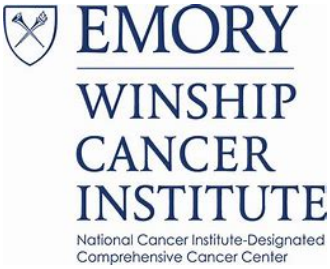

PROTOCOL TITLE: Strategy to Reduce Bladder Activity with rhPSMA 7.3: Comparison of 18F-rhPSMA 7.3 PET/CT with and without Furosemide in Biochemical Recurrence of Prostate Cancer

WINSHIP PROTOCOL #:

COORDINATING CENTER: Emory University Healthcare, Atlanta, GA

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VERSION: Version 6: JUN/6/2024

FUNDING SOURCE: Blue Earth Diagnostics (BED IIT-439)

INVESTIGATIONAL PRODUCT (IP): 18F-rhPSMA 7.3 PET/CT, Blue Earth Diagnostics.
OTHER AGENT(S): N/A

IND #: 162587; Sponsor-Investigator: David Schuster, MD
☐ **Study Exempt from IND Requirements per 21 CFR 312.2(b).**

REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	JUN/06/2023	e-Consent process option has been added to **Section 15. Consent Process** on page 33.
2	JUN/13/2023	Change inclusion criteria to patients with detectable serum PSA >0.1ng/mL following prostatectomy for prostate cancer.
3	JUL/10/2023	The PI made the edit to the protocol stating 2 weeks after the second PET/CT.
4	DEC/13/2023	Edits clarifying follow-up after each PET/CT for consistency with the study schema, pertinent medical history, urinary incontinence, removal of SOC saline flushes in the procedures
5	JUN/6/2024	The PI is switched to David Schuster. The Sponsor-Investigator is switched to David Schuster as he is the new IND162587 Holder.

Table of Contents

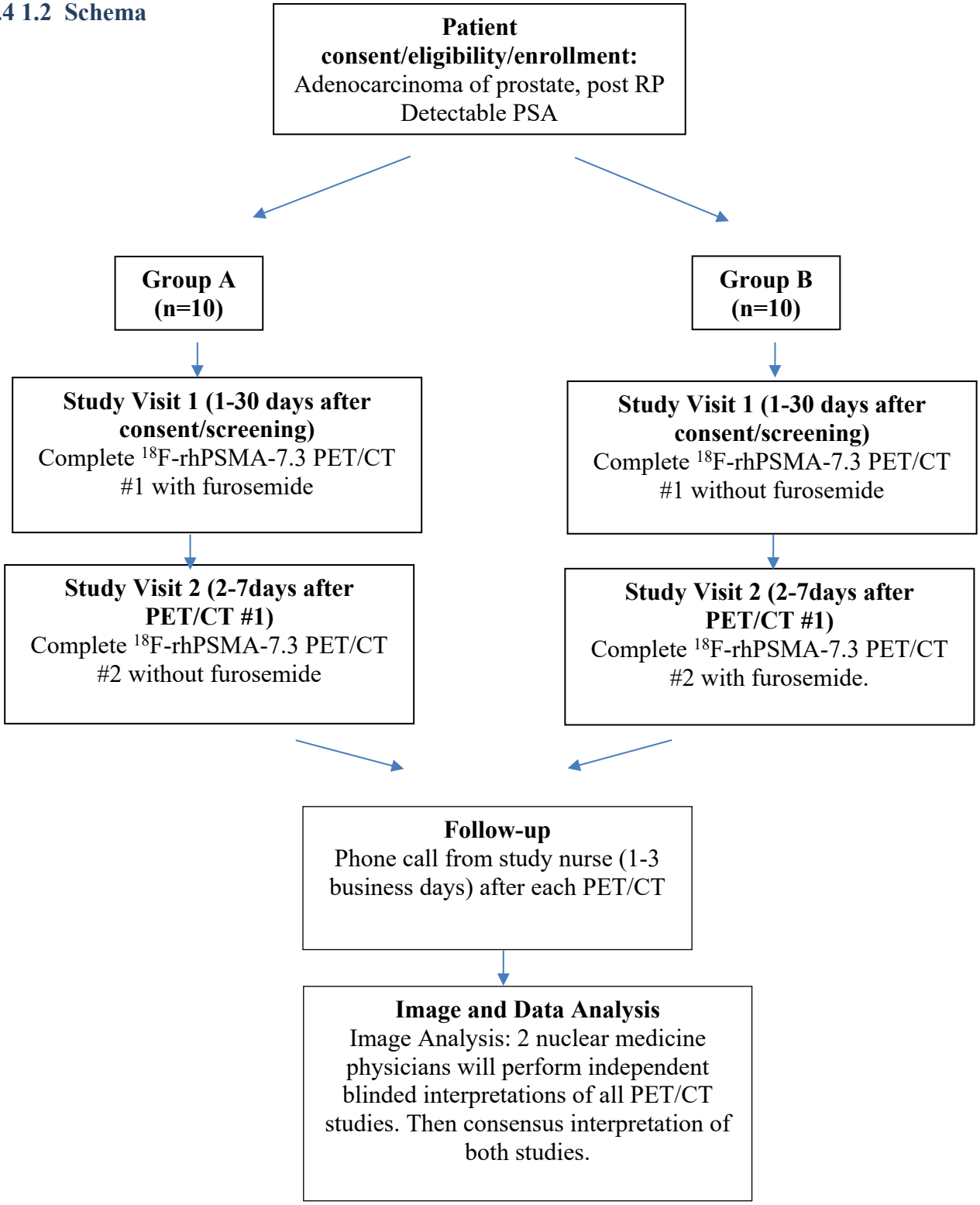
1. Study Summary

1.3 1.1 Synopsys

Title:	Strategy to Reduce Bladder Activity with rhPSMA 7.3: Comparison of 18F-rhPSMA 7.3 PET/CT with and without Furosemide in Biochemical Recurrence of Prostate Cancer
Study Description:	This research study is a single arm, Phase II study, designed to evaluate if administering furosemide at the time of 18F-rhPSMA 7.3 administration for PET/CT evaluation of prostate cancer patients with biochemical recurrence, significantly reduces bladder activity compared with the same patient scanned without furosemide as internal control
Objectives:	**Primary Objective**: To determine if administering 20 mg furosemide IV at the time of radiotracer injection significantly reduces bladder activity compared with the same patient scanned without furosemide as internal control **Secondary Objectives:** • To compare detection rates of recurrent disease in blinded interpretations between the furosemide and non-furosemide 18F-rhPSMA-7.3 PET/CT scans, with patients serving as their own internal controls • To compare reader confidence in identifying prostate bed and other recurrent lesions on a 18F-rhPSMA-7.3 PET/CT with furosemide compared with 18F-rhPSMA-7.3 PET/CT without furosemide
Endpoints:	**Primary Endpoint:** Determine the difference in the urinary bladder activity on ^{18}F-rhPSMA-7.3 PET/CT with furosemide compared with ^{18}F-rhPSMA-7.3 PET/CT without furosemide in biochemical recurrence of prostate cancer post radical prostatectomy (Specific Aim 1). **Secondary Endpoints:** Compare lesion detection and confidence between rhPSMA7.3 PET without and with furosemide.
Study Population:	The patient population consists of 20 subjects ≥18 years of age with biochemical recurrence of prostate cancer after radical prostatectomy.
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	• Emory University Hospital, Clifton Campus • Emory University Hospital Midtown • Emory University Hospital Johns Creek • Emory University Hospital St. Joseph's

Description of Study Intervention:	Radiotracer production: Blue Earth Diagnostics Ltd, manufacturers of ^{18}F-rhPSMA-7.3, has pledged support with gratis radiotracer unit doses supplied from PET-NET Solutions, a commercial radiopharmacy who made similar unit doses under IND #141561 for the Phase 3 trial also completed at our center. This study IND #162587 is held by Dr. David Schuster.
Study Duration:	5 years

1.4 1.2 Schema


Patient consent/eligibility/enrollment: Adenocarcinoma of prostate, post RP Detectable PSA
Group A (n=10)
Group B (n=10)
Study Visit 1 (1-30 days after consent/screening) Complete 18F-rhPSMA-7.3 PET/CT #1 with furosemide
Study Visit 1 (1-30 days after consent/screening) Complete 18F-rhPSMA-7.3 PET/CT #1 without furosemide
Study Visit 2 (2-7days after PET/CT #1) Complete 18F-rhPSMA-7.3 PET/CT #2 without furosemide
Study Visit 2 (2-7days after PET/CT #1) Complete 18F-rhPSMA-7.3 PET/CT #2 with furosemide.
Follow-up Phone call from study nurse (1-3 business days) after each PET/CT
Image and Data Analysis Image Analysis: 2 nuclear medicine physicians will perform independent blinded interpretations of all PET/CT studies. Then consensus interpretation of both studies.

