^{68}Ga PSMA-HBED-CC in Intermediate to High-Risk Preprostatectomy Patients

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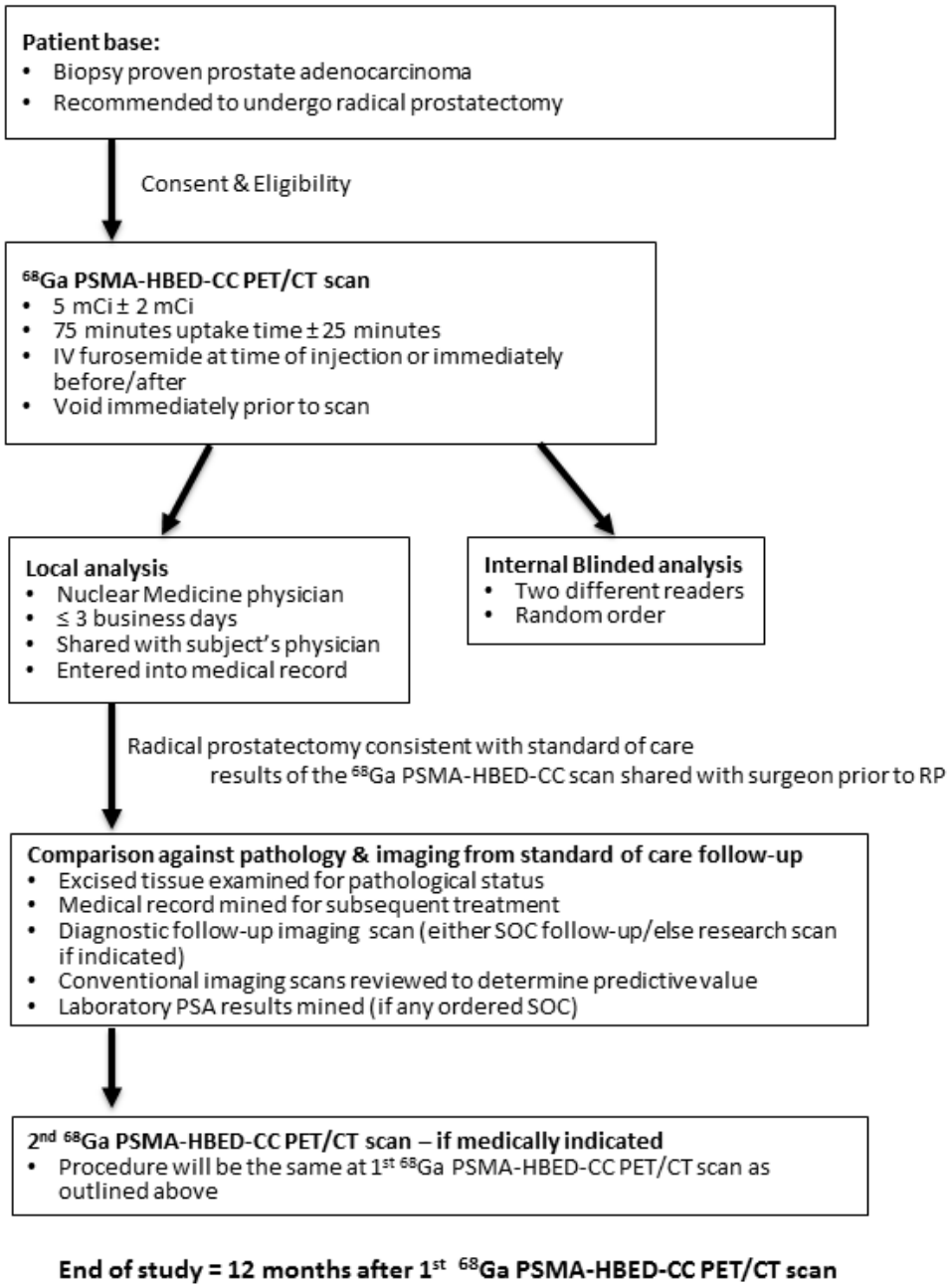
Amendment 2 – 21 November 2017
Amendment 1 – 31 October 2017
FDA approved protocol - 20 April 2017

SUMMARY OF CHANGES

Section	Change
September 18, 2018	
Cover Page	Updated version and date
TOC	Updated TOC
3.1	- Added eligibility criteria of needing a PSA level result within 2 months of assessing eligiblity. - Clarified the KPS should be within 3 months of assessing eligibility.
11	Updated study calendar to match updates to eligibility
January 23, 2018	
Throughout protocol	Formating
Cover Page	Updated version and date
Schema	Updated Schema
TOC	Updated TOC
5	Removed any mention of a 2nd research only scan during the 1st imaging PSMA imaging visit. The 2nd research only scan, detailed in Section 11-Correlative studies, is no longer part of the project.
5.1.3	Removed the option to obtain a diagnostic CT with the PSMA scan.
5.5	Updated references to tables and other sections since Correlative studies section was removed.
5.6	Continuing with surgery is at the discretion of the referring physican after reviewing the PSMA imaging results.
5.7.1	Added the option to repeat PSMA imaging.
5.10	Removed "Extraordinary medical circumstances", not appropriate for this study.
6.1	Changed baseline data collection window from 30 day to 3 months prior to PSMA imaging.
6.2	Clarified pre-imaging assessments.
6.3	Clarified post-imaging assessments.
6.4	Added laboratory section
11	Removed Correlative studies section. The research only scan will not be obtained.
11	Study Calendar updated to reflect changes in the protocol.
12	Updated all references to tables and other sections since Correlative studies section was removed.
13	Updated all references to sections since Correlative studies section was removed.
November 28, 2017	
Cover Page	Updated version and date, and added a biostatistician
12	Added optional 2nd PSMA PET/CT scan if medically indicated
November 21, 2017	
Cover Page	Corrected IND # 135,727, updated version and date
7.1	Corrected ^{68}Ga PSMA-HBED-CC IND # 135,727

October 31, 2017	
Cover Page	Added IRB #, IND #, and updated dated version and date
Schema	Updated Schema
TOC	Updated TOC
1.1.1	Specifide regional “pelvic” nodal metastases
5.4.5	Changed from central blind reader to internal blind readers. Also clarified reference to central blind reader to internal blind readers through remainder of study protocol.
5.5	Referenced Section 13 rather than having same information in multiple places in the protocol.
6	Clarified Patient Assessment section, added potencial research CT if clinical follow-up imaging is not obtained.
7.1	Added ^{68}Ga PSMA-HBED-CC IND # 135,272
12	Clarified footnotes in study calendar
13	Updated Efficacy Assessment – This is the same information that was in the previous section 13, however, laid out in a way to more easily evaluate the PSMA scam, conventional imaging and pathology assessment.
14.1	Statistical Justification section added
14.2	Updated section references throughout, as information in Section 13 was moved around.
14.3	Updated section references throughout, as information in Section 13 was moved around.
April 20, 2017	v0.06
Receipt	Initial submission to FDA, 1571 0000

SCHEMA



End of study = 12 months after 1st ^{68}Ga PSMA-HBED-CC PET/CT scan

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1. OBJECTIVES

1.1. Primary objective

1.1.1. Determine sensitivity, specificity, positive, and negative predictive value of ^{68}Ga PSMA-HBED-CC PET for detection of regional pelvic nodal metastases compared to pathology at radical prostatectomy (per patient, using nodal regional correlation).

