Comparison of ^{68}Ga-PSMA Positron Emission Tomography (PET)/CT to Conventional Imaging in Men with High Risk Prostate

Protocol Number:

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National Clinical Trial (NCT) Identified Number:

04614363

Principal Investigator:

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151520

Funded by:

Houston Methodist Research Institute

Version Number: 5

07/08/2021

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STATEMENT OF COMPLIANCE

(1) The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Comparison of 68Ga-PSMA Positron Emission Tomography (PET)/CT to Conventional Imaging in Men with High Risk Prostate Cancer
Study Description:	This is a prospective, single-center, open-label pilot study of 68GA-PSMA-11 given at a single time prior to PET/CT imaging in men with localized high risk prostate cancer or biochemical recurrence. Eligible participants will undergo baseline assessments using conventional 99-Tc Bone Scan and CT of the Abdomen and Pelvis or multi-parametric MRI imaging of the prostate

Objectives:

Primary Objective

1. To evaluate the tissue distribution of 68GA-PSMA-11 PET/CT imaging in normal tissues and biopsy proven tumor and non-tumorous regions of the prostate, and also pelvic lymph nodes in high risk patients undergoing standard of care prostatectomy and bilateral lymph node dissection.

2. To determine the proportion of patients in which 68GA-PSMA-11 PET/CT altered the planned clinical management.

Secondary Objective:

1. To correlate the intensity of 68GA-PSMA-11 PET/CT uptake with respect to pathological findings.

2. To compare suspicious lesions visualized on 68GA-PSMA-11 PET /CT with standard of care diagnostic imaging modalities, additional biopsy results, or clinical follow-up performed at the discretion of the referring physician.

Endpoints:

Primary Endpoints:

1. Proportion of patients with cTxNoMo (clinically localized disease) found on final histological examination to have lymph node involvement as determined by 68GA-PSMA-11 PET/CT.

2. Proportion of patients in which 68GA-PSMA-11 PET/CT altered the planned clinical management.

Secondary Endpoints:

1. 68GA-PSMA-11 PET/CT intensity is variable, and we will evaluate what intensity endpoint is predictable of tissue involvement.

2. To compare and contrast findings in 68GA-PSMA-11 PET/CT with standard diagnostic modalities of bone scan, CTs and MRIs.

Study Population:	Male patients, aged 21 or older, diagnosed with histopathological proven prostate adenocarcinoma, with no evidence of other malignancy, and Eastern Cooperative Oncology Group (ECOG) performance of 0-1.
Phase:	Pilot, phase I/2
Description of Sites/Facilities Enrolling Participants:	This is a single site trial that will be conducted at the Houston Methodist Hospital.
Description of Study Intervention:	This is a prospective, open label, single-center, single-arm, pilot diagnostic accuracy study to evaluate the tissue distribution of 68Ga-PSMA Positron Emission Tomography (PET)/CT in 80 patients with high risk localized prostate cancer or biochemical recurrence. Subjects will receive a single IV dose of 3-7 mCi of 68Ga-PSMA (study drug) followed by PET/CT imaging 60-90 minutes after injection. All patients will be closely monitored with vital signs (blood pressure and heart rate), before and 2 hours following radiotracer administration. Patients will receive a phone call 2 days following PET/CT to assess for adverse events. To minimize bias, all PET/CT images will be interpreted by a board-certified radiologist. The radiologist evaluating the images will be blinded to the final outcome, such as the histopathology of any biopsies and the outcome of subsequent imaging. Patients with study-defined high-risk features who are eligible and scheduled for radical prostatectomy or with biochemical recurrence will undergo 68Ga-PSMA-11 PET/CT injection. The results of the 68Ga-PSMA-11 PET/CT may alter patient

management in one of several ways, including the decision to not pursue surgical extirpation (e.g. in the event of extensive distant metastasis) in favor of systemic therapy. It is also possible that the extent of surgical resection may be altered, such as non-regional pelvic or retroperitoneal lymph node dissection. The alteration in planned surgical treatment from standard of care will be recorded as a secondary-end point.

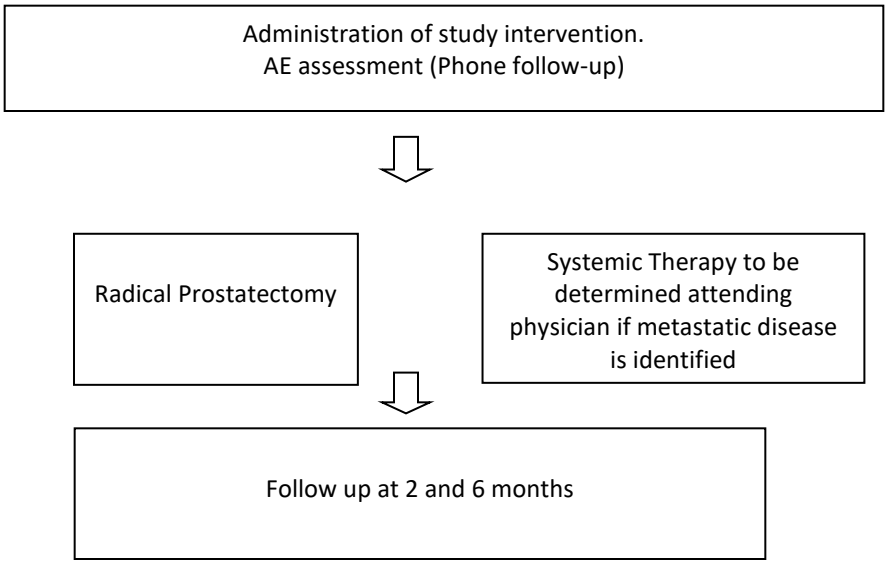
Study Duration:	18 months.
Participant Duration:	6 months.