1.5 1.3 Schedule of Assessments

Procedures	**Enrollment/Screening (-30 days)**	**Study Visit 1 PET/CT 1 (Within 30 days of enrollment)**	**(Study Visit 2 PET/CT 2 (Within 2-7 days of Visit 1)**	**Follow up (1-3 business days after each PET/CT)**
Informed consent	X			
Demographics	X			
Pertinent Medical history	X			
Administer study intervention		X	X	
AE assessment		X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
1. To determine if administering 20 mg furosemide IV at the time of radiotracer injection significantly reduces bladder activity compared with the same patient scanned without furosemide as internal control 20 patients with biochemical recurrence of prostate cancer following radical prostatectomy will be sequentially assigned to either undergo 18F-rhPSMA-7.3 PET/CT without furosemide first followed by a second PET/CT with furosemide at 2-7 days afterward, or vis-versa (10 in each group). Patients will be encouraged to void during the uptake phase up to 15 minutes before being placed on the scanner for imaging. Bladder activity (SUVmax, SUVmean, and bladder volume), ureteral activity (SUVmax, SUVmean), as well as renal activity (SUVmax, SUVmean), will be recorded. The presence and degree of halo artifacts around the bladder and kidney will also be recorded. Exclusion criteria for this trial will include urinary incontinence that may interfere with performing the study and contraindications to furosemide. As always, patients will be encouraged to arrive well hydrated and to drink an additional 500-1000 ml of water during the uptake phase.	Determine the difference in the urinary bladder activity on ^{18}F-rhPSMA-7.3 PET/CT with furosemide compared with ^{18}F-rhPSMA-7.3 PET/CT without furosemide in biochemical recurrence of prostate cancer post radical prostatectomy (Specific Aim 1).
Secondary	
1. To compare detection rates of recurrent disease in blinded interpretations between the furosemide and non-furosemide 18F-rhPSMA-7.3 PET/CT scans, with patients serving as their own internal controls Lesion detection rates on a patient and region basis will be recorded in addition to the ratio of	Compare lesion detection and confidence between rhPSMA7.3 PET without and with furosemide

OBJECTIVES	ENDPOINTS
the lesion to background activity including blood pool, liver, spleen and parotid. Test retest of lesions and background measurements between the studies with furosemide and without furosemide will be performed. **2. To compare reader confidence in identifying prostate bed and other recurrent lesions on a 18F-rhPSMA-7.3 PET/CT with furosemide compared with 18F-rhPSMA-7.3 PET/CT without furosemide** The readers'(total two readers) confidence in the assessment of findings in the prostate bed and other locoregional and distant lesions will be rated using a five-point Likert scale with 1 being definitely benign and 5 being definitely malignant. The readers' confidence scores for both the PET/CT scans (with and without furosemide) will be compared. The readers will be blinded to the furosemide injection.	
Tertiary/Exploratory	

2. Background

Prostate cancer is the most common cancer diagnosed in men in 2021 and accounted for 11% of all cancer-related deaths in men in the United States. Early diagnosis is desirable so that definite treatment with curative intent can be offered. RP is a suitable definitive therapy offered to patients with early-stage disease. Complete tumor resection during RP with or without pelvic lymph node dissection results in serum PSA level decline below detectable limits. PSA can then subsequently be used as a sensitive and specific tumor marker in the early detection of disease recurrence. The American Urological Association and European Association of Urology guidelines define biochemical recurrence after RP as an initial PSA value of 0.2 ng/mL or greater, measured 6 weeks after surgery to allow appropriate washout of any residual PSA. This result is confirmed by a subsequent PSA value of 0.2ng/mL or greater to rule out a laboratory error[1, 2]. The risk of biochemical recurrence is associated with the baseline risk categorization of the disease, with patients in higher-risk groupings having

shorter biochemical failure-free survival. Following confirmation of biochemical failure with a rising serum PSA level, imaging is used to localize the recurrent lesion and for the planning of salvage therapy. Early detection of recurrent disease is vital as lesions at this stage of the disease tend to be localized to the pelvis (prostate bed and pelvic lymph nodes), making targeted salvage therapy with curative intent feasible.

Recent advances in functional imaging of prostate cancer recurrence with PET/CT have identified two groups of radionuclides with superior performance for localizing the site of recurrence of prostate cancer. ^{18}F-fluciclovine, a radiolabeled synthetic amino acid developed and validated at Emory University Hospital, targets amino acid uptake by prostate cancer cells [3]. ^{18}F-fluciclovine PET/CT performs better than conventional imaging and, when used to guide salvage radiotherapy, leads to favorable treatment outcomes[4]. One of the strengths of ^{18}F-fluciclovine PET/CT in prostate cancer imaging is its lack of significant early urinary excretion [5]. The second category of approved radionuclides for BCR of prostate cancer imaging targets PSMA, a transmembrane protein significantly overexpressed in prostate cancer cells. ^{68}Ga-PSMA is one such agent in this group with a high lesion detection rate at low serum PSA levels[6]. ^{68}Ga-PSMA and ^{18}F-DCFPyL, the two FDA-approved PSMA-targeting radionuclides, have a high urinary excretion with a potential for limiting the accurate detection of prostate bed recurrence.

Efforts are ongoing towards improving the detection rates of PSMA targeted imaging of BCR of prostate cancer. The desirable radioligand should preferably be labeled to F-18 and have low renal excretion into the urinary bladder. ^{18}F-PSMA-1007 is a PSMA ligand labeled with F-18 and is excreted mostly via the biliary route. While these kinetic characteristics make it suitable, especially in the assessment of prostate bed recurrence, a high incidence of non-specific ^{18}F-PSMA-1007 uptake especially in bones leading to a high false positivity rate has been a significant drawback[7, 8]. Radiohybrid (rhPSMA) is a new class of PSMA-targeting radioligand. rhPSMA ligands are not only suitable for labeling with F-18, but the molecule can be labeled with diagnostic and therapeutic radiometals[9, 10]. Coming in the wake of the recent FDA approval of PSMA-targeted radionuclide therapy for metastatic castration-resistant prostate cancer (mCRPC), rhPSMA is a true theranostic agent where the same molecule labeled with a diagnostic radionuclide such as F-18 can be used for imaging and labeled to a therapeutic radionuclide such as Lutetium-177. In a recent study of 261 patients with BCR of prostate cancer after RP and a median serum PSA level of 0.96 ng/mL, ^{18}F-rhPSMA-7 PET/CT detected disease recurrence in 81% of patients. Stratified according to serum PSA levels, the detection rates were 71%, 86%, 86%, and 95% at PSA levels of 0.2 to <0.5 ng/mL, 0.5 to <1 ng/mL, 1 to <2 ng/mL, and ≥2 ng/mL, respectively[11]. There are four stereoisomers of rhPSMA-7, of which rhPSMA-7.3 has shown to be the preferred molecule based on its higher uptake in tumor, lower uptake by the kidneys, and improved clearance from the background[12]. In a single-center retrospective review of 242 patients with a median PSA level of 0.6 ng/mL who were imaged with ^{18}F-rhPSMA-7.3 PET/CT for the localization of the site of recurrence of prostate cancer, Rauscher and colleagues reported an overall positivity rate of 72.7%. At serum PSA levels of 0.2 to <0.5, 0.5 to <1, 1 to <2, and ≥2 ng/mL, lesion detection rates were 61.8%, 67.9%, 81.1%, and 95.7%, respectively[13].
Based on the encouraging diagnostic performance of ^{18}F-rhPSMA-7.3 PET/CT for the localization of BCR of prostate cancer, prospective trials have been undertaken to confirm these earlier results. In a phase 1 trial evaluating the safety, biodistribution, and radiation dosimetry of ^{18}F-rhPSMA-7.3 in healthy adult volunteers, Tolvanen and colleagues reported that ^{18}F-rhPSMA-7.3 was well tolerated in all volunteers (a single case of mild headache not requiring medication for treatment was judged to be due to rhPSMA-7.3 injection while others were not) with a calculated effective dose of 0.0141 mSv/MBq, which is lower compared to effective dose due of other PSMA ligands [10]. ^{18}F-rhPSMA-7.3 showed a urinary route of excretion with bladder activity seen from 7 minutes post tracer injection,