1.2. Secondary objective

1.2.1. Determine sensitivity, specificity, positive, and negative predictive value of ^{68}Ga PSMA-HBED-CC PET for detection of extra-pelvic nodal metastases, visceral metastases, and osseous metastases compared to biopsy and imaging follow-up.

1.3. Exploratory objectives

1.3.1. Determine sensitivity, specificity, positive, and negative predictive value for detection of regional nodal metastases in comparison to cross-sectional imaging performed contemporaneously with ^{68}Ga PSMA-HBED-CC PET.

1.3.2. Compare progression free survival at one year (as measured by PSA) between patients with, and without, nodal metastases.

1.3.3. Correlate SUVmax from ^{68}Ga PSMA-HBED-CC PET and short-axis diameter (of nodal disease on cross-sectional imaging) to presence of true pathology.

1.3.4. Quantify and describe the incidence of osseous and distant metastatic lesions.

2. BACKGROUND AND RATIONALE

2.1. Current imaging of prostate cancer

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 is NaF PET/CT for the detection of osseous metastasis. Due to this limitation, numerous approaches to stage patients have been evaluated.

C-11 and F-18 Choline PET imaging have been frequently used, as prostate cancer exhibits increased choline uptake that has been associated with increased cell membrane proliferation and increased levels 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, although sensitivity is somewhat lower 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 shows more lesions than cross section imaging or bone scan in patients with known disease.[11] In 2012, the Mayo Clinic obtained a new drug application approval from the FDA for the use of C-11 choline.

A separate approach is to image prostate specific membrane antigen (PSMA). PSMA is expressed on the majority of prostate cancer cells, and so is an ideal target to image. The initial imaging approach to target PSMA was done 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 does not adequately visualize osseous metastasis[15] and has limited sensitivity, 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 relates to both the size of the monoclonal antibody and its slow pharmacokinetics. Additionally, Prostascint 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 have been continued efforts to develop agents that target the extracellular domain of the PSMA protein. The Ga-68 labeled PSMA-HBED-CC compound has become of particular interest due to two important publications. The first study demonstrated that PSMA-HBED-CC 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-HBED-CC in detecting 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]

2.2. ^{68}Ga PSMA-HBED-CC (^{68}Ga PSMA-11)

Current evidence regarding detection rate of biochemical recurrence (BCR) with ^{68}Ga-HBED-CC PSMA PET/CT from two recent papers:

- Detection rate was 50% when PSA was below 0.5 ng/mL, 69% for PSA 0.5–2.0 ng/mL, and 86% when PSA was above 2.0.19
- Detection rate was 57.9% for PSA 0.2 to <0.5 ng/mL, 72.7% for PSA 0.5 to <1, 93.0% for 1 to <2.0, and 96.8% for ≥ 2.0.20

2.3. Prior human subjects experience

Safety. No adverse drug reactions have been reported in the literature for ^{68}Ga PSMA-HBED-CC. As a PET tracer, the drug should remain pharmacologically inert and not perturb the biological system. Afshar-Oromieh and colleagues[17,18] as well as Green *et al*.[21] have clearly stated that no adverse events or pharmacologic events were observed during their studies. Adverse events were not discussed in other reviewed studies[20,22-28] or case reports.[29,30] In total, these papers provide data regarding more than 1200 subjects without any noted adverse reactions.

Efficacy. To date, there have been 11 studies[17,18,20,23,24,26,27,38-41] describing use of ^{68}Ga PSMA-HBED-CC and 4 clinical trials.[21,25,28] Tables with key information of reviewed papers are provided (Tables 6-1, 6-2, and 6-3) in the body of the IND application.

Maurer *et al.* (2014) [Germany].[23] The purpose of this retrospective study was to investigate the diagnostic efficacy of ^{68}Ga PSMA-HBED-CC -PET imaging when compared against radical prostatectomy, templated lymph node dissection, and conventional imaging (CT, MRI). The primary inclusion criterion was intermediate-to-high risk prostate cancer scheduled to undergo radical prostatectomy. The only exclusion criterion was presence, or history, of a secondary malignancy. A total of 130 patients were reviewed. A contrast enhanced diagnostic CT was performed at the same imaging session as the PET scan. A double-trained board certified radiologist-nuclear medicine physician blinded to post-operative histopathological results analyzed all the imaging data sets (^{68}Ga PSMA-PET/CT and PET/MR). Conventional imaging was read prior to the ^{68}Ga PSMA-PET data. Results yielded a patient-based ROC AUC of 0.835 (95% CI 0.763 – 0.908) for ^{68}Ga PSMA-PET and an AUC of 0.691 (95% CI 0.592-0.789) for conventional imaging. For ^{68}Ga PSMA-PET patient-based sensitivity was 65.9 %, specificity was 98.9%, and overall accuracy of 88.5%. In contrast, conventional imaging had a patient-based sensitivity of 43.9%, specificity of 85.4%, and an overall accuracy of 72.3%. On a template-based analysis driven by lymph node dissection, the ^{68}Ga PSMA-PET sensitivity was calculated as 78.2%, specificity as 99.1%, and accuracy as 95.7%. Conventional imaging resulted in a sensitivity of 29.1%, specificity of 97.2%, and accuracy of 86.1%.

Van Leeuwen *et al.* (2014) [Australia].[25] The purpose of this prospective trial was to assess accuracy of ^{68}Ga PSMA-HBED-CC -PET/CT for lymph node staging in intermediate- and high-risk prostate cancer. Criteria for selection included planned radical prostatectomy, treatment naïve, negative bone scan, no concurrent (or history of) a secondary malignancy, and at >5% risk of metastatic lymph nodes. Patients with suspected extra-nodal disease on prior contrast-enhanced CT were excluded. ^{68}Ga PSMA-HBED-CC PET/CT was performed <4 weeks before the radical prostatectomy and lymph node dissection. A total of 30 men were enrolled and evaluated. A non-contrast enhanced CT was performed at the same imaging session of the ^{68}Ga PSMA-HBED-CC -PET. Images were analyzed by two nuclear medicine physicians; it is not stated if the physicians were blinded to the pathologic results or if the scan interpretations were completed prior to surgery. Results yielded a patient-based specificity of 95%, sensitivity of 64%, positive predictive value of 88%, and negative predictive value of 82%. Lymph node analysis yielded specificity of 100%, sensitivity of 58%, PPV of 94% and NPV of 98%. The mean size of true-positive metastatic lymph nodes was 4.7 mm (± 1.4mm) and false-negative size was 2.7mm (± 1.3mm).

Eiber *et al.* (2015) [Germany].[20] The purpose of this retrospective study was to investigate the detection rate of ^{68}Ga PSMA-HBED-CC PET/CT in men with

biochemical recurrence (PSA ≥ 0.2 ng/mL). Only men who had undergone a radical prostatectomy, had not received chemotherapy, and had a diagnostic CT done with the PSMA imaging study were included. Men undergoing antiandrogen therapy (n=70) were included. A total of 248 subjects were included in the analysis. The active comparator was the diagnostic CT done simultaneously with the PET imaging. Scans were interpreted by a board certified radiologist and a board certified nuclear medicine physician. The reviewers were not blinded. No significant detection effect was observed with antiandrogen use (p=0.0783). PSMA was able to identify additional areas of disease involvement in 61 subjects (24.6%) whereas CT showed additional regions in 17 subjects (6.9%). A significant limitation of the study was a lack of histopathology for outcome comparisons. Sensitivity, specificity, positive and negative predictive values are not provided.