SCHEMA

Screening Visit 1

Total:80 patients - Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, physical exam, height/weight, ECOG, safety labs

Visit 2



Visit 3 and 4

1.2 SCHEDULE OF ACTIVITIES (SOA)

The schedule below is provided as an example and should be modified as appropriate.

	Screening	Enrollment	Post Dose		Surgery/Pre-surgery Follow up/Early Termination	Follow up	Follow up
	Day -28 to 0	Day 0	Day 0: Hour 1-2	Day 2	Day 10 +/- 7	Month 2 +/- 7	Month 6 +/- 7
	Visit 1	Visit 2		Phone call		Visit 3	Visit 4
Informed Consent	R						
Demographics	R						
Inclusion/Exclusion Criteria	R						
Medical History[1]	R						
Performance Status	R						
Vital Signs[2]	R		R[3]				
Administer Study Intervention 68Ga PSMA 11		R					
Whole body PET/CT		R					
PSA	R					SOC	SOC
Bone Scan[4]	SOC						
CT abdomen/pelvis[4]	SOC						
MRI of prostate	SOC						
Adverse event evaluation			R	R	R		
Prostate Biopsy	SOC						
Telephone call				R			
Prostatectomy					SOC		

Pathology porcessing					SOC		

[1] *Medical history includes review of prostate cancer treatment and prior radiographic exams.*

[2] *Vital Signs Assessment includes measurement of blood pressure and heart rate.*

[3] *On days of dosing, vital signs will be collected pre-dose and post-dose.*

[4] *If not performed within 6 months of Screening, diagnostic CT or MR scans and or Bone scan are to be obtained prior to surgery, only if clinically indicated*

2 INTRODUCTION

2.1 STUDY RATIONALE

Prostate cancer (PCa) remains the most common non-cutaneous cancer diagnosis in males, with an estimated 174,650 new cases in 2019[2]. After lung cancer, PCa accounts for the second highest mortality in men. Localized PCa, often screen-detected using prostate specific antigen (PSA) based blood tests, is highly variable in clinical course and risk of progression. Treatment is therefore matched on this basis, and includes Active Surveillance for Low-Risk PCa, whereas Intermediate- and High-Risk PCa are treated by radiation therapy (external beam or brachytherapy) or surgery (radical prostatectomy). While durable cure can be achieved by these modalities, biochemical relapse occurs in approximately 35% of who have undergone treatment for localized disease[3].

There is significant interest in identifying individuals at highest risk of biochemical relapse, using a variety of approaches, including genomic-based biomarkers. Identification of metastatic disease beyond of the prostate is critical, not only for potentially targeted local-therapy (e.g. surgical resection of recurrence or targeted radiation therapy) but earlier use of aggressive adjuvant radiation or systemic therapies. Imaging based identification of low volume disease outside of

the prostate has been limited by the sensitivity of cross-sectional tomography (CT), which relies on nodal morphology (size). The sensitivity of CT or MRI based imaging for the detection lymph node metastasis is in the range of 30-80%[4]. Detection of bone metastasis once present as osteoblastic lesions can be identified by bone-scintigraphy, again with limed sensitivity, especially in asymptomatic patients with PSA levels below 20[5]. In spite of these limitations, CT and whole body bone scans are widely accepted as the primary imaging modality for staging patients, particularly with localized PCa.

2.2 BACKGROUND

Molecular imaging using various targets and positron emission tomography (PET) tracers have been used to improve detection of recurrent prostate cancer. 18F- or 11C labeled choline as well as 11C-acetate have been previously investigated[6,7]. Their clinical utility has been limited by non-specific uptake in benign tissue, including benign prostatic hypertrophy[8]. 18F-Fluciclovine has recently been approved owing to it improvement over 11C[9]. Targeting of prostate-specific membrane antigen (PSMA) by radiotracer has gained the most contemporary clinical interest. PSMA (glutamate carboxypeptidase II, N-acetyl-a-linked acidic dipeptidase I, or folate hydrolase) is a type II transmembrane glycoprotein belonging to the M28 peptidase family is preferentially overexpressed in prostate cancer cells relative to other cells. Other tissues may also express PSMA, including kidney, small intestine or salivary glands. Importantly, PSMA expression is maintained and may increase through the full spectrum of prostate cancer, including advanced disease[10].

Methods have focused on labeling ligands (Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)] also known as 68-PSMA-11) to PSMA with 68-Ga, allowing internalization and significant differential contrast between normal and cancerous tissues which aids in optimal imaging characteristics[11,12]. Initial studies showed that labeling of PSMA-ligand with 68-Ga allowed improved identification of PCa recurrence and metastasis [13].

Early data has demonstrated the utility of 68Ga-PSMA with respect to improved accuracy of detection and in turn significant impact on treatment decisions[14]. A recent meta-analysis of 68Ga-PSMA PET studies showed promising detection of metastasis following biochemical recurrence, even at low PSA levels [PSA >0.2

ng/ml (33% detection rate) and PSA 0.2–0.5 ng/ ml (45% detection rate)][15]. Importantly, the vast majority of these studies have been reported from retrospective data.