which increased progressively thereafter. The renal urinary excretion of ^{18}F-rhPSMA-7.3 was lower compared with excretion of other PSMA ligands such as ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL, but higher than that of ^{18}F-PSMA-1007[10]. Continued effort geared towards a further reduction in the urinary excretion of ^{18}F-rhPSMA-7.3 is pertinent to improve detection rates.

Forced diuresis with co-administration of furosemide and the radiotracer is a strategy that has been explored in decreasing the urinary activityof other PSMA radioligands with a urinary route of excretion. In a study comparing the local prostate bed recurrence detection between patients who received hydration and furosemide administration at the time of ^{68}Ga-PSMA-11 injection versus patients who did not, Uprimmy et al. reported a higher local prostate bed recurrence detection in patients who received hydration with intravenous furosemide versus patients who did not (25.5% versus 17.3%, p=0.048)[14]. The frequency of equivocal findings for prostate bed recurrence was more prevalent among patients who did not receive furosemide injection compared with those who did (16.8% versus 12.3%). Lower urinary activity did not influence the intensity of tracer uptake in prostate cancer recurrent lesions between the two groups with comparable SUV max in recurrent lesions. Similar improved diagnostic confidence with the assessment of disease in the prostate bed has been reported in other studies[15]. In an analysis of data from Technical University of Munich, a cohort of 17 patients imaged with ^{18}F-rhPSMA-7 (White Paper Prepared for Syncona: Evaluation of ^{18}F-rhPSMA7, Unpublished) demonstrated bladder SUVmean mean (SD) (range): 4.57 (6.4) (1.4-28.8). Yet as shown in a subanalysis, this lower bladder activity is highly dependent on the use of furosemide. Mean bladder SUV mean (n=5) without furosemide is 9.24, while with furosemide (n=12), bladder SUVmean is 2.63. In the joint guidelines of the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the use of furosemide was recommended for ^{68}Ga-PSMA-11 PET/CT imaging of prostate cancer[16].

2.3 3.1 Study Rationale

We hypothesize that the administration of intravenous furosemide at the time of radiotracer injection will reduce the activity of 18F-rhPSMA-7.3 in the urinary bladder and facilitates the identification of prostate bed recurrence in men with rising serum PSA post-prostatectomy. We also hypothesize that reduced urinary activity of 18F-rhPSMA-7.3 will improve readers' confidence in assessing prostate bed recurrence of prostate cancer. An improved lesion detection will influence management decisions.

To test these hypotheses with the highest scientific rigor, we propose a study including men with BCR post-prostatectomy. Each patient will undergo two sets of 18F-rhPSMA-7.3 PET/CT scans, one with and the other without furosemide, and the level of urinary bladder activity, the detection rate of prostate bed recurrence and other lesions, will be compared between the two scans. In this manner, each patient will serve as their own control. We expect that the results from this study may generate sufficient evidence that may affect the workflow of 18F-rhPSMA-7.3 PET/CT imaging of BCR of prostate cancer, especially after FDA approval for use in routine clinical care.

2.4 3.2 Clinical Experience

Our preliminary data support a key scientific premise that the intravenous administration of furosemide at the time of radiotracer injection leads to lower radiotracer concentration in the urinary bladder. This finding is supported by published studies in the literature showing that intravenous administration of furosemide at the time of 68Ga-PSMA-11 administration causes a reduction in

bladder activity, improves detection of local prostate bed recurrence, and improves reader confidence.
Study Intervention/Investigational Agent

2.5 4.1 Description

IV injection of 8 mCi (296 MBq) ± 20% of rhPSMA-7.3 (18F) diluted up to 10 mL will be used for each of the two PET scans. This dose is based on dosimetry data obtained from published phase I study data [21], and the dose utilized in the approval phase III trial that was recently concluded [NCT04186845]. The study will be performed under IND #162587 held by Dr. David Schuster.

2.6 4.2 Drug/Device Handling

- Radiotracer handling and administration: Each individual dose of radiotracer will be specifically ordered and delivered on the day of the study for the research subject and administered by authorized personnel per standard radiotracer administration protocol of the institution and division.
- The IND for the study is held by Dr. David Schuster (IND #162587)

2.7 4.3 Accountability

The study drug provided for this study will be supplied by a 3rd party radiopharmacy. The pharmacy will utilize a single-use cassette-based proprietary automated synthesis platform for radiolabeling, purification, and formulation (Scintomics GRP; Scintomics GmbH) and using an in-house remotely operated sterile filtration device for aseptic filling, in accordance with good manufacturing practices and according to the facility's standard operating procedures. The study drug is single-use, and any remaining drug will be destroyed as directed in the IB. The PI is responsible for maintaining strict control over the investigational drug to ensure that it is used only for subjects enrolled in the study. The principal investigator or health care providers on the research team will administer study drug by injection. Study site personnel will account for all study drugs received at the site.

Study drug will be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The PI or designated study personnel will maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.

The Drug Accountability Log will capture the following:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.
• The Drug Accountability Log may be reviewed by the monitor during site visits and at the completion of the study.

Drug dispensing will also be captured in the source document at each patient visit. Drug accountability may be noted by the internal monitor during site visits and at the completion of the study.

3. Procedures Involved

Overall Design
We will undertake a study with 20 patients with biochemical recurrence of prostate cancer status post radical prostatectomy. Consideration for inclusion in this study will be based on detectable PSA after radical prostatectomy (PSA ≥ 0.1 ng/ml). Histology proof of recurrence will not be required. All patients will be recruited from the radiation oncology unit and other oncology units under Emory Healthcare. All 20 patients will undergo two sets of ^{18}F-rhPSMA-7.3 PET/CT scans, one with and the other without intravenous administration of 20 mg of furosemide at the time of radiotracer injection. All patients will have oral hydration with 500 to 1000 ml of water during the uptake phase. The first set of 10 patients will have a ^{18}F-rhPSMA-7.3 PET/CT without-furosemide followed by a ^{18}F-rhPSMA-7.3 PET/CT with-furosemide 2-7 days afterward. The second set of 10 patients will have their two ^{18}F-rhPSMA-7.3 PET scans in the reverse order, with-furosemide first followed by without-furosemide 2-7 days afterward. Vital signs will be measured before and after each radiotracer administration. Each patient will undergo both imaging techniques, and the results will be interpreted blindly. A minimum of 2 days is required between the two ^{18}F-rhPSMA-7.3 to allow for the complete decay of the radiotracer from the first scan before the second scan (physical half-life of ^{18}F is 110 minutes). Patients will be allowed to void during the 60-70 minutes uptake period between ^{18}F-rhPSMA-7.3 radiotracer administration and the commencement of PET/CT imaging. Patients will be encouraged to void at approximately 50 minutes post injection and encouraged to refrain from voiding 15 minutes before the commencement of the PET/CT (60-70 min post injection), if possible, to facilitate bladder distension.