Afshar-Oromieh *et al.* (2015) [Germany].[18] The purpose of this retrospective study was to analyze the diagnostic value of ^{68}Ga PSMA-HBED-CC PET/CT in a large cohort with multiple variables. The cohort was designed to align with a generalized population; men were included if they had suspected progressive disease following conventional therapy (radiation therapy and/or radical prostatectomy, n=292) or to determine metastatic disease burden prior to initial therapy (n=27). Of those with suspected recurrence, 86 were on antiandrogen therapy. A non-contrast enhanced diagnostic CT scan was performed at the same imaging session as the PET scan; additionally, a low-dose attenuation scan was performed for the ^{68}Ga PSMA-HBED-CC PET. Scans were interpreted by two board-certified nuclear medicine physicians. No adverse events or clinically detectable pharmacological effects were noted in any of the subjects following injection of the PSMA-HBED-CC radiotracer. A total of 901 tumor lesions were observed in 319 subjects. Lesion-based analysis yielded sensitivity of 76.6%, specificity of 100%, negative predictive value of 91.4%, and positive predictive value of 100%. Because all patients were assumed to have tumor and therefore could not be considered 'true negative,' the authors did not provide a per-patient calculation.

Green *et al.* (2017) [Indiana University School of Medicine, Indiana, US]. The purpose of this small study was to estimate human radiation dosimetry for ^{68}Ga PSMA-HBED-CC under approval of an RDRC research protocol. Both biodistribution and pharmacokinetics were evaluated in subjects (n = 9). Administered dose of ^{68}Ga PSMA-HBED-CC was 3.04 mCi and images were acquired at 15 minutes post-injection, 60 minutes post-injection, and 90 minutes post-injection. Subjects reported no symptoms or adverse reactions following radiopharmaceutical administration. Organ dose estimates were provided for 22 organs and for whole body.

It should be noted that radiolabeled PSMA ligands have been shown to be taken up by rectal carcinoma,[31] gastrointestinal stromal tumors,[32] renal cell carcinoma,[33] pancreatic serous cystadenoma,[34] stromal hyperplasia of the breast,[35] B-cell follicular non-Hodgkin's lymphoma,[36] and Paget disease.[37]

Summary. To date, a prospective, well-controlled clinical trial evaluating the efficacy of ^{68}Ga PSMA-HBED-CC PET/CT has not been performed for prostate cancer. Robust trials for both initial diagnosis as well as those men with suspected recurrence needs to be designed and performed. Current retrospective review of ^{68}Ga PSMA-HBED-CC PET/CT done in foreign nations suggests strong efficacy of the ^{68}Ga PSMA-HBED-CC radiotracer. Currently, three clinical trials are underway – two foreign, one domestic.[42-44] Additional pivotal phase 3 trials should be completed in the U.S. to determine effectiveness in the generalized population and determine requirements for implementation if found to be effective.

2.4. Rationale

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 (^{68}Ga PSMA-HBED-CC) in order to determine its utility. We plan to utilize this data to obtain further approvals of the ^{68}Ga PSMA-HBED-CC compound, so that this agent will become widely available for clinical imaging in prostate cancer patients.

^{68}Ga PSMA-HBED-CC has been shown to be superior to choline based Carbon-11 and Fluorine-18 PET imaging agents for the staging of prostate cancer. However, ^{68}Ga PSMA-HBED-CC was not patented and therefore no company or private entity will make the investment required to bring it to market. In the vacuum of availability, academic groups are taking the lead in order to collect the necessary data for future FDA approval.

The rate of prostatectomy is increasing in high-risk prostate cancer patients (1), which means that there is an increasing unmet need to detect regional and distant metastases prior to surgery. Two published studies to date using ^{68}Ga PSMA-HBED-CC PET in intermediate to high-risk patients prior to prostatectomy, demonstrated a per patient sensitivity for nodal metastases of 64-66% (2,3), much improved compared to conventional imaging modalities. We aim to study the ability of ^{68}Ga PSMA-HBED-CC to detect pelvic nodal disease in intermediate and high-risk preprostatectomy patients.

3. SUBJECT SELECTION

3.1. Eligibility Criteria

3.1.1. Biopsy-proven prostate adenocarcinoma

3.1.2. Intermediate to high-risk disease, defined as one of the following factors: PSA > 10, T2b or greater, or a Gleason score of 7 or greater.

3.1.3. A PSA level result within the last 2 months.

3.1.4. Planned prostatectomy with lymph node dissection

3.1.5. Karnofsky performance status (KPS) of ≥ 50 (ECOG/WHO 0, 1, or 2) within the last 3 months.

3.1.6. Must be treatment naïve (not have received neoadjuvant chemotherapy, radiation therapy, hormonal therapy, androgen deprivation therapy, or focal ablation techniques (e.g., HiFu)

3.1.7. Not receiving any other investigational agents (i.e., unlabeled drugs or drugs under an IND for initial efficacy investigations

3.1.8. Ability to understand and the willingness to provide informed consent.

3.2. Exclusion Criteria

3.2.1. Cannot receive furosemide.

3.2.2. Allergy to sulfa or sulfa-containing medications.

3.2.3. History of Stevens-Johnson syndrome

3.2.4. Known Paget's disease

3.2.5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4. REGISTRATION PROCEDURES

Once informed consent is signed:

- Attach scanned copy of completed eligibility checklist in OnCore for review by the CRSO/designated safety monitor at the time of quarterly audits.
- Enter subject into the OnCore database of the Holden Comprehensive Cancer Center.
- Scan the record of consent into the subject's medical record.

5. PROCEDURES

Protocol should not supersede standard of care procedures for patient safety.

5.1. Imaging preparation

5.1.1. **Oral hydration.** Participants will be encouraged to maximize hydration the day before and day of ^{68}Ga PSMA-HBED-CC imaging.

5.1.2. **Furosemide**. 20 mg furosemide (IV push) will be administered concurrently or immediately after radiotracer administration to minimize PET scatter artifacts from excreted radiotracer accumulation in the kidney and urinary

bladder.

5.1.3. **Contrast**. Imaging contrast will not be ordered as part of this study.

5.1.4. **Voiding**. Participants will be asked to void their bladder immediately prior to radiotracer injection and before imaging.

5.2. **^{68}Ga PSMA-HBED-CC administration**

5.2.1. **Dose**. 3-7 mCi (111 – 259 MBq). Target 5 mCi.

5.2.2. **Route of administration.** Intravenous.

5.2.3. **Frequency**. Once per PET scan.

5.2.4. **Uptake time**. 75 minutes ± 25 minutes. Target 75 minutes

5.3. **Prohibited Medications**

None.

5.4. **PET/CT Imaging Procedures**

5.4.1. **Scan coverage**. 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. Subject to void immediately prior to imaging.

5.4.2. **Bed position.** Scan time will be dependent on scanner capabilities. At a minimum, 3 minutes per bed position will be used.

5.4.3. **Discharge.** Subject must be monitored for adverse events for a minimum of 2 hours post-injection.

5.4.4. **Local Analysis.** A board-certified nuclear medicine physician on-site will interpret the images within 3 business days of the imaging study. These interpretations will not be used for final evaluation, however regional positivity results will be collected as study data.

5.4.5. **Internal Blinded Reads.** Imaging data will be interpreted by two different readers in a random order at separate reading sessions. Cross sectional imaging from the PET will be available for anatomic correlation. Final reads for each subject will be interpreted as positive or negative for the presence of pelvic nodal disease, and positive or negative for the presence of osseous metastatic disease and soft tissue metastases outside of the pelvis. All readers will have undergone ^{68}Ga PSMA PET training.

