

NCT# 03803475

Gallium-68 PSMA-11 PET in prostate cancer patients

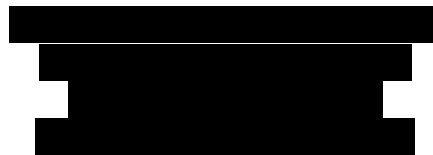
Study Drug: Gallium-68 PSMA-11

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Principal Investigator (Sponsor-Investigator)

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Revision History

Version 1.0	10/06/2018
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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with CHR policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

Printed Name

Signature

Date

Abstract

Title	Gallium-68 PSMA-11 PET in prostate cancer patients
Patient population	Patients with biopsy proven prostate cancer who have a concern for metastatic disease.
Rationale for Study	Gallium-68 PSMA-11 has been shown to have a higher sensitivity for the detection of metastatic prostate cancer than conventional imaging.
Primary Objective	Determine detection rate of PSMA-11 PET broken down by PSA
Study Design	This is a single center open label study.
Number of patients	Total population of patients will be 1,000 patients.
Duration of Therapy	The study will involve a single imaging study.
Duration of Follow up	No follow-up will be performed.
Duration of study	The study will reach completion two years from the time the study opens to accrual.
Study Drugs	Gallium-68 labeled PSMA-11 (PSMA-HBED-CC)
Safety Assessments	The patients will also be asked to report adverse events.

List of Abbreviations

AE	adverse event
CHR	Committee on Human Research (UCSF IRB)
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
Ga-68	Gallium 68
HDFCCC	Helen Diller Family Comprehensive Cancer Center
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
IV	intravenous
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PET	Positron Emission Tomography
PK	pharmacokinetics
PRC	Protocol Review Committee (UCSF)
PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
SD	standard deviation

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1 Introduction

1.1 Overview

Imaging and staging of prostate cancer is critical for surgical and treatment planning. We aim to image patients with suspected metastatic prostate cancer using Gallium-68 labeled HBED-CC PSMA (more commonly called ^{68}Ga -PSMA-11) in order to demonstrate its utility. We plan to utilize this data to obtain further approvals of the ^{68}Ga -PSMA-11 compound, so that this agent will become available for clinical imaging in prostate cancer patients.

This compound has been shown to be superior to choline based PET agents for the staging of prostate cancer, both Carbon-11 and Fluorine-18 compounds. But this compound was not patented and therefore no company or private entity will make the investment required to bring PSMA-11 to market. In the vacuum of availability, academic groups must take the lead in order to collect the necessary data for future FDA approval. This protocol was developed in collaboration with the Clinical Trials Network of the Society of Nuclear Medicine and Molecular Imaging. The inclusion criteria and study endpoints have been aligned so that inter-institutional sharing of data can be performed in order to pool data for final NDA submission.

1.2 Background

Prostate cancer is the most commonly diagnosed cancer and second leading cause of cancer death in American men (1). Existing conventional imaging (CT, MRI and bone scans) has a low sensitivity in detecting local recurrence or metastatic disease (2). The one exception being NaF PET/CT for the detection of osseous metastasis. Due to this limitation, numerous approaches to stage patients have been evaluated.

Choline imaging has been frequently used, as prostate cancer exhibits increase choline uptake that has been associated with the presence of choline kinase (3). Choline uptake is increased in comparison to FDG in both androgen dependent and independent prostate cancer patients (4). Choline has also been shown to be sensitive for the detection of recurrent tumor in patients with PSA (prostate specific antigen) values of less than 1.0 ng/ml (5). There are two forms of choline that are used in imaging prostate cancer, C-11 and F-18 choline. C-11 choline has a short half-life of 20 minutes, which limits its detection for metastatic disease but results in improved local detection due to decreased urinary activity at the time of imaging. F-18 choline has significant urinary excretion that limits evaluation of the prostate but, but has been shown to have better detection rates for distant metastatic disease (6). C-11 choline has limited sensitivity for osseous metastasis, possibly due to the decreased uptake time (7). Additionally, the sensitivity of C-11 choline is limited in patients with PSA values < 1.0 ng/ml (8-10). Although choline PET may be limited in sensitivity, it clearly delineates more lesions than cross section imaging or bone scan in patients with known disease (11). In 2012, the Mayo Clinic obtained NDA (new drug application) approval from the FDA for the use of C-11 choline.