Two nuclear medicine physicians, Drs. Marcus and Schuster, who are coinvestigators in this work, will independently interpret the two scans of the entire 20 patients within 2 weeks of completion of the 2nd PET/CT for each patient. The readers will be blinded to all imaging and furosemide administration, including the other PET/CT done as part of the study. All suspicious lesions with non-physiologic activity above background for loco-regional spread and distant disease will be identified and rated for suspicion of malignancy on a 5-point Likert scale (where 1 = definitely benign and 5 = definitely malignant). Image interpretation will be done on an advanced workstation (MIM Software). Metabolic parameters (SUV max, SUV mean, SUVpeak of all identified lesions with be determined and recorded. The bladder volume on each scan will be determined and recorded. SUV max and SUV mean of background organs, including the parotid, aortic arch, liver, spleen, kidney, ureters and the urinary bladder, will be determined and recorded. The presence and degree of dropout or halo artifacts around the bladder and kidney will also be recorded. After the individual blind reads, the two readers will perform an unblinded consensus read for the reconciliation interpretation of the two scans for each patient. Concordant and discordant lesions between each PET/CT study and conventional imaging will be reported.

Scientific Rationale for Study Design
Our preliminary data support a key scientific premise that the intravenous administration of furosemide at the time of radiotracer injection leads to lower radiotracer concentration in the urinary bladder. This finding is supported by published studies in the literature showing that intravenous administration of furosemide at the time of ^{68}Ga-PSMA-11 administration causes a reduction in bladder activity,

improves detection of local prostate bed recurrence, and improves reader confidence. We hypothesize that the administration of intravenous furosemide at the time of radiotracer injection will reduce the activity of ^{18}F-rhPSMA-7.3 in the urinary bladder and facilitates the identification of prostate bed recurrence in men with rising serum PSA post-prostatectomy. We also hypothesize that reduced urinary activity of ^{18}F-rhPSMA-7.3 will improve readers' confidence in assessing prostate bed recurrence of prostate cancer. An improved lesion detection will influence management decisions.
To test these hypotheses with the highest scientific rigor, we propose a study including men with BCR post-prostatectomy. Each patient will undergo two sets of ^{18}F-rhPSMA-7.3 PET/CT scans, one with and the other without furosemide, and the level of urinary bladder activity, the detection rate of prostate bed recurrence and other lesions, will be compared between the two scans. In this manner, each patient will serve as their own control. We expect that the results from this study may generate sufficient evidence that may affect the workflow of ^{18}F-rhPSMA-7.3 PET/CT imaging of BCR of prostate cancer, especially after FDA approval for use in routine clinical care.

Justification for Dose
IV injection of 8 mCi (296 MBq) ± 20% of rhPSMA-7.3 (^{18}F) diluted up to 10 mL will be used for each of the two PET scans. This dose is based on dosimetry data obtained from published phase I study data [21], and the dose utilized in the approval phase III trial that was recently concluded [NCT04186845]. The study will be performed under IND #162587 held by Dr. David Schuster.

PET Acquisition
^{18}F-rhPSMA-7.3 PET/CT Imaging: PET/CT will be acquired on a state-of-the-art GE Discovery 690 TOF PET-CT scanner at Emory University Hospital or similar device. Patients do not need to fast prior to the scans. All patients will receive one PET/CT scan with 20mg furosemide administered intravenously at the time of radiotracer administration and will be encouraged to orally hydrate with 500-1000mL of water during the uptake phase of 60-70 minutes. Patients will be encouraged to void during the uptake phase up to 15 minutes prior to the commencement of the scan, if possible. PET images will be acquired from proximal thigh to skull base, approximately 3 minutes per bed position. All PET scans will be acquired in a 3-dimensional mode and the emission data will be corrected for randoms, dead time, scatter and attenuation. The images will be reconstructed using an iterative algorithm. Vital signs will be measured before and after administration of the radiotracer.

End of Study Definition
The study will be closed to recruitment once all 20 patients have been recruited, scanned with the 2 PET/CTs each and have completed follow-up (1-3 business days after each PET/CT). The study will be formally closed once all manuscripts have been published and all follow-up completed. There will be no other study-specific visits after the second PET/CT scan (visit 2), though the patient will be called by the study nurse within 1-3 business days after each study to ensure no delayed AEs occurred. The follow-up phone call for one study will be performed before the patient undergoes the subsequent scan.

3.3 5.2 Dosing and Administration

IV injection of 8 mCi (296 MBq) ± 20% of rhPSMA-7.3 (18F) diluted up to 10 mL will be used for each of the two PET scans. This dose is based on dosimetry data obtained from published phase I study data [21], and the dose utilized in the approval phase III trial that was recently concluded [NCT04186845]. The study will be performed under IND #162587 held by Dr. David Schuster.

3.4 5.3 Risks and/or adverse events

- Radiation Risks: The principal risk associated with a radiation dose is the possibility of developing radiation-induced cancer later in life. However, the additional risk of radiation-induced cancer from these diagnostic procedures is low compared to the risks from the disease itself. Human dosimetry data for 18F-rhPSMA-7.3 from the phase I study of Tolvanen and co-workers[18]: The (radiation absorbed) effective dose from the administration of 225 MBq of 18F-rhPSMA-7.3 is 0.0138 mSv/MBq at a 1-hour voiding interval. The organs with the highest absorbed radiation dose are the adrenals (0.184 mGy/MBq), the kidneys (0.172 mGy/MBq), and the submandibular glands (0.148 mGy/MBq).The effective dose from the CT component of the study is 15.7mSv.
- Allergic or other reactions to radiotracer: The risk of AEs and SAEs from PET radiotracers is exceedingly low. A significant shift from baseline can be attributable to the radiotracer injection and not the patient's medical condition will be considered an unexpected AE. An event greater than 24 hrs will not be considered related to study procedure AE since the radiotracer has effectively decayed by 20 hours. There have been no previous instances of allergic reactions. In prior studies where 18F-rhPSMA-7.3 was used in human subjects, the risk of adverse events which can be attributed to the radiotracer is extremely low, and of minimal medical impact such as burning at IV site or headache.
- Risks related to IV for PET scan: A small amount of radioactive material will be injected by either a hand-held needle or a machine. Such injections are generally quite safe, but any injection involves some risks. The injection could harm a nerve, artery, or vein, or cause infection. The radioactive material could also leak from veins, causing swelling and discomfort.
- False positive on PET: It is possible that a lesion identified on the experimental PET procedures may be false-positive, thus potentially leading to an inappropriate biopsy. While further evaluation of imaging finding to confirm true positivity may occur according to the standard of care practice, a biopsy of the imaging-identified lesion is not in the scope of this trial, nor is it a requirement.
- Furosemide: The risk from the low dose (20mg) of furosemide is minimal. It will temporarily cause increased urination. Though unlikely, other side effects may include: nausea or vomiting, diarrhea, constipation, stomach cramping, vertigo, dizziness, headache, blurred vision, itching or rash.

3.5 5.4 Dose Modification

Not applicable

3.6 5.5 Concomitant medication

Not applicable

3.7 5.6 Study Procedures

Screening Phase

Adult patients with biochemical recurrence of prostate cancer, status post prostatectomy who meet the eligibility criteria will be enrolled in the study.

Inclusion Criteria

i. Adenocarcinoma of the prostate, post-prostatectomy.
ii. Biochemical recurrence of prostate cancer following RP with or without adjuvant or salvage therapy: PSA ≥0.1 ng/mL
iii. Age over 18.
iv. Ability to provide written informed consent.
v. Patients with standard of care creatinine ≤1.3mg/dL performed within 90 days prior to enrollment

Exclusion Criteria

i. Inability to undergo ^{18}F-rhPSMA PET-CT, contraindications to furosemide or urinary incontinence that may interfere with performing the study.