5.4.6. **Results dissemination.** Results will be shared with the subject's urologist and will be included in the subject's medical record.

5.5. **Visual Interpretation of PET data (Internal blinded reads)**

Regions of suspected disease will be graded on a two-point scale by each reader (0=Negative or 1=Positive). A region will be judged as positive if at least one lesion in this region is visually positive. Regions are defined in Table 12.1. in Section 12. Criteria for visual interpretation positive for disease are detailed in Section 12. 1.1.

5.5.1. **Lymph nodes.** Considered positive if ^{68}Ga PSMA-HBED-CC uptake is focal and greater than adjacent background. Pelvic lymph nodes will be subclassified according to their localization as follows: R/L obturator, R/L

external iliac, R/L internal iliac, and other pelvic nodes (total of 7 subgroups).

5.5.2. **Visceral lesions**. Considered positive if the ^{68}Ga PSMA-HBED-CC uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

5.5.3. **Bone lesions**. Considered positive if the ^{68}Ga PSMA-HBED-CC uptake is focal and greater than physiologic bone marrow.

5.6. **Post-Imaging Prostatectomy**

Prostatectomy and pelvic nodal dissection will be performed at the discretion of referring physican after reviewing imaging results. Nodal dissection should follow standard of care.

5.6.1. **Negative imaging.** Subjects without evidence of positive nodal or metastatic disease on ^{68}Ga PSMA-HBED-CC PET imaging will undergo radical prostatectomy and pelvic nodal dissection. The pelvic nodal dissection will be performed regardless of imaging results.

5.6.2. **Positive imaging.** The urologist will be informed of the location of any ^{68}Ga PSMA-HBED-CC PET positive (or suspicious) regional pelvic nodes prior to surgery. The surgeon should attempt to capture the suspicious node during the nodal dissection.

5.6.3. **Nodal dissection.** Nodes will be marked by location using the standard procedures. For example, if the urologist removed left and right nodal regions separately, the subject will have two nodal regions (left/right). If the nodes are removed in six groups (bilateral internal/external/obturator nodes), the subject will have six nodal regions analyzed.

5.6.4. **Pathology**: Specimens from prostatectomy will be evaluated for the presence of nodal metastasis. This will be reported on a per patient basis, and by region as positive or negative. The pathology report should list the number of nodes counted during the exam.

5.6.5. **Immunohistochemical staining (IHC) (optional).** Although not routinely performed during standard practice, IHC staining for PSMA of tumor specimens (primary and lymph node metastases) is preferred.

5.7. **Post-Prostatectomy Procedures**

5.7.1. **PSMA-positive with negative pathology.** Subjects with ^{68}Ga PSMA-HBED-CC positive nodes without positive nodes on pathology, may be rescanned with CT (or MRI) to determine if the suspicious node was thought to be removed. Additionally, clinicans will have the option to order a 2nd ^{68}Ga PSMA-HBED-CC PET/CT as described in Section 6.4.4.

5.7.2. **PSMA-positive osseous or metastatic lesions.** ^{68}Ga PSMA-HBED-CC positive osseous or distant metastatic lesions will be followed by other imaging (bone scan, NaF PET, CT or MRI) at the treating physician's discretion and local standard of care.

5.7.3. **Biopsy.** Biopsies to determine metastases or provide information for re-staging should be performed at treating physician's discretion and per local

standard of care.

5.7.4. **CT or MRI.** Subjects should undergo routine standard of care imaging.

5.7.5. Positive disease identified by either ^{68}Ga PSMA-HBED-CC PET/CT or follow-up conventional imaging will trigger locally performed anatomic measurement of lesion size(s) on both the baseline CT or MRI, and the follow-up CT or MRI of suspected site of disease.

5.8. **General Concomitant Medication and Supportive Care Guidelines**

In general, subjects may receive full concomitant and supportive care throughout this trial with the following considerations:

- Subjects may not receive any other approved or investigational anti-neoplastic therapies for the treatment of prostate cancer from time of consent through prostatectomy.

5.9. **Follow-Up**

5.9.1. **Active follow-up.** Subjects will be actively followed for acute adverse events for 10 radioactive half-lives rounded up to the calendar day (as per the established standard). Since Gallium-68 has a half-life of 67.71 minutes the active follow-up will be a minimum of 1 calendar day.

5.9.2. **Long term follow-up.** After the active follow-up period, the subject will return to standard follow-up with their physician. Subject's outcome should be followed through passive chart review. Data collected must minimally include subsequent PSA measurements, and any evidence of disease progression. Contact with subject and/or subject's treating physicians may occur to better define treatment outcomes.

5.10. **Criteria for removal from study**

- **Consent**. Subjects must be able to continue to provide consent for this study. If a treating physician or study team member believes a subject can no longer provide prospective consent, the investigator will be contacted to determine if the subject can provide consent and is able to continue on study.
- **Refusal to continue treatment**. In this event, the reasons for withdrawal will be documented.

6. PATIENT ASSESSMENTS

6.1. **Post-consent Baseline Data Collection**

Post-consent, the following data should be collected

6.1.1. **Pathology.** A copy of the pathology report documenting the Gleason score should be obtained. Also, obtain a copy of any pathology reports 3 months prior to the ^{68}Ga PSMA-HBED-CC PET/CT.

6.1.2. **Bone scan.** If a bone scan was performed within 3 months of ^{68}Ga PSMA-HBED-CC PET/CT, obtain a copy of the images and the report.

6.1.3. **MRI**. If an MRI was performed within 3 months of ^{68}Ga PSMA-HBED-CC PET/CT, obtain a copy of the images and the report.

6.1.4. **CT scan**. If a CT was performed within 3 months of ^{68}Ga PSMA-HBED-CC

PET/CT, obtain a copy of the images and the report.

6.1.5. **PSA.** Baseline PSA lab tests within 3 months of ^{68}Ga PSMA-HBED-CC PET/CT should be obtained.

6.2. **Pre-Imaging Assessments (Baselines)**

6.2.1. **Constitutional adverse events.** A baseline evaluation will be obtained prior to injection and graded according to NCI's Common Toxicity Criteria (CTCAE v4).

6.2.2. **Vital signs**. Heart rate, blood pressure, and temperature will be obtained immediately before and after injection of ^{68}Ga PSMA-HBED-CC, in a supine position.

6.3. **Post-Imaging Assessments**

6.3.1. **Vital signs**. Heart rate, blood pressure, and temperature will be obtained when subject is supine immediately after the imaging session.

6.3.2. **Constitutional adverse events.** Prior to discharge from the PET Imaging Center the subject will be assessed for untoward medical event(s) that have occurred since injection of ^{68}Ga PSMA-HBED-CC. These will be graded with CTCAE.

6.3.3. **Symptom review**. Subject will be contacted by telephone or in person between 1 to 3 business days after PSMA-HBED-CC imaging to screen for adverse events. Subject must be contacted at least once after 24 hours post-injection.

6.4. **Follow-up**

6.4.1. **Pathology**. Results from pathology ordered per standard of care up to 12 months post ^{68}Ga PSMA-HBED-CC PET/CT, will be obtained for study analysis.

6.4.2. **Follow-up imaging**. Conventional imaging ordered per standard of care up to 12 months post ^{68}Ga PSMA-HBED-CC PET/CT, will be obtained for study analysis. If the 1st Ga-68 PSMA-HBED-CC PET/CT scan shows lesions outside the pelvic region AND if imaging is NOT obtained per standard of care the research study will obtain a CT (abdomen and pelvis w/ contrast if contrast not contraindicated). Readers will be unblinded to all results and will be specifically informed of the location of the ^{68}Ga PSMA-HBED-CC PET positive lesions so follow-up measurements may be performed on the same lesions.