In our study we plan to prospectively study the accuracy and utility of 68Ga-PSMA 11 and its impact of the treatment related decisions.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.2 KNOWN POTENTIAL BENEFITS

The investigational study may determine the presence of disease outside of the prostate that is resectable at the time of the surgery and that may improve long term outcomes.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

- **Study Imaging Drug Risk:** Possible side effects such as rash, nausea, headache or fatigue. In clinical studies that used 68Ga-PSMA-11 in the same amount being used in this study, no serious adverse events were reported.
- **PET/CT scan radiation risk:** the maximum amount of radiation from this study is equivalent to 2.43 mSv and less than 1 mSv for non-diagnostic CT scan performed to process the PET data. The total radiation dose from the study procedure is less than 1/10th the annual exposure allowed for occupational workers. Although there are no proven harmful effects from this amount of radiation, long-term effects, such as cancer, cannot be ruled out with certainty. This dose estimate takes into account only the exposure to research procedures in this study.
- **Other risk:** pain and infection at the site of the needle stick for the study drug injection or for blood drawn for the blood tests.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
1. To evaluate the tissue distribution of 68GA-PSMA-11 PET/CT imaging in normal tissues and biopsy proven tumor and non-tumorous regions of the prostate, and also pelvis lymph nodes in patients undergoing standard of care prostatectomy and bilateral lymph node dissection in high risk patients 2. To determine the proportion of patients in which 68GA-PSMA-11 PET/CT altered the planned clinical management	1. Proportion of patients with cTxNoMo (clinically localized disease) found on final histological examination to have lymph node involvement as determined by 68GA-PSMA-11 PET. 2. Proportion of patients in which 68GA-PSMA-11 PET/CT altered the planned clinical management.	1. Determining the usefulness of PSMA PET/CT requires defining its' ability to identify lymphatic or metastatic spread that heretofore has not been detectable by standard radiographic means. 2. Understanding whether and why 68GA-PSMA-11 PET/CT findings alter treatment plans is critical in defining its role in the diagnostic tools urologists use to manage their patients with prostate cancer.
Secondary		
1. To correlate the intensity of 68Ga-PSMA-11 uptake	1. 68Ga-PSMA-11 PET/CT intensity is variable, and we will evaluate	1. To identify those patients in whom more localized or extended therapy might be indicated, it is important

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
with respect to pathological findings. 2. To Compare suspicious lesions visualized on 68Ga-PSMA-11 PET/CT with standard of care diagnostic imaging modalities, additional biopsy results, or clinical follow-up performed at the discretion of the referring physician	what intensity endpoint is predictable of tissue involvement. 2. To compare and contrast findings in 68Ga-PSMA-11 PET/CT with standard diagnostic modalities of bone scans, CTs and MRIs	to know in equivocal 68Ga-PSMA PET/CT readings what the true positive results histopathologically are in order to avoid possible over / under treatment. 2. Based on histologic results comparing standard radiographic modalities to 68Ga PSMA 11 PET/CT findings will add value as to whether they are complimentary or one or more might be deleted in the workup of these men. .

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, open label, single-center, single-arm, pilot diagnostic accuracy study to evaluate the tissue distribution of 68Ga-PSMA Positron Emission Tomography (PET)/CT in 80 patients with high risk localized prostate cancer or biochemical recurrence.

At screening: participants will sign an approved informed consent, medical history and vital signs will be completed. Labs will be drawn for PSA. Eligibility criteria will be verified and completed.

Day of the injection:

Subjects will receive a single IV dose of 3-7 mCi of 68Ga-PSMA (study drug) followed by PET/CT imaging 60-90 minutes after injection. Scan time will be determined based on the capacity of the PET scanner. Scanning will start from the mid-thighs (to minimize radiotracer artifact from accumulation in the bladder) to the base of the skull. There may be exceptions based on clinical relevance that the scan coverage may be extended.

All patients will be closely monitored with vital signs, to be assessed before and after injection of 68Ga-PSMA-11 (Blood Pressure, Heart Rate). Patients will be monitored with respect to vital signs and adverse events during, and 2-hours following radiotracer administration for adverse events.

Post injection:

Patients will receive a phone call 2 days following PET/CT to assess for adverse events that may have develop in a delayed fashion. If there are any concerning study-related adverse events, this will be escalated to clinical evaluation by the study primary investigators.

To minimize bias, all PET/CT images will be interpreted by a board certified radiologist with experience in reading such modalities. They will be blinded to the final outcome, such as the histopathology of any biopsies and the outcome of subsequent imaging.

68-Ga-PSMA PET/CT positivity or negativity will be interpreted, stratified by different anatomic regions as previously defined [1].

REGION	DESCRIPTION
1	Prostate and Prostate Bed
2	Pelvis, excluding prostate bed, but including lymph nodes
3	Extra-pelvic soft tissue, including lymph node involvement and metastasis to other organs
4	Bone Metastasis

The presence of prostate cancer (positive or negative) will be reported within these regions.

A. **Lymph nodes** - considered positive if the 68Ga-PSMA-11 uptake is localized/focal and is greater than the adjacent or mediastinal blood pool. The location of the lymph nodes will be recorded according to one of 7 sub-categories as previous defined[1]:

1	Right Hypogastric/Internal-iliac
2	Left Hypogastric/Internal-iliac
3	Right Obturator
4	Left Obturator
5	Right External-iliac
6	Left External-iliac
7	Other

B. **Visceral lesions –** These will be considered positive if the 68Ga-PSMA-11 uptake is focal and greater than the physiologic background activity in the organ of interest.

C. **Bone lesions –** These will be considered positive if the 68Ga-PSMA-11 uptake is focal and greater than physiologic background activity in normal bone marrow.

D. **Prostate bed –** These will be considered positive if the 68Ga-PSMA-11 activity is focal and greater than the physiologic, background activity in the prostate bed.

Validation of positive 68Ga-PSMA-11 will be based on a combination of histo-pathology from biopsy or surgical specimens, and follow up imaging. Definition of

true positivity and false negative based on imaging follow previously published methodology[1].