Study population:
_(Y) 1. Adult patients with a diagnosis of adenocarcinoma of the prostate, post radical prostatectomy
_(Y) 2. Biochemical recurrence as defined by PSA ≥ 0.1
_(Y) 3. Age over 18 years and ability to give informed consent
_(N) 4. Inability to undergo ^{18}F-rhPSMA-7.3 PET/CT
_(N) 5. Contraindications to furosemide such as true allergy or urinary incontinence that may interfere with performing the study

3.8 5.7 Description of Study Procedures

Overall Design

We will undertake a study with 20 patients with biochemical recurrence of prostate cancer status post radical prostatectomy. Consideration for inclusion in this study will be based on a detectable serum PSA after radical prostatectomy (PSA ≥ 0.1 ng/ml). Histology proof of recurrence will not be required. All patients will be recruited from the radiation oncology unit and other oncology units under Emory Healthcare. All 20 patients will undergo two sets of 18F-rhPSMA-7.3 PET/CT scans, one with and the other without intravenous administration of 20 mg of furosemide at the time of radiotracer injection. All patients will have oral hydration with 500 to 1000 ml of water during the uptake phase. The first set of 10 patients will have a 18F-rhPSMA-7.3 PET/CT without-furosemide followed by a 18F-rhPSMA-7.3 PET/CT with-furosemide 2-7 days afterward. The second set of 10 patients will have their two 18F-rhPSMA-7.3

PET scans in the reverse order, with-furosemide first followed by without-furosemide 2-7 days afterward. Vital signs will be measured before and after each radiotracer administration. Each patient will undergo both imaging techniques, and the results will be interpreted blindly. A minimum of 2 days is required between the two 18F-rhPSMA-7.3 to allow for the complete decay of the radiotracer from the first scan before the second scan (physical half-life of 18F is 110 minutes). Patients will be allowed to void during the 60-70 minutes uptake period between 18F-rhPSMA-7.3 radiotracer administration and the commencement of PET/CT imaging. Patients will be encouraged to void at approximately 50 minutes post injection and encouraged to refrain from voiding 15 minutes before the commencement of the PET/CT (60-70 min post injection), if possible, to facilitate bladder distension.

Two nuclear medicine physicians, Drs. Marcus and Schuster, who are coinvestigators in this work, will independently interpret the two scans of the entire 20 patients. The readers will be blinded to all imaging and furosemide administration, including the other PET/CT done as part of the study. All suspicious lesions with non-physiologic activity above background for loco-regional spread and distant disease will be identified and rated for suspicion of malignancy on a 5-point Likert scale (where 1 = definitely benign and 5 = definitely malignant). Image interpretation will be done on an advanced workstation (MIM Software). Metabolic parameters (SUV max, SUV mean, SUVpeak of all identified lesions with be determined and recorded. The bladder volume on each scan will be determined and recorded. SUV max and SUV mean of background organs, including the parotid, aortic arch, liver, spleen, kidney, ureters and the urinary bladder, will be determined and recorded. The presence and degree of dropout or halo artifacts around the bladder and kidney will also be recorded. After the individual blind reads, the two readers will perform an unblinded consensus read for the reconciliation interpretation of the two scans for each patient. Concordant and discordant lesions between each PET/CT study and conventional imaging will be reported.

Scientific Rationale for Study Design

Our preliminary data support a key scientific premise that the intravenous administration of furosemide at the time of radiotracer injection leads to lower radiotracer concentration in the urinary bladder. This finding is supported by published studies in the literature showing that intravenous administration of furosemide at the time of 68Ga-PSMA-11 administration causes a reduction in bladder activity, improves detection of local prostate bed recurrence, and improves reader confidence. We hypothesize that the administration of intravenous furosemide at the time of radiotracer injection will reduce the activity of 18F-rhPSMA-7.3 in the urinary bladder and facilitates the identification of prostate bed recurrence in men with rising serum PSA post-prostatectomy. We also hypothesize that reduced urinary activity of 18F-rhPSMA-7.3 will improve readers' confidence in assessing prostate bed recurrence of prostate cancer. An improved lesion detection will influence management decisions.

To test these hypotheses with the highest scientific rigor, we propose a study including men with BCR post-prostatectomy. Each patient will undergo two sets of 18F-rhPSMA-7.3 PET/CT scans, one with and the other without furosemide, and the level of urinary bladder activity, the detection rate of prostate bed recurrence and other lesions, will be compared between the two scans. In this manner, each patient will serve as their own

control. We expect that the results from this study may generate sufficient evidence that may affect the workflow of 18F-rhPSMA-7.3 PET/CT imaging of BCR of prostate cancer, especially after FDA approval for use in routine clinical care.

Justification for Dose

IV injection of 8 mCi (296 MBq) ± 20% of rhPSMA-7.3 (18F) diluted up to 10 mL will be used for each of the two PET scans. This dose is based on dosimetry data obtained from published phase I study data [21], and the dose utilized in the approval phase III trial that was recently concluded [NCT04186845]. The study will be performed under IND #162587 held by Dr. David Schuster.

PET Acquisition

18F-rhPSMA-7.3 PET/CT Imaging: PET/CT will be acquired on a state-of-the-art GE Discovery 690 TOF PET-CT scanner at Emory University Hospital or similar device. Patients do not need to fast prior to the scans. All patients will receive one PET/CT scan with 20mg furosemide administered intravenously at the time of radiotracer administration and will be encouraged to orally hydrate with 500-1000mL of water during the uptake phase of 60-70 minutes. Patients will be encouraged to void during the uptake phase up to 15 minutes prior to the commencement of the scan, if possible. PET images will be acquired from proximal thigh to skull base, approximately 3 minutes per bed position. All PET scans will be acquired in a 3-dimensional mode and the emission data will be corrected for randoms, dead time, scatter and attenuation. The images will be reconstructed using an iterative algorithm. Vital signs will be measured before and after administration of the radiotracer.

End of Study Definition

The study will be closed to recruitment once all 20 patients have been recruited, scanned with the 2 PET/CTs each and have completed follow-up (1-3 business days after each PET/CT). The study will be formally closed once all manuscripts have been published and all follow-up completed. There will be no other study-specific visits after the second PET/CT scan (visit 2), though the patient will be called by the study nurse within 1-3 business days after each study to ensure no delayed AEs occurred. The follow-up phone call for one study will be performed before the patient undergoes the subsequent scan.

3. Sharing of Results with Participants

PET findings will be used for research purposes within the context of the clinical trial as noted above. The key findings of the PET/CT and all incidental findings will be recorded in the clinical research form and emergent incidental findings will be communicated to the patient's physician who is also an investigator in this study. The non-emergent findings will be conveyed to the patient at the discretion of the patient's physician after a discussion of the risk versus benefit since this investigational radiotracer is not FDA approved for clinical use.

Incidental Findings

a. All incidental findings noted by the imager will be discussed with the attending physician who is a co-investigator and documented in the electronic medical record.

b. The oncologist will educate the patient about the nature of the incidental finding, how to seek care from a clinician or specialist, obtaining health insurance to secure treatment, and/or referral to a clinical specialist, if one is required.
c. Language to this effect is present in the consent form.

4. Study Timelines

The total duration of the study is 5 years, with an accrual rate of approximately 4 patients per year. For the individual study participant, the patient participation is complete after the 2nd PET/CT study. However, the participating patients may be followed up for correlation for up to 5 years after the study.

5. Inclusion and Exclusion Criteria

Adult patients with biochemical recurrence of prostate cancer, status post prostatectomy who meet the eligibility criteria will be enrolled in the study.

Inclusion Criteria
Adenocarcinoma of the prostate, post-prostatectomy.
Biochemical recurrence of prostate cancer following RP with or without adjuvant or salvage therapy: PSA ≥0.1 ng/mL
Age over 18.
Ability to provide written informed consent.
Patients with standard of care creatinine ≤1.3mg/dL performed within 90 days prior to enrollment

Exclusion Criteria
Inability to undergo 18F-rhPSMA PET-CT, scontraindications to furosemide or urinary incontinence that may interfere with performing the study.