6.4.3. **Laboratory**. Results from laboratory reports related to prostate cancer monitoring (e.g. PSA levels) ordered per standard of care up to 12 months post ^{68}Ga PSMA-HBED-CC PET/CT, will be obtained for study analysis.

6.4.4. **Second ^{68}Ga PSMA-HBED-CC PET/CT (if medically indicated)**. If the 1st ^{68}Ga PSMA-HBED-CC PET/CT scan shows lymph nodes or visceral (soft tissue) lesions positive for prostate cancer disease, but surgery or biopsy results in negative pathology; the subject may be asked to return to complete a 2nd Ga-68 PSMA-HBED-CC PET/CT imaging visit.

7. DRUG INFORMATION

7.1. ^{68}Ga PSMA-HBED-CC IND 135,727 (M. Graham, sponsor)

7.1.1. **Availability**. Drug is available from the P E T Drug Manufacturing Unit at the University of Iowa Hospitals & Clinics.

7.1.2. **Compatibility**. No known compatibility issues.

7.1.3. **Storage and stability**. Store drug in shielded container as per local institutional guidelines. Drug has a 3 hour stability. Expiration is provided on label.

7.1.4. **Toxicities**. No known toxicities.

8. DOSE MODIFICATIONS & DELAYS

Not applicable.

9. ADVERSE EVENTS: REPORTING REQUIREMENTS

This study will also be monitored by internal oversight specialists at the University of Iowa. The Data and Safety Monitoring Plan of the Holden Comprehensive Cancer Center provides standard operating procedures to monitor all clinical cancer trials at the UIHC. All investigator-initiated trials are automatically monitored by the Data and Safety Monitoring Committee (DSMC). A detailed data and safety monitoring plan for this study is on file with the DSMC. This study has been assigned as a risk level 4 as an IND phase 2b/3 study.

9.1. Determination of Reporting Requirements

The clinical research team is responsible for collecting and recording the research data. As these results are collected, all toxicities and adverse events will be identified and reported to the principal investigator (PI). The PI will determine final relationship of the event to the investigational products (^{68}Ga PSMA-HBED-CC):

- Grade 1 and 2 events do not require attributions assigned.
- Grade 3 and higher adverse events require attribution assigned to 68Ga PSMA-HBED-CC.
- All serious adverse events (SAEs) require attribution to 68Ga PSMA-HBED-CC.

Toxicity will be graded according to NCI's Common Toxicity Criteria (CTCAE v4). The principal investigator will have final responsibility for determining the attribution of toxicity as it is related to the investigational product.

9.2. Institutional Review Board reporting requirements

Adverse events that meet criteria of both *serious* and *attributed* (possible, probable, or definite) to the study agent. Thus:

- Serious adverse events *only*
- Attributable to ^{68}Ga PSMA-HBED-CC

Report to the IRB via HawkIRB within 10 business days of event

9.3. FDA reporting requirements [M. Graham, sponsor]

Adverse events that meet criteria of *serious, unexpected,* and *attributed* (possible, probable, or definite) to ^{68}Ga PSMA-HBED-CC must be reported to the sponsor or the sponsor's appointed designee:

- Serious adverse events only [21 CFR 312.32]
- Attributable to 68Ga PSMA-HBED-CCwith a causal relationship as described [21 CFR 312.32 (c)(1)(i)]
- Unexpected, as defined by the FDA: "…not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator 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, as amended."

9.4. Routine Adverse Event Reporting Requirements to DSMC

For non-serious adverse events, documentation must begin at radiotracer injection and continue through 24 hours post injection.

Routine adverse events will be reported by submission of an adverse events log to the DSMC at the time of DSMC review.

9.5. Serious Adverse Event Reporting to DSMC

Serious adverse events occurring after ^{68}Ga PSMA-HBED-CC injection will require a notification to the DSMC within 1 business day of learning of the event. The SAE capture window will be from the administration of ^{68}Ga PSMA-HBED-CC through 24 hours after administration. Serious adverse events that occur after this window are reportable if they are deemed reasonably attributed to the investigational drug, ^{68}Ga PSMA-HBED-CC .

10. CLINICAL TRIAL MONITORING

Clinical trial monitoring will be conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol and/or amendment, with good clinical practice (GCP), and with applicable regulatory requirement(s).

10.1. University of Iowa's Human Subjects Office

The University of Iowa's Human Subjects Office (HSO) provides five different monitoring visits (post-approval responsibilities review, post-approval monitoring and education visit, directed monitoring, department of defense sponsored research monitoring, student principal investigator review). The HSO also provides an IND educational visit combined with a post-approval responsibilities review.

- Monitoring is performed by the HSO from their roster of qualified individuals.
- Monitoring is on-site.
- An educational IND visit will be requested by the PI. This will be done after IRB approval. The IRB indicate if accrual can begin prior to this visit.

- For the educational IND visit, if subjects have been consented, all signed consent documents will be reviewed.
- For the educational IND visit, the principal investigator will be provided a copy of the report documenting the visit within 1 month.
- Monitoring plans are not study specific. The plans are maintained by the HSO and are available for public review on-line.

10.2. **The Holden Comprehensive Cancer Center**

The Holden Comprehensive Cancer Center (HCCC) will provide monitoring for this investigator-initiated trial in compliance with their overarching monitoring plan on file with the National Cancer Institute (NCI) as well as with the individual clinical monitoring plan on file for this trial. Specifically:

- Monitoring is performed by the HCCC from their roster of qualified individuals.
- Eligibility review is ongoing, through remote review from OnCore, the clinical trials software
- Monitoring is on-site and begins with the accrual of the first subject and will be performed at least twice per year. Frequency is adjusted based on risk, reported SAEs, compliance, patient population, and accrual rate.
- A minimum of 25% of subjects will be monitored for the entire study.
- Items reviewed include: eligibility, consent document, compliance to protocol, SAE reporting per institutional and federal requirements, accuracy of data against primary source, and investigational drug documentation.
- The sponsor-investigator will be provided draft copies of the report within one month of the visit.
- Independent audits will be conducted by the HCCC to verify monitoring is being performed per the filed clinical monitoring plan. The audit procedures are documented in their Quality Assurance Management Plan on file with the NCI.

11. STUDY CALENDAR

	Screening	Baseline	V1 - PSMA-HBED-CC PET/CT [b,c]		Follow-up	
			Injection	Scan	Immediate	Long-term
Karnofsky PS[a]	X					
informed consent	X					
PSA		≤3 mo V1				X[d]
imaging pull		≤3mo V1				X[d]
pathology pull	X	≤3 mo V1				X[d]
^{68}Ga PSMA-HBED-CC			5 mCi			
20 mg IV furosemide			X			
HR, BP, Temp			supine[e]	supine[e]		
voiding				X[f]		
Adverse event query[g]		X	X	X[g]		

a within 3 months of date eligibility is assessed.
b Scan will be clinically interpreted, and entered into the medical record.
c A 2nd ^{68}Ga PSMA-HBED-CC PET/CT imaging visit may occur, if medically indicated. The 2nd scan will be obtained identical to 1st scan.
d data from follow-up imaging, laboratory PSA levels, and pathology as ordered for standard of care or study purposes will be analyzed and mined for outcomes
e HR, BP, temp performed with subject supine immediately before and after injection and post-imaging of the scan
f subject should void immediately prior to the scan.
g final adverse event assessment is done 1 to 3 days post-injection but no earlier than 24 hours post-injection

12. EFFICACY ASSESSMENTS

Determination of efficacy requires two primary assessments.

