will request the rhPSMA-7.3 (18F) PET MRI scans. The PI or other co -PI's interpret the MRI and determine if a second scan is necessary per protocol criteria.

16 Conflict of Interest Policy

The PI, nor the co-PI's have any conflicts of interest with the sponsor of the study

17 References

1. Llukani E, Lepor H. Aetiology and management of earlier vs later biochemical recurrence after retropubic radical prostatectomy". BJU Int. 2017 Oct;120(4):505-510.
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5. Mannweiler S;Amersdorfer P;Trajanoski S;Terrett JA;King D;Mehes G; "Heterogeneity of Prostate-Specific Membrane Antigen (PSMA) Expression in Prostate Carcinoma with Distant Metastasis." *Pathology Oncology Research : POR*, U.S. National Library of Medicine, https://pubmed.ncbi.nlm.nih.gov/18802790/.
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19 Schedule of Events

Activity	Visit 1	Visit 2 **rhPSMA-7.3 (18F) PET/MRI scan #1** When PSA 0.2 ng/ml following RP	Visit 3 **rhPSMA-7.3 (18F) PET/MRI scan #2** 12 Mo from rhPSMA-7.3 (18F) scan #1, or when PSA>0.5 ng/ml
Study team procedures			
Confirming eligibility	X		
Study review with possible participant	X		
Informed consent	X		
Vital sign measurement before injection of the radiotracer		X	X
Study drug/device dispensation		X	X
Vital sign measurement after injection of the radiotracer		X	X
Participant study ligand Adverse Events survey		X	X