Population
_(Y) 1. Adult patients with a diagnosis of adenocarcinoma of the prostate, post radical prostatectomy
_(Y) 2. Biochemical recurrence as defined by PSA ≥ 0.1
_(Y) 3. Age over 18 years and ability to give informed consent
_(N) 4. Inability to undergo 18F-rhPSMA-7.3 PET/CT
_(N) 5. Contraindications to furosemide such as true allergy or urinary incontinence that may interfere with performing the study

6. Local Number of Participants

All 20 patients will be recruited from Emory Healthcare

7. Recruitment Methods

All patients will be recruited from the radiation oncology unit and other oncology units such as medical oncology and urology under Emory Healthcare

8. Withdrawal of Participants

Anticipated withdrawal of patients is expected to be minimal in this small cohort of patients who will undergo a diagnostic PET/CT study. Anticipated causes include, unable to undergo PET/CT study due to issues with patient comfort such as severe claustrophobia. In case of early termination, the cause of the termination will be documented, and further imaging will not be performed. If for some reason a patient is unable to complete the second study after the first, this will be considered a withdrawal and another patient will be recruited in their place.

9. Risks to Participants

1. Radiation Risks: The principal risk associated with a radiation dose is the possibility of developing radiation-induced cancer later in life. However, the additional risk of radiation-induced cancer from these diagnostic procedures is low compared to the risks from the disease itself.
   Human dosimetry data for ^{18}F-rhPSMA-7.3 from the phase I study of Tolvanen and co-workers[18]: The (radiation absorbed) effective dose from the administration of 225 MBq of ^{18}F-rhPSMA-7.3 is 0.0138 mSv/MBq at a 1-hour voiding interval. The organs with the highest absorbed radiation dose are the adrenals (0.184 mGy/MBq), the kidneys (0.172 mGy/MBq), and the submandibular glands (0.148 mGy/MBq).
   The effective dose from the CT component of the study is 15.7mSv.
2. Allergic or other reactions to radiotracer: The risk of AEs and SAEs from PET radiotracers is exceedingly low. A significant shift from baseline can be attributable to the radiotracer injection and not the patient's medical condition will be considered an unexpected AE. An event greater than 24 hrs will not be considered related to study procedure AE since the radiotracer has effectively decayed by 20 hours. There have been no previous instances of allergic reactions. In prior studies where ^{18}F-rhPSMA-7.3 was used in human subjects, the risk of adverse events which can be attributed to the radiotracer is extremely low, and of minimal medical impact such as burning at IV site or headache.
3. Risks related to IV for PET scan: A small amount of radioactive material will be injected by either a hand-held needle or a machine. Such injections are generally quite safe, but any injection involves some risks. The injection could harm a nerve, artery, or vein, or cause infection. The radioactive material could also leak from veins, causing swelling and discomfort.
4. False positive on PET: It is possible that a lesion identified on the experimental PET procedures may be false-positive, thus potentially leading to an inappropriate biopsy. While further evaluation of imaging finding to confirm true positivity may occur according to the standard of care practice, a **biopsy of the imaging-identified lesion is not in the scope of this trial, nor is it a requirement**.
5. Furosemide: The risk from the low dose (20mg) of furosemide is minimal. It will temporarily cause increased urination. Though unlikely, other side effects may include: nausea or vomiting, diarrhea, constipation, stomach cramping, vertigo, dizziness, headache, blurred vision, itching or rash.

10. Potential Benefits to Participants

The primary benefit of participating in this study is more accurate localization of the site of BCR of prostate cancer which impacts the choice of patient management. Early BCR of prostate cancer occurs in the prostate bed, especially at the vesicourethral anastomosis. A full bladder with excreted radiotracer as is present with the commercially available PSMA radiotracers has the potential to obscure the visualization of this common site of recurrence. rhPSMA has been shown to have a high PPV for localization of prostate cancer lesions (ASCO-GU 2022)[17].

11. Data Management and Confidentiality

The study will be approved by the Emory IRB per standard institutional requirements and informed written consent obtained.

To maintain patient confidentiality, medical records will be accessed only by IRB-approved study personnel (e.g. CRC). A partial HIPAA waiver will be obtained to allow screening of provider schedules for the identification of potentially eligible research subjects. Upon medical record review and identification of a potentially eligible research subject, the patient's full name, MRN, EMPI, and full dates (e.g., DOB, procedure dates, admission dates, etc.) will be stored on a screening log and used by study coordinators for the subsequent study activities. The screening log will be kept on the HIPAA compliant shared folder and will be accessible only to limited IRB-approved study personnel (e.g., CRC). Sensitive data will always be stored on the HIPAA compliant shared folder and will never be stored on local or portable drives that are not encrypted per Emory IS standards.

Each study participant will be assigned a unique study identification (ID) number at the time that informed consent is given. Personal identifying information and study data, including the unique study ID, will be entered in the Microsoft Database that will be kept on the HIPAA compliant shared folder accessible to approved study personnel only. Only de-identified data will be shared with those outside the study team to ensure adequate protection of sensitive data.

Study identifiers will be kept indefinitely.

To maintain participant confidentiality, no identifying information about any of the study participants will be published. Any data published (including demographic information about the study sample as a whole) will be in aggregate/summary form only.

Plans to monitor the data to ensure safety of participants and data integrity

☐ **No more than minimal risk** - Study not required to follow DSMP guidance

☒ **More than minimal risk** – Continue below.

Study Complexity
☐ Medium Complexity
☒ High Complexity Category A
☐ High Complexity Category B

If choosing this category for a study under an IND or IDE because you believe the study intervention does not significantly impact morbidity or mortality, please provide your rationale:

Monitoring Table 2

DSMP Requirement	How this Requirement is Met	Frequency	Responsible Party(ies)
Real-time review of participant data during initial data collection.	This requirement will be met per Winship's NCI approved DSMP	This will occur every time new information is obtained.	DSMC
Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.	This requirement will be met per Winship's NCI approved DSMP	Biannually	DSMC
100% review of regulatory files	DSMC monitors will review the protocol, amendments, informed consent documents, IRB submissions and meet with the principal investigator for clarification of study objectives	Reviewed at first and close-out visits	DSMC
100% review of consent forms	Monthly QA check of 5-10 randomly selected consents to validate Central Subject Registration (CSR) and PRMS to conduct QA consent checks in real time as subjects are registered in OnCore vis CSR process	Biannually	PRMS, QM
Review of credentials, training records, the delegation of responsibility logs (if applicable)	Clinical trials monitor will review the electronic regulatory binder and compare them against the staff listed on the DOA log. The monitor also reviews the site's source documents to ensure that all study staff have been properly listed on the DOA and have corresponding documentation (CV, ML, GCP certs, training log) filed in the	Biannually	DSMC

	electronic regulatory study binder		
Comparison of case report forms (CRF) to source documentation for accuracy and completion	The PI is responsible for ensuring that instances of egregious data insufficiencies that may impact the scientific integrity of the trial	Biannually	DSMC
Review of documentation of all adverse events	During the monitoring process, the DSMB reviews trial safety data for stopping rules, deviations, study amendments, accrual rates and monitoring reports for therapeutic investigator-initiated clinical trials and any other trial as deemed necessary	Biannually	DSMC
Monitoring of critical data points (eligibility, study endpoints, etc.)	The assigned monitor will randomly select subject(s) for review based on parameters in Table 1 or 2 as noted above. Although the principal investigator and applicable study team members will receive notification of trial monitoring in advance, the subject selection will not be revealed in advance of the monitoring visit.	Biannually	DSMC
Laboratory review of processing and storage of specimens	The assigned monitor will randomly select subject(s) for review based on parameters in Table 1 or 2 as noted above	Reviewed at first and close-out visits and at least biannually	DSMC
Assessment of laboratory specimens stored locally	QM will monitor data entered into the study database against the site source documents, including laboratory reports. During visits to the laboratory, QM will ensure study specimens are being properly stored, handled and shipped according to the protocol and lab manual.	Reviewed at first and close-out visits and at least annually	Winship Quality Management Department
Test article accountability review	Clinical research pharmacy at Grady Memorial Hospital	Reviewed at first and close-out visits	Research Pharmacist

		and at least biannually	
Accountability logs, dispensing records, and other participant records	QM will review accountability and dispensing log, including IP administration forms.	Annually	Winship Quality Management Department
For FDA regulated studies, the following requirements apply:	Monitoring activities meet the FDA's requirements as delineated in 21 CFR 50, 21 CFR 56, 21 CFR 812 for studies conducted under an IDE and 21 CFR 312 for studies conducted under an IND.	Biannually	DSMC
Monitoring methods (may include centralized, on-site, and self-monitoring)	The internal monitoring team is independent from any study protocol and does not perform any trial-related specific duties in order to uphold an unbiased approach to study monitoring. Oversight of the monitoring process and identification/assignment of studies for monitoring is provided by the Manager of the Internal Monitors.	Biannually	DSMC
*For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations.			