The first assessment is the clinical read of the ^{68}Ga-PSMA-HBED-CC PET/CT scan. Trained readers will identify lesions positive for prostate cancer disease, and based on these results, will categorize specifically defined anatomical regions of the subject (Table 12.2) as positive for disease by ^{68}Ga-PSMA-HBED-CC PET/CT. Criteria are described in Section 12.1 below.

The second assessment is the reference standard determination of disease positivity or negativity also performed on the same specifically defined anatomical regions (Table 12.2). The reference standard definitions are described below, and consist of a combination of pathological confirmation, conventional imaging follow-up evidence, and serial PSA measurements. Criteria are described in Section 12.2 below.

For purposes of endpoints, four major regions are identified for final analysis as defined in Table 12.1. Each region is divided into subregions as defined in Table 12.2. All primary data from ^{68}Ga-PSMA-HBED-CC PET interpretations, pathology results, and conventional imaging results, will be collected per the subregions defined below. The final region assignments and results will be derived from the subregion data as applicable.

Region	Description
1	Prostate Bed
2	Pelvis outside of prostate bed including lymph nodes
3	Extrapelvic soft tissue, lymph nodes and organ metastases (non-bone)
4	Bone metastases

Table 12-1. Major Analysis Regions

Region 2: Pelvis outside of prostate bed	Region 3: Extrapelvic soft tissue	Region 4: Bone metastases
Right obturator	Lung	Spine
Left obturator	Liver	Ribs
Right external iliac	Pancreas	Pelvis
Left external iliac	Spleen	Extremities
Right internal iliac	Intestine	Skull
Left internal iliac	Mesentary	Sternum
Other pelvic regions	Brain	Clavicle
	Other soft tissue	Other bone
	Abdominal nodes	
	Thoracic nodes	
	Other nodes	

Table 12-2. Subregion Classification

12.1. **^{68}Ga-PSMA-HBED-CC PET Results Definition**

Imaging interpretation ^{68}Ga-PSMA-HBED-CC PET:

Local Interpretations: PET images will initially be interpreted by a board certified nuclear medicine physician or a board-certified radiologist experienced in reading PET at the time of the imaging study at the institution that the study is being performed. These interpretations will not be used for evaluation of the primary endpoint.

Blinded Read Logistics: Imaging data will be de-identified. PET data will be interpreted by two different readers in a random order at separate reading sessions. Cross sectional imaging (CT or MRI) from the ^{68}Ga-PSMA-HBED-CC PET will be available for anatomic correlate. The blinded readers will be blinded to all other imaging results and all other clinical data.

Reader Positivity and Negativity Definition: Sub-regions defined in Table 12.2 will be graded for the presence of suspected disease on a two-point scale by each reader (0=Negative or 1=Positive). A region will be judged as positive if at least one lesion in this region is visually positive..

12.1.1. Criteria for visual interpretation:

Sub-regions of suspected disease will be graded on a two-point scale by each blinded reader (0=Negative or 1= Positive). A region will be judged as positive if at least one lesion in this region is visually positive.

12.1.1.1. Lymph nodes will be considered positive if the ^{68}Ga-PSMA-HBED-CC uptake is focal and greater than blood pool (adjacent or mediastinal blood pool).

- Lymph nodes will be classified further by region: pelvic, retroperitoneal, thoracic and other. Additionally, pelvic lymph nodes will be sub-classified according to their localization as follows: R/L obturator, R/L external iliac, R/L internal iliac and other (total of 7 subgroups). These pelvic sub-regions will be correlated with reference standard results in these sub-regions, however this sub-region data will not be directly used for evaluation of the primary or secondary endpoints, but for exploratory analysis.

12.1.1.2. Visceral lesions will be considered positive if the ^{68}Ga-PSMA-HBED-CC uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

- Visceral lesions will be classified further by major organ: lung, liver, pancreas... as defined in Table 2. These sub-regions will be correlated with reference standard results in these sub-regions, however this sub-region data will not be directly used for evaluation of the primary or secondary endpoints, but for exploratory analysis.

12.1.1.3. Bone lesions will be considered positive if the ^{68}Ga-PSMA-

HBED-CC uptake is focal and greater than physiologic bone marrow.

- Bone lesions will be classified by further by region: spine, ribs, pelvis, extremities, skull, sternum, and clavicle, as Defined in Table 12.2. These sub-regions will be correlated with reference standard results in these sub-regions, however this sub-region data will not be directly used for evaluation of the primary or secondary endpoints, but for exploratory analysis.

12.1.1.4. Prostate bed and prostate lesions will be considered positive if the ^{68}Ga-PSMA-HBED-CC uptake is focal and greater than physiologic background activity of the involvement organ or anatomic site.

12.2. **Reference standard definition:**

12.2.1. Histopathology/Biopsy will be the primary determinate of tissue positivity and negativity for prostate cancer disease. Pathology date, organ, and location as well as any notes related to the pathology will be obtained from the subject chart. The anatomical region/sub-region the pathology occurred in will be assigned by the investigator team:

^{68}Ga-PSMA-HBED-CC positive findings are aimed to be confirmed by histopathology/biopsy if clinically feasible. Pathology performed 60 days before or after the ^{68}Ga-PSMA-HBED-CC PET will be available for correlation.

Histopathological procedures and biopsies will be performed as clinically indicated and as per institutional protocol.

12.2.1.1. Lymph Nodes, Visceral Lesions, and Bone Lesions positive for disease by pathology.

– Lesions with positive pathologic confirmation will be regarded as positive for disease. The regionality of the resected tissue will be assigned into respective regions and sub-regions as described above in Table 12.2.

12.2.1.2. Lymph Nodes and Visceral Lesions negative for disease by pathology.

– Tissue removed and negative for pathology are considered negative for prostate cancer disease, unless subsequent conventional imaging or ^{68}Ga-PSMA-HBED-CC PET imaging demonstrates that targeted tissue were not resected. In this case:

i. Subjects can be rescanned with dedicated CT, MRI, or ^{68}Ga-PSMA-HBED-CC PET/CT to determine if the suspicious ^{68}Ga-PSMA-HBED-CC tissue was removed. If the tissue is confirmed as removed, this is considered negative for disease.

ii. If ^{68}Ga-PSMA-HBED-CC PET/CT positive tissue is still present, a needle biopsy can be pursued at the discretion of the treating physician. Images of the procedure will be reviewed to determine if the correct tissue was biopsied.

- If the ^{68}Ga-PSMA-HBED-CC PET/CT positive tissue was biopsied, a negative pathologic finding of the biopsied tissue is considered negative for disease.

- If the ^{68}Ga-PSMA-HBED-CC PET/CT positive tissue was biopsied, a positive pathologic finding of the biopsied tissue is considered positive for disease.

- If biopsy or re-biopsy is not performed, or the wrong tissue was biopsied, change in node size as measured by conventional imaging and as defined below will be the criteria by which disease status will be defined.

12.2.1.3. Bone lesions: Given the high rate of false negative biopsies for osseous metastases in subjects with prostate cancer, subjects with negative bone biopsies of ^{68}Ga-PSMA-HBED-CC PET positive lesions will be further evaluated:

- If pathology demonstrates an alternative diagnoses that is known to be ^{68}Ga-PSMA-HBED-CC positive (eg Renal Cell Carcinoma metastases, Paget's disease), then this will be considered negative for disease.