Surgery (prostatectomy) will take place between ~~7~~ 3 and 14 days after the 68Ga-PSMA 11 injection.

If patients with BR show metastasis, attending urologist will evaluate for surgery, radiation or chemotherapy.

Follow up in clinic will occur at 2 and 6 months after study drug injection. (Visits 3 and 4)

In patients with biochemical recurrence, will repeat the PSMA scan within 1 year, after they completed treatment and when their PSA still increases when initial PSMA was negative, at PI's discretion if needed.

See Appendix 1. Schedule of Events table

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is an exploratory, single arm, open label pilot study evaluation of 68Ga-PSMA Positron Emission Tomography with intraprostatic and/or pelvic lymph node uptake determination by PET/CT imaging, with histological confirmation of disease localized and staging. Methodical evaluation of 68Ga-PSMA intraprostatic and or pelvic lymph node will provide important preliminary data upon which further clinical studies can be based.

4.3 JUSTIFICATION FOR DOSE

68Ga-PSMA-11 will be used as the radiopharmaceutical agent for PET imaging at a dose of 3-7 mCi given intravenously. Dosimetry data are available from published data and will reference the Weil Cornell IND application to the FDA.

In summary, the published literature and safety studies in humans indicates no observed adverse events to the radiopharmaceutical[1,7,16]. Measured dosimetry showed that the critical organs affected are, in descending order, the spleen, stomach wall, pancreas and bladder. The reported effective dose of 68Ga-PSMA-11 is 0.0129 mSv/MBq, which is the lowest of the 68Ga based tracers, including those used in imaging of neuro-endocrine tumours such as DOTA-TOC, DOTA-NOC, DOTA-TATE[17–19].
68Ga-PSMA can only be administered via intravenous infusion. The proposed dose (3-7 mCi) is based upon joint guidelines from the European Association of Nuclear Medicine and The Society of Nuclear Medicine and Molecular Imaging, who recommend a dose of 0.049-0.06 mCi/kg. In an average 75kg adult patient, this would be approximately 3.7-4.5 mCi [20].

The 68-Ga-PSMA agent will be manufactured using previously reported procedures using a generator. Agent release criteria, and validation standards for each batch produced will be followed.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.
Patients who do not complete surgery would be considered Early Termination (pre-surgery).
The investigator may withdraw a subject from the trial for any of the following reasons:

1. Protocol violation,
2. Serious or intolerable adverse event (that in the opinion of the Investigator, requires the subject's discontinuation),
3. The Investigator withdraws the subject (at the Investigator's discretion for reasons other than an adverse event),
4. The Principal Investigator terminates the study,
5. The subject requests to be discontinued from the study, or
6. The subject is lost to follow-up.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1) Male aged 21 years or older
2) Ability to understand and provide written informed consent
3) All patients must have histopathological proven adenocarcinoma of the prostate
4) ECOG performance status 0-1
5) No evidence of other malignancy (except squamous or basal cell skin cancers)
6) Consent to use acceptable form of birth control following the imaging period (condoms for a period of seven days after injection if sexually active)

7) a) inclusion criteria specific for the pre-prostatectomy group: Untreated prostate Cancer with high-risk features, as defined as having at least one of the following criteria:

i. PSA ≥ 20.0 ng/mL
ii. ISUP Gleason Grade Group 3, 4 or 5
iii. Clinical stage T3

b) inclusion criteria specific for biochemical recurrence:

(i) Histopathological proven prostate adenocarcinoma
(ii)Rising PSA after definitive therapy with prostatectomy or radiation (therapy (external beam or brachytherapy).

1. Post radical prostatectomy (RP), PSA greater than or equal to 0.2 ng/ml measured more than 6 weeks after RP.
2. Post-radiation therapy, PSA that is equal to or greater than 2 ng/ml rise above PSA nadir

5.2 EXCLUSION CRITERIA

1) Unable to tolerate a PET/CT (e.g. unable to lie flat)

2) Recent history of a secondary malignancy in the past year, excluding non-melanoma skin cancer (non-metastatic)
3) Known allergic reactions to 68-Ga, or gadolinium-based contrast agents.
4) Treatment with another investigational drug or other intervention 2 years.
5) Patient has any medical, psychological or social condition that, in opinion of the investigator will make difficult for the participant to tolerate study intervention.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Fluid and Food Intake

Subjects should follow their normal diet before and after the administration of the study drug. Subjects will be encouraged to increase fluid intake at baseline and after the image acquisition to maintain proper hydration throughout the study period and decrease radiation exposure to the urinary bladder. To enhance imaging, subjects will be encouraged to void prior to collection of study imaging post-68Ga-PSMA-11 injection.

There are no dietary or food restrictions for this trial.

5.3.2 Subject Activity Restrictions

The radioactivity administered in this study is similar to other radiopharmaceutical studies, therefore the only activity restriction is:

- Participants whom are sexually active are required to consent to use acceptable form of birth control following the imaging period (condoms for a period of seven days after injection if sexually active)

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

- Target study sample: 80 male patients, age 21 and older, diagnosed with high risk adenocarcinoma of prostate. We anticipate will need to screen 200 patients in order to reach the target enrollment. Study will enroll participants

from Houston Methodist Hospital-Department of Urology, or from external referrals by sub-investigators or other physicians. Once a possible candidate is identified, the study team will approach him over the phone/e-mail or personally during a standard of care appointment, to present information about the study. If patient expresses interest, he will be scheduled for a screening visit.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

See Appendix A

Study Drug

Each milliliter of the sterile, apyrogenic drug product contains approximately 18.5-74 MBq (0.5 – 2 mCi) of active ingredient (68Ga-PSMA-11), 6 mL of sodium chloride (Sodium Chloride Injection (0.9%) without preservatives USP), and 10% of ethanol (v/v). Each dose of 68Ga-PSMA-11 solution for intravenous injection should be stored at room temperature and administered by the labeled expiration time.