A separate approach is to image the prostate specific membrane antigen (PSMA). PSMA is expressed on the majority of prostate cancer cells, and so would be an ideal cell membrane protein to image. The initial imaging approach to PSMA imaging target the intracellular domain using Indium-111-capromab (Prostascint), a murine monoclonal antibody (12,13). Although there was early promise for the detection of nodal metastasis (14), the agent was never able to adequately visualize osseous metastasis (15). Although combination with SPECT/CT does

improve lesion detection (16). One main limitation to In-111-capromab is that it takes a prolonged time to localize to the target tissue, which likely relates to both the size of the monoclonal antibody and the fact that agent targets the intracellular domain of the PSMA protein. Additionally, Proscint also recognizes an intracellular epitope so the antibody must cross the membrane to be effective. This likely only occurs in permeable dead or dying tumor cells.

Because of the limitations of In-111 capromab, there has been continued effort to develop agents that target the extracellular domain of the PSMA protein. The Ga-68 labeled PSMA-11 compound has become of particular interest because in the last year there have been two important articles. The first demonstrates that PSMA-11 has a higher sensitivity for the detection of disease than F-18 choline in a head-to-head intra-patient comparison that included 37 patients (17). The second paper looked at the sensitivity of PSMA-11 in the detection of metastatic lesions in patients with recurrent prostate cancer (18). Their results demonstrated a detection rate of 50% for patients with a PSA less than 1 ng/ml, and detection rate above 85% for patients with a PSA greater than 2 ng/ml. These detection rates are significantly higher than that reported by groups using choline (5).

Because of the improved resolution and image quality with PET, ability to quantitate uptake, increased sensitivity compared to choline, we intend to evaluate the utility of Ga-68 PSMA-11 for the imaging of prostate cancer. We expect that the data from this study will support applications for clinical approval of this imaging agent, leading to wider availability within the United States.

1.3 Previous experience with PSMA-11

We have completed numerous trials evaluating ⁶⁸Ga-PSMA-11 at UCSF and in conjunction with other institutions. These studies are currently being developed into an NDA application for submission to the FDA.

2 Objectives of the Study

2.1 Primary

- Sensitivity on a per-patient and per-region-basis (Table 1) of ⁶⁸Ga-PSMA-11 PET for detection of tumor location confirmed by histopathology/biopsy, clinical and conventional imaging follow-up.

3 Study Design

3.1 Characteristics

This is a prospective, single center, open-label study in patients with prostate cancer. Eligible participants will undergo baseline assessments at enrollment. Study participants will receive a one-time administration of Ga-68 PSMA-11 and undergo a PET/CT or PET/MRI imaging study.

3.2 Number of Subjects

It is anticipated that 1,000 patients will be enrolled in this study.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the administration of the radiopharmaceutical and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study:

3.3.1 Inclusion Criteria

1. Male, age \geq 18.
2. Histopathologically proven prostate adenocarcinoma.
3. Concern for metastatic disease in one of the following settings:
 - a. Initial staging with intermediate to high risk prostate cancer.
 - b. Biochemical recurrence after initial therapy.
4. Ability to understand a written informed consent document, and the willingness to sign it.

3.3.2 Exclusion Criteria

1. Patient unlikely to comply with study procedures, restrictions and requirements and judged by the Investigator to be unsuitable for study participation.

3.4 Duration of Follow Up

There will be no follow-up as part of this protocol.

3.5 Study Timeline

3.5.1 Primary Completion

The study will reach primary completion 24 months from the time the study opens to accrual.

3.5.2 Study Completion

The study will reach study completion 24 months from the time the study opens to accrual.

4 Study Drugs

4.1 Description, Supply and Storage of Investigational Drugs

4.1.1 Investigational Drug #1

Ga-68 labeled PSMA-11 (or PSMA-HBED-CC) is a radiopharmaceutical that will be produced under cGMP.

5 Treatment Plan

5.1 Dosage and Administration

The imaging agent (Ga-68 PSMA-11 or PSMA-HBED-CC) will be administered on an outpatient basis. It will be administered a single time intravenously prior to the PET imaging. The injected dose will be 3 to 7 mCi \pm 10% of ^{68}Ga -PSMA-11.