- If pathology is indeterminate, then follow-up imaging as described below will be performed as per clinical standards at the site.

12.2.1.4. Although not routinely performed during standard practice, immunohistochemical staining for PSMA of tumor specimens (primary and lymph node metastases) may be performed, although not required.

12.2.1.5. All regions not sampled for biopsy/histopathology will be designated as indeterminate for disease by pathology. Conventional imaging follow-up may be used in these cases to determine tissue status.

12.2.2. Follow-up Imaging will be used as a secondary assessment for prostate cancer in the event pathology information is not available:

All subjects will be tracked for follow-up conventional imaging between 3-12 months post ^{68}Ga-PSMA-HBED-CC (dedicated CT, MRI and/or bone scan) as per site standard of care. If no follow-up imaging has been performed within the 9 months following the ^{68}Ga-PSMA-HBED-CC scan, then the research study will pay for an additional follow-up CT scan to be performed in the 9-12

month window post-^{68}Ga-PSMA-HBED-CC scan. Follow up imaging will only be performed on subjects that have positive ^{68}Ga-PSMA-HBED-CC findings because conventional imaging assessment for disease is primarily targeting suspicious lesions identified by ^{68}Ga-PSMA-HBED-CC PET/CT. Interpretation of follow-up imaging will be performed by local read. Preferably, the follow-up conventional imaging should be the same modality/modalities as the initial staging work-up to allow for reproducible and accurate comparisons. Conventional imaging standards as described below will be used to determine tissue positive for prostate cancer disease. Conventional imaging will not be used to determine negative prostate cancer disease regions due to its inherently low negative predictive value.

Tissue positive for prostate cancer disease based on follow-up imaging:

12.2.2.1. Lymph nodes will be assessed by change in size.

i. Positive for disease:

a. -For subjects undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, visually suspicious lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter and PSA declines by more than 50%.

- If PSA increases by more than 25% (PCWG3 definition of recurrence) on systemic therapy, then an increase in the size of lesion by more than 20% in the short axis diameter will be considered a positive for disease.

b. In subjects with localized suspected lymph node(s) receiving targeted treatment without concomitant systemic treatment there are two ways to achieve positive for disease designation:

- If the subject shows a decrease of PSA by greater than 50% after targeted treatment and the lymph node does not enlarge (change in size less than 20% in the short axis diameter or less than 3 mm increase in short axis diameter) [*OR*]

- If on post-treatment follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI decrease by more than 30% in short axis diameter (with a minimum of 3 mm in change in size)

c. For untreated subjects: If on follow-up imaging within 3-12 months, lymph nodes seen on CT or MRI increase by more than 20% in short axis diameter (with a minimum of 3 mm in change in size).

ii. Negative for disease:

- Conventional Imaging follow-up will not be used for assessment of negativity for disease.

iii. Indeterminate for disease

- Regions with no lymph nodes determined to be positive by the conventional imaging criteria described above and without pathology will be designated regions indeterminate for prostate cancer disease.

- Subjects that have had neither pathology sampling, nor conventional imaging follow up will have all regions designated as indeterminate for disease by reference standard.

12.2.2.2. Visceral lesions (non-lymph node soft tissue or organ) and prostate bed and prostate lesions will be assessed by change in size.

i. Positive for disease:

a. For subjects undergoing systemic treatment (alone or in combination with targeted treatment): If on post-treatment follow-up imaging within 3-12 months, visually conspicuous lesions seen on CT or MRI decrease by more than 30% in long axis diameter and PSA declines by more than 50%.

- If PSA increases by more than 25% (PCWG3 definition of recurrence) on systemic therapy, then an increase in the size of lesion by more than 20% in the long axis diameter will be considered positive for disease.

b. In subjects with localized suspected lesions(s) receiving targeted treatment without concomitant systemic treatment there are two ways to meet positive disease criteria:

- If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment [*OR*]

- If on post-treatment follow-up imaging within 3-12 months, lesions seen on CT or MRI decrease by more than 30% in long axis diameter (with a minimum of 3 mm in change in size)

c. For untreated subjects: If on follow-up imaging within 3-12 months, lesions seen on CT or MRI increase by more than 20%

in long axis diameter (with a minimum of 3 mm in change in size).

ii. Negative for disease:

- Conventional Imaging follow up will not be used for assessment of negativity for disease

iii. Indeterminate for disease

- Regions with no visceral lesions determined to be positive by the conventional imaging criteria described above and without pathology will be designated as visceral regions indeterminate for prostate cancer disease.

- Prostate bed and prostate regions not determined to be positive by the conventional imaging criteria described above and without pathology will be designated as prostate regions indeterminate for prostate cancer disease.

- Subjects that have had neither pathology sampling, nor conventional imaging follow up will have all prostate and visceral regions designated as indeterminate for disease by reference standard.

12.2.2.3. Bone lesions will be considered:

i. Positive for disease on baseline assessment:

- Any positive sclerotic lesion on the CT portion of the ^{68}Ga-PSMA-HBED-CC PET or on a separate CT obtained ≤ 30 days before or after the PET/CT.

- Focal uptake on the baseline bone scan performed within one month of ^{68}Ga-PSMA-HBED-CC PET.

- Any MRI lesion in bone read as positive on the initial MRI performed within one month of ^{68}Ga-PSMA-HBED-CC PET.

ii. Positive for disease on follow up:

- Any new positive sclerotic lesion on CT within 12 months of ^{68}Ga-PSMA-HBED-CC PET scan

- Any new MRI bone lesion within 12 months of ^{68}Ga-PSMA-HBED-CC PET scan

- Any new focal uptake in bone within 12 months of ^{68}Ga-PSMA-HBED-CC PET scan

- In subjects with localized suspected bone lesion(s) receiving targeted treatment without concomitant systemic treatment:

- If the subject demonstrates a decrease of PSA by greater than 50% after targeted treatment.

iii. Negative for disease:

- Conventional Imaging follow up will not be used for assessment of negativity for disease

iv. Indeterminate for disease:

- Regions with no bone lesions determined to be positive by the conventional imaging criteria described above and without pathology will be designated bone regions indeterminate for prostate cancer disease.

13. STATISTICAL CONSIDERATIONS

13.1. Statistical Justification

This study is a pilot study to determine target sensitivity for ^{68}Ga PSMA-HBED-CC for the detection of prostate cancer in the pre-prostatectomy population. Based upon literature, we anticipate sensitivities of > 80% in this patient population, but there are uncertainties, particularly related to the proposed reference standard. We plan to use the results of this pilot study, potentially combined with reported results from other sites across the US performing similar studies (same patient population, same methods, same reference standard definitions…) to determine most-appropriate primary endpoint sensitivities for a larger University of Iowa study to follow this one, so as to appropriately statistically power the larger study.

The primary objective of this pilot study is to obtain preliminary information on the sensitivity of physician reads for Ga-68 PSMA pre-prostatectomy; physicians' ability to correctly identify prostate cancer and metastates via Ga-68 PSMA relative to our pathology/conventional imaging reference standard. Due to the lack of clinical experience with this radiopharmaceutical, this pilot study is meant to gain meaningful information of the sensitivity of this agent in this patient population to generate hypotheses for further trials.