6.1.2 DOSING AND ADMINISTRATION

On Day 0 of the study, the study drug dose will be 185±74 MBq (5±2 mCi) and will be administered by IV injection as a slow bolus and flushed with approximately 10 mL of saline solution.
A whole-body positron emission tomography/Computed Tomography (PET/CT) scan will be obtained between 60-90 minutes post-injection of study drug.

Vital signs (BP and pulse) will be taken and recorded before injection and 2 hours post injection.

All study drug administration will be done at the clinical site under the supervision of the Investigator.

Details of study drug administration will be captured in each subject's source document and transcribe onto the case report form (CRF)

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

In accordance with International Conference on Harmonisation (ICH) and US Food and Drug Administration (FDA) requirements, the Investigator and/or Drug Dispenser must at all times be able to account for all study drug.

No study agent is to be used outside of this study. Record the use of the study agent on the appropriate record. All study radiopharmaceuticals must be accounted for, whether used or unused, during the course of and at the conclusion of the study.

The Investigator is responsible for ensuring that study drugs are recorded, handled and stored safely and properly in accordance with the Code of Federal Regulations (CFR), local/state laws and used in accordance with this protocol.

68Ga-PSMA 11 will be manufactured by the Cyclotron cGMP Core Facility at Houston Methodist Research Institute.

Principal Investigator will send requisition via email for the preparation of the product. The study drug will be dispensed in a sterile 10 ml polypropylene at room temperature to be administered to the subject.

Unused product will be disposed of according to institutional regulations. Record the use and/or disposal of the study agent on the Drug Accountability record.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Formulation and packaging: the finished final product 68Ga-PSMA-11 solution for intravenous administration contains 0.6 ml ethanol and 5.4 ml of sodium chloride (Sodium Chrloride Injection (0.9%) without preservatives USP, in a 30 ml sterile vial.
Appearance: It is clear and colorless solution, no visible particles.
Dispensing: The product solution is aseptically dispensed into a sterile 10-mL polypropylene syringe and stored at room temperature prior to its intravenous administration to the subject.
Labeling: the label will disclose the expiration date and "For investigational use only".

6.2.3 PRODUCT STORAGE AND STABILITY

Each dose of 68Ga-PSMA-11 solution for intravenous injection will be shipped to the PET Imaging Core and it should be stored at room temperature and administered before the labeled expiration time.

The drug product contains radioactive material and should only be handled by personnel trained in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use is limited to a facility licensed by the Federal or State office of Radioactive Substances. Unused or residual waste should be disposed of as radioactive waste following the institution's standard operating procedures (SOPs) and/or applicable regulations or guidance.

6.2.4 PREPARATION

The drug will be manufactured upon requisition from a qualified principle investigator with approved IND and IRB protocol. During drug product manufacturing, individual doses are aseptically dispensed into a sterile 10-mL polypropylene syringe and stored at room temperature prior to its intravenous administration to the patient. Each milliliter of the sterile, apyrogenic drug product contains approximately 18.5-75 MBq (0.5 – 2 mCi) of active ingredient (68Ga-PSMA-11), 0.9 mL of sodium chloride (Sodium Chrloride Injection (0.9%) without preservatives USP, and 0.1 mL of ethanol.

The drug product contains radioactive material and should only be handled by personnel trained in the use of radioactive isotopes with proper shielding and monitoring. Receipt and use is limited to a facility licensed by the Federal or State office Radioactive Substances. Unused or residual waste should be disposed of a radioactive waste following the institution's standard operating procedures (SOPs) and/or applicable regulations or guidance. Each dose of 68Ga-PSMA-11 solution will be administered as a slow bolus over approximately 30 sec followed by a 10 mL saline flush.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

To minimize bias, all PET/CT images will be interpreted by a board-certified radiologist. The radiologist evaluating the images will be blinded to the final outcome, such as the histopathology of any biopsies and the outcome of subsequent imaging.

6.4 STUDY INTERVENTION COMPLIANCE

To ensure maximum compliance, all doses of study drug solution will be administered by study staff.
Source documents will be completed with all relevant information. These will include: dose, time, vital signs (pre and post injection) and any side effects if occurred during procedures.

6.5 CONCOMITANT THERAPY

Not applicable

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Participant will be discontinued from the study if they are not able to lie on their back in the scanner table for 15-20 during the procedure or if the suffer from claustrophobia. This will be documented in the CRF with date and specific reason for discontinuation of the participant.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- 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
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are screened but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are screened and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit, during the following week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY AND SAFETY ASSESSMENTS

8.1 Informed Consent

All subjects must sign and personally date an IRB approved informed consent form after receiving detailed written and verbal information about the reason, the nature and the possible risks associated with the administration of the study agent prior to the initiation of any study-related procedures. This must be done according to the guidelines provided in the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice (GCP), and requirements of Title 21 CFR 50.20 through 50.27. The subject must be made aware and agree that personal information may be scrutinized during an audit by competent authorities and properly authorized persons. However, personal information will be treated as strictly confidential and will not be publicly available.

8.2 Medical History

A complete medical history, including prostate cancer history, will be obtained at the first screening visit. Site staff will record the subject's medical history in the subject's source records and transcribe the information onto the medical history section of the CRF. Historical information concerning allergies (including food, drug and/or environmental) will also be obtained.