Patients will be monitored by the technologists and/or study nurse before and after the studies for any adverse events/reactions. They will be given contact phone numbers to call if they experience any problems (i.e., problems with the IV site, any allergic reaction symptoms). Basic monitoring of adverse events during the 18F-rhPSMA-7.3 PET visit will be performed. This will consist of direct observation by our study staff during the visit with documentation of any adverse events or lack thereof in the electronic medical record. The physical half-life of the radiotracer is 110 minutes. Hence, adverse events are not expected to occur past 24 hrs after radiotracer administration.
Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

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.

Definition of unanticipated problems (UP) and reporting requirements
The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets all the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site

investigator's responsibility to report UPs to their IRB and to the DCC/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. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute of Emory University will oversee the conduct of this study. This committee will review all pertinent aspects of the study conduct including patient safety, compliance with protocol, data collection, and efficacy.
The DSMC will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. High-risk studies will be reviewed every 6 months. The committee reserves the right to conduct additional audits, if necessary, at any time-point. The Principal Investigator is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study.
The charter for the Winship DSMC is available upon request to the investigator or other study-related personnel.

As with our ongoing clinical trial, for the current proposal, we will adhere strictly to Winship's Data Safety Monitoring Plan which is provided in detail at the following link: https://winshipcancer.emory.edu/research/clinical-trials-office/data-and-safety-monitoring-committee.html

Data Safety Monitoring Board: Note that our proposed trial is an early phase clinical trial that will be conducted completely within the Emory system, so a formal and independent Data Safety Monitoring Board (DSMB) [which is required for multi-site studies or Phase III trials] is not required for our proposal. As described above, the DSMC of Winship Cancer Institute of Emory University will oversee the conduct of our study.

Fidelity to Protocol and Data Integrity:
Clinical trial performance and fidelity to the protocol will be monitored by the DSMC of Winship Cancer Institute of Emory University. The integrity of the data will be maintained by rigorous peer-review internally by all the clinical co-investigators in Radiation Oncology, Radiology/Nuclear Medicine, Surgical Oncology, and Medical Oncology.

Provisions to Protect the Privacy Interest of Participants
To maintain patient confidentiality, medical records will be accessed only by IRB-approved study personnel (e.g. CRC). A partial HIPAA waiver will be obtained to allow screening of provider schedules for the identification of potentially eligible research subjects. Upon medical record review and identification of a potentially eligible research subject, the patient's full name, MRN, EMPI, and full dates (e.g., DOB, procedure dates, admission dates, etc.) will be stored on a screening log and used by study coordinators for the subsequent study activities. The screening log will be kept on the HIPAA compliant shared folder and will be accessible only to limited IRB-approved study personnel (e.g., CRC). Sensitive data will always be stored on the HIPAA compliant shared folder and will never be stored on local or portable drives that are not encrypted per Emory IS standards.

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Study identifiers will be kept indefinitely.

To maintain participant confidentiality, no identifying information about any of the study participants will be published. Any data published (including demographic information about the study sample as a whole) will be in aggregate/summary form only.

11.1 Statistical consideration section:

The objective of this early phase study is to determine if administering 20mg furosemide IV at the time of radiotracer injection significantly reduces bladder activity compared with the same patient scanned without furosemide as control.

Sample size determination

We will image 20 patients with biochemical recurrence of prostate cancer post-prostatectomy for this study. Based on prior observation, we assume an SUV mean of 9.2 (SD=11.1) in those receiving 20mg furosemide IV at the time of radiotracer injection, and an SUV mean of 2.6 (SD=1.0) in those not receiving furosemide (White Paper Prepared for Syncona: Evaluation of 18F-rhPSMA7, Unpublished). Assuming a correlation between paired measurements of 0.5 which results in a standard deviation of change in SUV mean of approximately 10, we have 80% power to detect that change in SUV mean (9.2 vs. 2.6) with 20 patients, assuming a Type I error of 0.05, using a paired t-test. The sample size was calculated using PASS 2020 v20.0.3.

Populations for analyses

Efficacy set: All patients administered both 20mg furosemide IV at the time of radiotracer injection and without furosemide.

Safety set: All patients receive a dose of the radiotracer with each study.

Statistical analyses:

General Approach

Continuous variables will be summarized using mean, median, interquartile range, standard deviation, and min/max. Categorical variables will be summarized using frequencies and percentages. All tests will be two-sided with an alpha level of 0.05, unless otherwise noted. Testing assumptions will be

assessed and verified. Statistical analysis will be conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Analysis of the Primary Efficacy Endpoint

Change in bladder SUV mean: The primary endpoint is change in bladder activity, as measured by bladder SUV mean, between administration of 20mg furosemide IV at the time of radiotracer injection and without furosemide. Change in bladder SUV mean will be assessed using a paired t-test, or using a non-parametric equivalent such as a Wilcoxon signed rank test. Descriptively, change in bladder SUV mean will be reported for those administered 20mg furosemide IV at the time of radiotracer injection first (Group A), and those administered 20mg furosemide IV at the time of radiotracer injection second (Group B).

Analysis of the Secondary Endpoints:

Bladder and renal activity: Change in bladder and renal activity, as measured by bladder SUV max, bladder volume, and renal SUV mean/max, between administration of 20mg furosemide IV at the time of radiotracer injection and without furosemide will be assessed using paired t-tests, or using non-parametric equivalents such as a Wilcoxon signed rank tests. Descriptively, bladder and renal activity will be reported for those administered 20mg furosemide IV at the time of radiotracer injection first (Group A), and those administered 20mg furosemide IV at the time of radiotracer injection second (Group B).

Recurrent disease rate: Recurrent disease is defined as presence of unequivocal soft tissue radiotracer uptake that is characteristic of malignancy in the prostate bed and/or surrounding soft tissues and within pelvic lymph nodes. Recurrent disease rates will be compared (furosemide vs. non-furosemide 18F-rhPSMA-7.3 PET scans using McNemar's tests. Rates will be reported, along with 95% exact confidence intervals using the Clopper-Pearson method. Descriptively, recurrent disease rate will be reported for those administered 20mg furosemide IV at the time of radiotracer injection first (Group A), and those administered 20mg furosemide IV at the time of radiotracer injection second (Group B).

Confidence score: The readers' confidence in identifying prostate bed, pelvic and retroperitoneal nodal disease and other recurrence on 18F-rhPSMA-7.3 PET/CT with furosemide compared with the 18F-rhPSMA-7.3 PET/CT without furosemide will be scored using a 5-point Likert scale. This analysis will be descriptive, with summary statistics reported with and without furosemide.

Safety Analyses: Not applicable.

Baseline Descriptive Statistics

Patient characteristics will be summarized descriptively, using mean, median, interquartile range, min/max, and standard deviation for continuous variables, and using frequencies and percentages for categorical variables.

Interim Analysis: N/A

16.2 Data/specimens:

Patients will be monitored by the technologists and/or study nurse before and after the studies for any adverse events/reactions. They will be given contact phone numbers to call if they experience any problems (i.e., problems with the IV site, any allergic reaction symptoms). Basic monitoring of adverse events during the 18F-rhPSMA-7.3 PET visit will be performed. This will consist of direct observation by our study staff during the visit with documentation of any adverse events or lack thereof in the electronic medical record.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute of Emory University will oversee the conduct of this study. This committee will review all pertinent aspects of the study conduct including patient safety, compliance with protocol, data collection, and efficacy.