5.1.1 Other Modality(ies) or Procedures

5.1.1.1 PET imaging

a) ^{68}Ga -PSMA-11 PET preparation and injection:

The intravenously injected dose will be 111-259 MBq (3-7 mCi \pm 10%) of ^{68}Ga -PSMA-11 PET. A dose of 20 mg of furosemide (Lasix) is recommended to be injected i.v. together with, shortly before or after administration of the radiotracer in order to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary bladder that can occur with the gallium-68 radionuclide. Oral hydration is recommended on the day of the scan. Voiding is recommended immediately before start of the scan. Furosemide should not be administered in patients with medical contraindications to Furosemide administration including allergies and adverse reactions including sulfa allergies. (Note: Application of Furosemide can be omitted as part of the PET imaging protocol if a second-generation scatter correction algorithm is available for the PET scanner used in this protocol). PET imaging will begin 50-100 minutes after injection, but may be possible in certain circumstances for imaging to be delayed due to patient workflow or equipment issues. Scan time per bed position will be determined based on each sites PET scanner capabilities.

b) Patient preparation: no fasting is required.

c) PET protocol: Scan coverage will extend from mid thigh to the base of the skull, starting from the mid-thighs to prevent urinary bladder radiotracer accumulation at the start of PET imaging. Bed position scan time will be dependent on each sites scanner capabilities. At a minimum, 3 minutes per bed position will be used. In certain

circumstances, coverage may be extended to the toes. Contrast may be administered if requested by the referring clinician and is decided site dependent.

5.2 Monitoring and Toxicity Management

Each patient receiving Ga-68 PSMA-11 will be evaluable for safety. The safety parameters include spontaneous reports of adverse events reported to the investigator by patients.

6 Study Procedures and Observations

6.1 Schedule of Procedures and Observations

Screening assessments must be performed within 90 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the investigator. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

Data collected from the study visits will be stored in a study-specific Research Electronic Data Capture (REDCap) system.

6.1.1 Screening Assessments

The screening procedures and assessments must be completed within 90 days of the Day 1 Visit.

1. PSA.
 - A clinically drawn PSA that was performed prior to the patient signing the ICF, but was performed within the screening window, may be used as the Screening PSA.

6.1.2 Treatment Period

6.1.2.1 Study Procedures, Imaging Day 1

- ⁶⁸Ga-PSMA-11 administration
- PET imaging using either PET/CT or PET/MRI
- Administration of intravenous contrast (for MRI or CT as clinically indicated)
- Evaluation of adverse events

6.2 Prohibited Medications

There are no prohibited medications.

7 Reporting and Documentation of Results

7.1 Evaluation of Side Effects

7.1.1.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of ⁶⁸Ga-PSMA-11.

7.2 Evaluation of Safety

Analyses will be performed for all patients receiving ⁶⁸Ga-PSMA-11. The study will use the [CTCAE v4.0](#) for reporting of adverse events.

7.3 Definitions of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse Reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be recorded using the NCI CTCAE v4.0. The Investigator will assign attribution of the possible association of the event with use of the investigational drug.

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE <i>is clearly NOT related</i> to the intervention
	Unlikely	The AE <i>is doubtfully related</i> to the intervention
Related to investigational drug/intervention	Possible	The AE <i>may be related</i> to the intervention
	Probable	The AE <i>is likely related</i> to the intervention
	Definite	The AE <i>is clearly related</i> to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none, mild, moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.6 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or

qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Data and Safety Monitoring Committee Contacts

DSMC Chair:	[REDACTED]	DSMC Monitors
Phone:	[REDACTED]	Box 0128
Email:	[REDACTED]	UCSF Helen Diller Family
Address:	UCSF, Box 1705	Comprehensive Cancer Center
	San Francisco, CA 94158	San Francisco, CA 94143

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) and the San Francisco VA Medical Center within 5 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 6.1.30)
- Unexpected (as defined in 0)
- Serious (as defined in 6.1.5)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8 Statistical Considerations and Evaluation of Results

8.1 Study Endpoints

Detection rate stratified by PSA level.

8.1.1 Randomization

There will be no randomization performed.

8.2 Determination of Sample Size and Accrual Rate

8.2.1 Sample Size and Power Estimate

1,000 patients will be enrolled as part of this study over two years.

8.2.2 Accrual estimates

We estimate that roughly 500 patients with prostate cancer will be enrolled in this trial per year. Over a two-year period, this will result in up to 1000 patients being enrolled in the study.

8.3 Analyses Plans

8.3.1 Analysis of Primary Endpoints

Based on local reads for the detection of metastatic disease, the rate of localization abnormal focus of radiotracer will be stratified based upon the PSA prior to imaging.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10 Protection of Human Subjects

10.1 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendices

Appendix 1 Schedule of Study Procedures and Assessments

	Screening (Day -90 to Day 1)	Imaging (Day 1)
Informed Consent	X	
Inclusion/Exclusion Criteria Assessment	X	
PSA	X	
⁶⁸ Ga-PSMA-11 Administration		X
Imaging (PET/CT or PET/MRI)		X
Adverse Event Collection		X