To evaluate sensitivity, patients must undergo both Ga-68 PSMA imaging and evaluation for prostate cancer by pathology, follow-up conventional imaging, or both. Sensitivity is defined as:

$$Sensitivity = \frac{number\ of\ true\ positives\ (TP)}{number\ of\ true\ positives\ (TP) + number\ of\ false\ positives\ (FP)}$$

The table below provides 95% confidence interval half-widths for a range of sensitivity values based on a planned sample size of 30 patients using a normal approximation.

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Sensitivity	Half-Width
70%	16.4%
75%	15.5%
80%	14.3%
85%	12.8%
90%	10.7%

13.2. **Primary Endpoint:**

The sensitivity, specificity, positive and negative predictive values of ^{68}Ga PSMA-HBED-CC PET/CT for the detection of disease on a per patient basis will be summarized by descriptive statistics.

No statistical significance will be generated due to the pilot nature of the project.

The below criteria will be used for evaluation of a per patient basis with nodal regional correlation (Primary endpoint 1):

13.2.1. True positive patient:

13.2.1.1. **^{68}Ga PSMA-HBED-CC PET/CT positive for a regional node by internal blind reader**: pathology at prostatectomy is positive for a regional node that correlates in location to the PET images (location on pathology is determined by the urologist at the time of the surgery). Only one node needs to correspond between imaging and pathology for a patient to be considered a true positive.

13.2.1.2. **^{68}Ga PSMA-HBED-CC PET/CT positive for regional nodes by internal blind reader**, pathology negative for regional nodes, imaging after prostatectomy demonstrates the same node was not removed at surgery, and follow-up biopsy or imaging demonstrates presence of nodal disease as defined in Section 12.2.1.2 .

13.2.1.3. **Conventional imaging criteria for positive node on follow-up imaging**: imaging within 3-12 months, the node decreases by more than 30% (for patients undergoing systemic treatment or focal therapy at this site) or increase by more than 20% in short axis diameter in the absence of treatment (with a minimum of 3 mm in change in size) as defined in Section 12.2.2.1 .

13.2.2. True negative patient:

13.2.2.1. **^{68}Ga PSMA-HBED-CC PET/CT negative for regional nodes by internal blind reader**; pathology at prostatectomy negative for regional nodes as defined in Section 12.2.1.2 .

13.2.3. False positive patient:

13.2.3.1. **^{68}Ga PSMA-HBED-CC PET/CT positive for regional nodes**

by internal blind reader, pathology at prostatectomy is negative, and imaging after prostatectomy demonstrates that node is no longer present as defined in Section 12.2.1.2.

13.2.3.2. **^{68}Ga PSMA-HBED-CC PET/CT positive for regional node by internal blind reader**, but pathology at prostatectomy is positive for node but in a different nodal region than the node seen on PSMA PET.

13.2.4. False negative patient:

13.2.4.1. **^{68}Ga PSMA-HBED-CC PET/CT negative for regional nodes by internal blind reader**, but pathology at prostatectomy is positive for regional nodes.

13.2.5. Non-evaluable patient:

13.2.5.1. Any subject that does not have sufficient data to meet the criteria for definition of true positive patient, true negative patient, false positive patient, or false negative will be classified as non-evaluable.

13.2.5.2. Patients with extrapelvic nodal metastases will not be included in this analysis for the primary endpoint if patients do not undergo prostatectomy.

13.3. **Secondary Endpoints:**

Analysis plan for Secondary Endpoints: We will report the sensitivity, specificity, positive and negative predictive value of ^{68}Ga PSMA-HBED-CC PET/CT over all imaged regions as well as sub-classified by the following regions:

- extra-pelvic nodal metastases
- visceral metastases
- osseous metastases

No statistical significance will be generated due to the pilot nature of the project.

Follow-up for extra-pelvic nodal metastases, visceral metastases and osseous metastases are defined as below:

13.3.1. True positive region

13.3.1.1. **^{68}Ga PSMA-HBED-CC PETCT positive for extra-pelvic node metastases by internal blind reader** – and pathology (if available) positive for that node, or, extra-pelvic node positive for disease by imaging as defined in Section 12.2.2.1.

13.3.1.2. **^{68}Ga PSMA-HBED-CC PET/CT positive for visceral metastases by internal blind reader** – and pathology (if available) positive for that visceral lesion, or, visceral lesion positive for disease by imaging as defined in Section 12.2.2.2.

13.3.1.3. **^{68}Ga PSMA-HBED-CC PET/CT positive for osseous metastases by internal blind reader** - and pathology (if available) positive for that osseous lesion, or, osseous lesion

positive for disease by imaging as defined in Section 12.2.2.3.

13.3.2. True negative region

13.3.2.1. **^{68}Ga PSMA-HBED-CC PET negative for extra-pelvic node metastases by internal blind reader** – and pathology (if available) negative for disease, and, extra-pelvic node not positive for disease by imaging.

13.3.2.2. **^{68}Ga PSMA-HBED-CC PET negative for visceral metastases by internal blind reader** – and pathology (if available) negative for disease, and, visceral lesion not positive for disease by imaging.

13.3.2.3. **^{68}Ga PSMA-HBED-CC PET negative for osseous metastases by internal blind reader** - and pathology (if available) negative for disease, and, osseous lesion not positive for disease by imaging.

13.3.3. False positive region:

13.3.3.1. **^{68}Ga PSMA-HBED-CC PET positive for extra-pelvic nodes by internal blind reader**, pathology (if available) is negative, and imaging after prostatectomy demonstrates that node is not positive for disease.

13.3.3.1.1. **^{68}Ga PSMA-HBED-CC PET positive for regional node by internal blind reader**, but pathology (if available) is positive for node but in a different nodal region than the node seen on PSMA PET.

13.3.3.2. **PSMA-HBED-CC PET positive for visceral lesion by internal blind reader**, pathology (if available) is negative, and imaging after prostatectomy demonstrates that the visceral lesion is not positive for disease.

13.3.3.2.1. **^{68}Ga PSMA-HBED-CC PET positive for visceral lesion by internal blind reader**, but pathology (if available) is positive for visceral lesion but in a different region than the visceral region seen on PSMA PET.

13.3.3.3. **^{68}Ga PSMA-HBED-CC PET positive for osseous lesion by internal blind reader**, pathology (if available) is negative, and imaging after prostatectomy demonstrates that the osseous lesion is not positive for disease

13.3.3.3.1. **^{68}Ga PSMA-HBED-CC PET positive for osseous lesion by internal blind reader**, but pathology (if available) is positive for osseous lesion but in a different region than the osseous region seen on PSMA PET.

13.3.4. False negative region:

13.3.4.1. **^{68}Ga PSMA-HBED-CC PET negative for extra-pelvic nodes**

by internal blind reader, and pathology (if available) positive for that node, or, extra-pelvic node positive for disease by imaging as defined in Section 12.2.2.1.

13.3.4.2. **^{68}Ga PSMA-HBED-CC PET negative for extra-pelvic nodes by internal blind reader**, and pathology (if available) positive for that visceral lesion, or, visceral lesion positive for disease by imaging as defined in Section 12.2.2.2.

13.3.4.3. **^{68}Ga PSMA-HBED-CC PET negative for extra-pelvic nodes by internal blind reader**, and pathology (if available) positive for that osseous lesion, or, osseous lesion positive for disease by imaging as defined in Section 12.2.2.3.

13.3.5. Non-evaluable region:

13.3.5.1. Any region that is does not have sufficient data to meet the criteria for definition of true positive region, true negative region, false positive region, or false negative region will be classified as non-evaluable.

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