8.3 Vital Signs

Vital signs will include measurement of blood pressure and heart rate. Vital signs will be obtained and recorded at the Screening visit, pre- and post- each study drug injection, and also 2 hours after the first injection.

8.4 Dispensing Study Drug

The radiopharmaceutical will be injected through the indwelling catheter at a 185±74 MBq (5±2 mCi) dose. The estimated radioactive dose will be determined by measuring the amount of radioactivity in the syringe pre- and post-injection, using an appropriately calibrated radioisotope dose calibrator in accordance with the nuclear medicine department's SOPs. The injected activity will be recorded in the subject's source records and transcribed into the CRF.

The injection will be given by slow intravenous bolus. Following completion of the 68Ga-PSMA-11 injection, a normal saline flush (approximately 10 mL) will ensure that all 168Ga-PSMA-11 remaining in the infusion line is injected.

Any administration complication of the drug (e.g., overdose, observable extravasation, medication error) will be reported to the Chief of Nuclear Medicine and the PI within 24 hours of the event and will be recorded in the subject's source records and transcribed onto the CRF. If the Chief of Nuclear Medicine and the PI determine an adverse event occurred after injection or because of extravasation this will be reported as outlined in **Section 7.**

8.5 Computed Tomgraphy (CT) and Magnetic Resonance (MR) Imaging

A diagnostic quality MR scan (abdomen and pelvis) may be obtained (if clinically indicated) prior to surgery if not done within 6 months of the screening visit, if clinically indicated. If collected as part of screening procedures, the scan should be contrast-enhanced, unless contra-indicated for the subject. If necessary, the scan maybe obtained between the first injection of study drug and surgery.

8.6 Bone Scan

If clinically indicated, a bone scan may be obtained prior to surgery if not done within 6 months of the screening visit. If necessary, the scan may be obtained between the first injection of study drug and surgery.

8.7 68Ga-PSMA-11 PET/CT Imaging

A whole-body positron emission tomography/Computed Tomography (PET/CT) scan will be obtained between 60-90 minutes post-injection of study drug.

8.7.1 Imaging Procedures

68-Ga-PSMA PET/CT positivity or negativity will be interpreted, stratified by different anatomic regions as previously defined[1].

REGION	DESCRIPTION
1	Prostate/Prostate Bed
2	Pelvis, excluding prostate bed, but including lymph nodes
3	Extra-pelvic soft tissue, including lymph node involvement and metastasis to other organs
4	Bone Metastasis

The presence of prostate cancer (positive or negative) will be reported within these regions.

A. **Lymph nodes** - considered positive if the 68Ga-PSMA-11 uptake is localized/focal and is greater than the adjacent or mediastinal blood pool. The location of the lymph nodes will be recorded according to one of 7 sub-categories as previous defined[1]:

1	Right Hypogastric/Internal-iliac
2	Left Hypogastric/Internal-iliac
3	Right Obturator
4	Left Obturator
5	Right External-iliac
6	Left External-iliac
7	Other

B. **Visceral lesions –** These will be considered positive if the 68Ga-PSMA-11 uptake is focal and greater than the physiologic background activity in the organ of interest.

C. **Bone lesions –** These will be considered positive if the 68Ga-PSMA-11 uptake is focal and greater than physiologic background activity in normal bone marrow.

D. **Prostate bed –** These will be considered positive if the 68Ga-PSMA-11 activity is focal and greater than the physiologic, background activity in the prostate bed.

8.7.1.1 Camera Quality Control
Quality control of the PET/CT scanner will be maintained throughout the study according to departmental SOPs.

8.7.1.2 Image Acquisition
PET scan and Quantitation: Following administration of Ga-68 tracer, each subject will have a PET/CT scans at 60-90 min on a Siemens mCT PET/CT scanner by using 10-12 bed positions and 3 min/bed. The CT parameters used for attenuation correction CT (CAREDose-4D) include a fixed 100 mA tube current and a peak voltage of 120 kVp with a 5-mm reconstruction interval. The PET scans will be reconstructed by using a Siemens time of flight reconstruction method, TrueX-TOF UltraHD-PET with a Gaussian filter, scatter correction, and 5/21 iterations/subsets.

For the study, using the decay-corrected coronal anterior maximum- intensity projections of PET scans, regions of interest (ROI) will be drawn manually around the major organs (liver, kidney, spleen, lungs, heart) and any other tissues (tumor, muscle) showing visually appreciable Ga-68 uptake. Time-activity curves will be constructed by using values of whole-organ activity at the time of imaging. Recently, several 18F labeled peptides have been evaluated for imaging studies and methods for quantifying biodistribution and tumor localization have been described.
We plan to follow similar methods in our protocol. The percent injected dose in each ROI and the clearance kinetics from each organ will be used to estimate the radiation dosimetry based on OLINDA/EXM for the adult male phantom.

In order to generate quantitative data of tumor localization for each Ga-68 tracer, SUVmean and SUVmax will be generated as previously described. When there is no resolution loss or uncertainty in the ROI boundary definition (such as in the liver), SUVmean will produce a reliable estimate. However, SUVmax may be a more reliable parameter since the maximum value within an ROI is typically invariant with respect to small spatial shifts of the ROI.

8.8 Prostatectomy
Subjects will undergo standard of care surgery as deemed appropriate by the patient's attending urologist.