The DSMC will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. High-risk studies will be reviewed every 6 months. The committee reserves the right to conduct additional audits, if necessary, at any time-point. The Principal Investigator is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study.

The charter for the Winship DSMC is available upon request to the investigator or other study-related personnel.

As with our ongoing clinical trial, for the current proposal, we will adhere strictly to Winship's Data Safety Monitoring Plan which is provided in detail at the following link: https://winshipcancer.emory.edu/research/clinical-trials-office/data-and-safety-monitoring-committee.html

Data Safety Monitoring Board: Note that our proposed trial is an early phase clinical trial that will be conducted completely within the Emory system, so a formal and independent Data Safety Monitoring Board (DSMB) [which is required for multi-site studies or Phase III trials] is not required for our proposal. As described above, the DSMC of Winship Cancer Institute of Emory University will oversee the conduct of our study.

Fidelity to Protocol and Data Integrity:

Clinical trial performance and fidelity to the protocol will be monitored by the DSMC of Winship Cancer Institute of Emory University. The integrity of the data will be maintained by rigorous peer-review internally by all the clinical co-investigators in Radiation Oncology, Radiology/Nuclear Medicine, Surgical Oncology, and Medical Oncology.

12. Provisions to Monitor the Data to Ensure the Safety of Participants

Patients will be monitored by the technologists and/or study nurse before and after the studies for any adverse events/reactions. They will be given contact phone numbers to call if they experience any problems (i.e., problems with the IV site, any allergic reaction symptoms). Basic monitoring of adverse events during the 18F-rhPSMA-7.3 PET visit will be performed. This will consist of direct observation by our study staff during the visit with documentation of any adverse events or lack thereof in the electronic medical record. The physical half-life of the radiotracer is 110 minutes. Hence, adverse events are not expected to occur past 24 hrs after radiotracer administration.

Written IND safety reports will be submitted to the FDA by the IND sponsor, for serious, unexpected suspected adverse reactions within 15 calendar days of learning of its occurrence. If the event is fatal or is deemed to be life threatening, the report will be made within 7 calendar days. The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

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

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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.

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets all the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/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. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute of Emory University will oversee the conduct of this study. This committee will review all pertinent aspects of the study conduct including patient safety, compliance with protocol, data collection, and efficacy.

The DSMC will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. High-risk studies will be reviewed every 6 months. The committee reserves the right to conduct additional audits, if necessary, at any time-point. The Principal Investigator is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study.

The charter for the Winship DSMC is available upon request to the investigator or other study-related personnel.

As with our ongoing clinical trial, for the current proposal, we will adhere strictly to Winship's Data Safety Monitoring Plan which is provided in detail at the following link: https://winshipcancer.emory.edu/research/clinical-trials-office/data-and-safety-monitoring-committee.html

Data Safety Monitoring Board: Note that our proposed trial is an early phase clinical trial that will be conducted completely within the Emory system, so a formal and independent Data Safety Monitoring Board (DSMB) [which is required for multi-site studies or Phase III trials] is not required for our proposal. As described above, the DSMC of Winship Cancer Institute of Emory University will oversee the conduct of our study.

Fidelity to Protocol and Data Integrity:

Clinical trial performance and fidelity to the protocol will be monitored by the DSMC of Winship Cancer Institute of Emory University. The integrity of the data will be maintained by rigorous peer-review internally by all the clinical co-investigators in Radiation Oncology, Radiology/Nuclear Medicine, Surgical Oncology, and Medical Oncology.

13. Provisions to Protect the Privacy Interests of Participants

To maintain patient confidentiality, medical records will be accessed only by IRB-approved study personnel (e.g. CRC). A partial HIPAA waiver will be obtained to allow screening of provider schedules for the identification of potentially eligible research subjects. Upon medical record review and identification of a potentially eligible research subject, the patient's full name, MRN, EMPI, and full dates (e.g., DOB, procedure dates, admission dates, etc.) will be stored on a screening log and used by study coordinators for the subsequent study activities. The screening log will be kept on the HIPAA compliant shared folder and will be accessible only to limited IRB-approved study personnel (e.g., CRC). Sensitive data will always be stored on the HIPAA compliant shared folder and will never be stored on local or portable drives that are not encrypted per Emory IS standards.

Each study participant will be assigned a unique study identification (ID) number at the time that informed consent is given. Personal identifying information and study data, including the unique study ID, will be entered in the Microsoft Database that will be kept on the HIPAA compliant shared folder accessible to approved study personnel only. Only de-identified data will be shared with those outside the study team to ensure adequate protection of sensitive data.

Study identifiers will be kept indefinitely.

To maintain participant confidentiality, no identifying information about any of the study participants will be published. Any data published (including demographic information about the study sample as a whole) will be in aggregate/summary form only.

14. Economic Burden to Participants

There will be no cost for the patients to participate in this study.

15. Consent Process

Informed consent is required prior to participation in the study. Patients will sign the written informed consent, if possible, at the time of enrollment. The patient will be sent a copy of the consent form prior to enrollment. The consent process will take place at the radiation oncology, oncology, or nuclear radiology clinics at Emory Healthcare. The consent will be obtained by one of the investigators or those who have been given the authority in the DOA log. The consent will take up to 30 minutes to explain to the patients and patients will be given time to ask questions. Special precautions will be taken to not influence patient's decision to take part in the study.

e-Consent

The PI and/or delegated co-I and/or delegated study team will have the option to consent the participants electronically using Zoom. The PI and/or delegated co-I and/or delegated study team will conduct the consent discussion via phone or Zoom. A copy of the study Emory IRB approved consent form will be sent to the participants to be signed using CFR Part 11 Compliant DocuSign. The PI and/or delegated co-I and/or delegated study team will ask the participants a security question to confirm their identity (security question: What was your mother's maiden name?). The participants will receive a copy of the electronically signed study consent form on their first research visit.

Non-English-Speaking Participants

Non-English-speaking participants may be considered for enrollment in this trial subjects with limited English proficiency (LEP) may be enrolled and study team members will use Emory IRB approved short forms to conduct the consent process. The subject will date and sign the consent form. The subject will receive a copy of the dated and signed consent form

16. Setting

All patients will be recruited from the radiation oncology unit and other oncology units under Emory Healthcare

17. Resources Available

PET/CT scanners: PET/CT will be acquired on a state-of-the-art GE Discovery 690 TOF PET-CT scanner at Emory University Hospital or similar device.
Radiotracer: The study will be performed under IND #162587 held by Dr. David Schuster.
Time allotment: PET/CT studies will be performed per protocol described above. The studies will be read by investigators as detailed above, Time taken for interpretation may vary per study.

Training: All study personnel will be adequately trained regarding the details of the protocol prior to study initiation.

18. References

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

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APPENDIX C Abbreviations and definition of terms

Abbreviation or special term	Explanation
AEs	Adverse effects
ADT	Androgen-deprivation therapy
CRC	Clinical Research Coordinator
CRF	Case Report Form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTEP	Cancer Therapy Evaluation Program
DSMC	Data and Safety Monitoring Committee
DSMP	Data Safety and Monitoring Plan
DSUR	Development Safety Update Report
EANM	European Association of Nuclear Medicine
F-18	Fluorine-18
FDA	Food and Drug Administration
^{18}Ga-PSMA	Gallium-68 prostate-specific membrane antigen
HIPAA	Health Insurance Portability Accountability Act
ICF	Informed consent form
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
MBq	Mega Becquerel
mGy	MilliGray
MRI	Magnetic resonance imaging
mSv	milliSievert
MTV	Metabolic tumor volume
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
PET/CT	Positron emission tomography/ computed tomography
rhPSMA	Radiohybrid prostate-specific membrane antigen
PSA	Prostate-specific antigen
RP	Radical prostatectomy
SAEs	Severe adverse effects
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SUV max	Maximum standardized uptake value
TLA	Total lesion activity