8.9 Surgical Pathology
Following radical prostatectomy and/or pelvic lymph node dissection, surgical specimens will be brought on ice to the Department of Surgical Pathology for tissue processing. Prostatectomy and lymph node specimens will be processed by the Department of Pathology in the standard fashion with hematoxylin and eosin (H&E) staining for grading and staging. Additionally, immunohistochemistry will be performed to confirm, at a microscopic level, that radiolabeled 68Ga-PSMA-11 co-localizes with tumor foci seen on H&E sections. Tumor foci identified on H&E sections will serve as the gold standard for imaging comparison.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, at any dose, which does not necessarily have a causal relationship with the treatment.
An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptoms or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose falls into one or more of the following categories:
• results in death

• is life-threatening
• i.e., an event which, in the view of the Investigator, places the subject at immediate risk of death from the event as it occurred and does not include an event which hypothetically might have caused death if it were more severe
• requires inpatient hospitalization or prolongation of existing hospitalization. For the seriousness criterion of inpatient hospitalization to apply, an overnight stay in the hospital is required. Admission to an ER and release without an overnight stay would not satisfy the inpatient hospitalization seriousness criterion.
• results in persistent or significant disability/incapacity
• where disability is defined as a substantial disruption of a person ability to conduct normal life functions, either reported or defined as per clinical judgment
• is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome to the child)
• is any other important medical event
• may not result in death, be life-threatening, or require hospitalization, but based upon appropriate medical judgment the event may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the serious definitions above. An important medical event may include development of drug dependency or drug abuse.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

8.2.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (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 intervention.

8.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be

collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Principal Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.2.5 ADVERSE EVENT REPORTING

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the study treatment is also an AE. Progression of the cancer under study is not considered an AE.

All AEs that occur after informed consent form signing must be reported by the investigator if they cause the subject to be excluded from the Study or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

AEs will not be collected for subjects during the prescreening period as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

The occurrence of AEs should be sought by non-directive questioning of the patient at each study visit. AEs may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

1. Severity grade (CTCAE Grade 1–4)
2. Duration (Start and end dates or if continuing at the Safety Follow-up Visit)
3. Relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a SAE is defined as in this protocol.

All AEs should be treated appropriately. Such treatment may include changes in study treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an AE is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether

there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

The Principal Investigator will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the Principal Investigator must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

In case of death, a comprehensive narrative report of the case should be prepared by the Investigator together with the SAER. If an autopsy is performed, a copy of the autopsy report should be actively sought by the Investigator and sent to the Principal Investigator or designee as soon as available. A copy of the autopsy report must remain on site with the CRF.
All deaths will be reported as SAEs regardless of their relationship to disease progression and reported via an SAER form from the time of signed informed consent until completion of the follow up period.
A new follow-up SAER form will be filled in by the Investigator if important follow-up information (i.e. diagnosis, outcome, causality assessment, results of specific investigations) are made available after submission of the initial form. The follow up SAER must be signed and dated by the Investigator. The follow-up form and any additional source documentation regarding the event will be sent to the Principal Investigator, or designee, as described above.
If a serious medical occurrence or death is reported to the Investigator outside the follow up window, which is believed to be related to the administration of the

investigational product, it is the Investigator's responsibility to report this occurrence.
Such occurrences will be reported using a SAER form or other form of communication deemed appropriate by the Investigator.

8.2.7 REPORTING EVENTS TO PARTICIPANTS

If SAEs are seen this study, the informed consent document will be updated with pertinent information.
Participants who had signed previous versions of the informed consent will be contacted and asked to sign updated version with new information.

8.2.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.2.9 REPORTING OF PREGNANCY

Not applicable

8.3 UNANTICIPATED PROBLEMS

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8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of 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 Institutional Review Board (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.

8.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

8.3.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Not applicable

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

Sample size for this pilot study was not statistically determined. Instead it was decided that up to 80 evaluable study subjects with prostate cancer are sufficient to adequately evaluate the tissue distribution of 185±74 MBq (5±2 mCi) 68Ga-PSMA-11 PET/CT imaging in tumor and non-tumorous regions of the prostate and/or pelvic lymph nodes (as determined by histopathology) in patients undergoing standard of care prostatectomy and/or pelvic lymph node dissection. Further, present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.

9.2 POPULATIONS FOR ANALYSES

The enrolled population will consist of all subjects who provided written informed consent and received the dosing of study drug.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

The detailed prospective procedures for the final data analysis are described in the Statistical Analysis Plan (SAP). Any changes in the original statistical methodology will be documented in the SAP. Descriptive statistics for all continuous variables (N, mean, standard deviation, minimum, median, and maximum) or for categorical variables (counts, percentages) will be generated and presented as appropriate.

9.3.2 SAFETY ANALYSES

The safety data will be summarized for all subjects dosed. Summary tables, including change from pre-dose to post-dose where applicable, will be presented for the following safety endpoints:

- Vital Signs
- TEASs

TEAEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) body system and preferred term, by intensity, and by causal relationship to study agent.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the

study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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 <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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 that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Houston Methodist Department of Urology. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Houston Methodist research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Houston Methodist Research Institute.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the Houston Methodist, Department of Urology. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Houston Methodist Research Institute, for use by other researchers including those outside of the study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator
Brian Miles, MD
Houston Methodist Hospital
6560 Fannin, suite 2100 *Houston, Texas 77030*
713-441-8111
bjmiles@houstonmethodist.org

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10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data is accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by a Research Coordinator from the department of Urology at Houston Methodist.

- The monitoring will be done on-site, after enrolling the 1st. patient and then every 3 months.
- The monitor will include verification of eligibility criteria, informed consent process, adverse events, source data verification (SDV), CRF completion and Investigational Product.
- Other documentation: training, delegation and screening logs.
- All information will be de-identified for the monitor.
- The monitor will provide reports that should be filled and forward to QA at Houston Methodist. The reports will provide a review of activities, progress, and issues of concern.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Subject data will be collected on source documents and transcribed on pre-printed CRFs provided by the Principal Investigator. The data on each CRF will be legibly handwritten with a ballpoint pen or typed. The Principal Investigator or his or her authorized designee will sign the CRF on the appropriate page(s) to verify that the data on the CRF were reviewed. Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/IEC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, and distribution and return records), and other Principal Investigator correspondence pertaining to the study will be kept in the appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. 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.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Red Cap, a 21 CFR Part 11-compliant data capture system provided by Houston Methodist. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. 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.

10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of

deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to Program Official Data Coordinating Center or sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the Principal Investigator.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with Houston Methodist has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial

NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

[1] Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68 Ga-PSMA-11 PET Accuracy in Localizing Recurrent Prostate Cancer A Prospective Single-Arm Clinical Trial 2019;0628. doi:10.1001/jamaoncol.2019.0096.

[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34. doi:10.3322/caac.21551.

[3] Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. J Clin Oncol 2007;25:1765–71. doi:10.1200/JCO.2006.08.0572.

[4] Oyen RH, Van Poppel HP, Ameye FE, Van de Voorde WA, Baert AL, Baert L V. Lymph node staging of localized prostatic carcinoma with CT and CT-guided fine-needle aspiration biopsy: prospective study of 285 patients. Radiology 1994;190:315–22. doi:10.1148/radiology.190.2.8284375.

[5] Tombal B, Lecouvet F. Modern Detection of Prostate Cancer's Bone Metastasis: Is the Bone Scan Era Over? Adv Urol 2012;2012:893193. doi:10.1155/2012/893193.

[6] Wachter S, Tomek S, Kurtaran A, Wachter-Gerstner N, Djavan B, Becherer A, et al. 11C-acetate positron emission tomography imaging and image fusion with computed tomography and magnetic resonance imaging in patients with recurrent prostate cancer. J Clin Oncol 2006;24:2513–9. doi:10.1200/JCO.2005.03.5279.

[7] De Visschere PJL, Standaert C, Fütterer JJ, Villeirs GM, Panebianco V, Walz J, et al. A Systematic Review on the Role of Imaging in Early Recurrent Prostate Cancer Biochemical recurrence Local neoplasm recurrence Metastases Imaging Positron emission tomography Computed tomography Magnetic resonance imaging Ultrasound Bone scintigraphy Prostate-specific membrane

antigen Prostate-specific antigen 2019. doi:10.1016/j.euo.2018.09.010.

[8] Souvatzoglou M, Weirich G, Schwarzenboeck S, Maurer T, Schuster T, Bundschuh RA, et al. The Sensitivity of [11 C]Choline PET/CT to Localize Prostate Cancer Depends on the Tumor Configuration. Diagnosis, Progn Clin Cancer Res 2011;17. doi:10.1158/1078-0432.CCR-10-2093.

[9] Nanni C, Zanoni L, Pultrone C, Schiavina R, Brunocilla E, Lodi F, et al. 18F-FACBC (anti1-amino-3-18F-fluorocyclobutane-1-carboxylic acid) versus 11C-choline PET/CT in prostate cancer relapse: results of a prospective trial. Eur J Nucl Med Mol Imaging 2016;43:1601–10. doi:10.1007/s00259-016-3329-1.

[10] Israeli RS, Powell CT, Corr JG, Fair WR, Heston WD. Expression of the prostate-specific membrane antigen. Cancer Res 1994;54:1807–11.

[11] Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann C. [68Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with 18F-FECH. Eur J Nucl Med Mol Imaging 2012;39:1085–6. doi:10.1007/s00259-012-2069-0.

[12] Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging 2013;40:486–95. doi:10.1007/s00259-012-2298-2.

[13] Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of Hybrid 68 Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. J Nucl Med 2015;56:668–74. doi:10.2967/jnumed.115.154153.

[14] Han S, Woo S, Kim YJ, Suh CH. Impact of 68 Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2018;74:179–90. doi:10.1016/j.eururo.2018.03.030.

[15] Perera M, Papa N, Roberts M, Williams M, Udovicich C, Vela I, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer—Updated Diagnostic Utility, Sensitivity, Specificity,

and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-. Eur Urol 2019. doi:10.1016/j.eururo.2019.01.049.

[16] Han S, Woo S, Kim YJ, Suh CH, Novara G. Impact of 68 Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis 2018. doi:10.1016/j.eururo.2018.03.030.

[17] Hartmann H, Zöphel K, Freudenberg R, Oehme L, Andreeff M, Wunderlich G, et al. Radiation exposure of patients during 68Ga-DOTATOC PET/CT examinations. Nuklearmedizin 2009;48:201–7. doi:10.3413/nukmed-0214.

[18] Pettinato C, Sarnelli A, Di Donna M, Civollani S, Nanni C, Montini G, et al. 68Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. Eur J Nucl Med Mol Imaging 2008;35:72–9. doi:10.1007/s00259-007-0587-y.

[19] Sandström M, Velikyan I, Garske-Román U, Sörensen J, Eriksson B, Granberg D, et al. Comparative biodistribution and radiation dosimetry of 68Ga-DOTATOC and 68Ga-DOTATATE in patients with neuroendocrine tumors. J Nucl Med 2013;54:1755–9. doi:10.2967/jnumed.113.120600.

[20] Fendler W, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, Giesel F, Haberkorn U, Hop[e T , Kopka K, Krause B, Mottaghy F, Schoder H, Sunderland J, Wan S, Wester H, Fanti S, Herrmann K. 68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl MED Mol Imaging (2017) 441014-1024 doi:10.1007/s00259-017-3670-z