

[¹⁸F]Fluciclovine-PET/MRI for Staging Newly Diagnosed High-Risk Prostate Cancer and Evaluating Response to Initial Androgen Deprivation Therapy

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Protocol UAB 1767: Pretreatment Staging of High-Risk Prostate Cancer with F-18 Fluciclovine PET/MRI

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Data Coordinator

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1.0 Introduction and Study Rationale

1.1 Overview

There is great need for improved pretreatment imaging in men with high-risk prostate cancer. We propose to develop an optimized simultaneous PET/MRI protocol for local, regional and whole body pre-therapeutic initial staging of high-risk prostate cancer in a single imaging session using the amino acid PET tracer, [^{18}F]fluciclovine. This PET tracer has recently received FDA approval for use in biochemically recurrent prostate cancer, but its utility for staging prior to therapy and for monitoring response to therapy has not been established. Despite advances in the diagnosis and treatment of prostate cancer, the pretreatment staging of men with prostate carcinoma (PCa) is currently problematic. Conventional imaging is falsely negative for regional lymph node metastases in a substantial fraction of men. In particular, approximately 35% of men with high-risk prostate cancer will have biochemical recurrence even after optimal surgical resection. Therefore, we plan to examine patients at high risk for metastatic disease and who will predominantly be offered nonsurgical management of their prostate carcinoma. We will compare mpMRI alone to simultaneous fluciclovine-PET/MRI in terms of lesion detection in pelvic nodal stations. We will also correlate these imaging findings with established risk-prediction models to indirectly assess accuracy, as the vast majority of these patients will be managed non-operatively in this study. A second follow-up [^{18}F]fluciclovine-PET/MRI study will be performed after completion of therapy. This repeat study after therapy will be used as part of a standard of truth (i.e. findings should resolve with effective therapy) and to generate preliminary data regarding the utility of fluciclovine-PET/MRI for assessing response to therapy.

If this preliminary study suggests a benefit of [^{18}F]fluciclovine-PET/MRI in the pretreatment setting, additional larger studies will be designed based on these results. Because [^{18}F]fluciclovine and PET/MRI are clinically available and FDA-approved for biochemically recurrent prostate cancer, this study has the potential for rapid and widespread impact. If [^{18}F]fluciclovine-PET/MRI can reliably and accurately detect nodal metastases in high-risk prostate cancer patients, surgeons may use this new technology to decide if a high-risk prostate cancer patient is eligible for surgery, to extend the pelvic lymph node dissection to include suspicious lymph nodes identified by imaging, and for making decisions regarding initiating androgen-deprivation therapy. We will also generate preliminary data regarding the utility of [^{18}F]fluciclovine-PET/MRI for assessing response to therapy.

1.2 Background and Rationale

Prostate cancer is a common malignancy with an estimated 180,890 new cases and 26,120 deaths in 2016.¹ Screening for prostate cancer is currently performed utilizing digital rectal exam and serum prostate specific antigen (PSA). Due to the high frequency of indolent prostate cancer, approximately 80% of cancers detected by screening are localized to the prostate. For these patients, the 5-year survival is nearly 100%.

However, there is a substantial minority of patients with high-risk prostate adenocarcinoma that are at significant risk for regional nodal and distant metastases at the time of diagnosis. In contrast to localized disease, the 5-year survival for patients with distant metastatic disease is 29%. Disease risk is stratified with the Gleason score on prostate biopsy, PSA, and clinical staging. These values provide estimated risks of organ-confined disease and extraprostatic disease based on established nomograms and Partin tables.² In these patients who undergo radical prostatectomy and bilateral pelvic lymph node dissection, approximately 30% experience biochemical recurrence. The 5-year disease-free survival rate drops from 85% of patients with no nodal metastases to 50% in those patients with nodal metastases. This is thought to be due to lack of detection of small volume metastatic disease not identified on conventional preoperative imaging. Because current imaging techniques have limited sensitivity for nodal metastases, many high-risk men are assumed to have metastatic disease and not offered potentially curative surgery. More accurate pretreatment staging has the potential to alter surgical planning or to prompt the earlier use of radiation or systemic therapy to decrease the risk of recurrence and improve survival. Through this study, we will generate key preliminary data assessing the ability of fluciclovine-PET coupled with simultaneous PET/MRI to improve the accuracy of pretreatment staging in men with high-risk prostate cancer.

While prostate MRI is valuable for the detection of occult primary lesions, its sensitivity and specificity for the detection of pelvic lymph node metastases is limited to RECIST criteria and nodal morphology. It is well known that normal-appearing lymph nodes on CT and MRI can harbor small volume metastatic disease not detected based on size and morphological criteria. Molecular imaging has great potential to supplement MRI and increase diagnostic accuracy, and simultaneous PET/MRI can provide both dedicated regional PET and MRI imaging for regional staging as well as whole body staging in a single imaging session.

Amino acid metabolism is upregulated by prostate cancer cells, with increased expression of the ASCT2 and LAT1 transporters. As a result, multiple amino acid analogues have been developed to image prostate cancer. Recently, the ¹⁸F-labeled amino acid *anti*-1-amino-3-[¹⁸F]fluorocyclobutane-1-carboxylic acid ([¹⁸F]FACBC, otherwise known as fluciclovine) received FDA approval for use in biochemically recurrent prostate cancer. Fluciclovine-PET/CT has been shown to be particularly effective for detecting nodal metastases and distant metastases in recurrent prostate cancer. Fluciclovine is a transport substrate for ASCT2 and to a lesser extent LAT1, but is not metabolized intracellularly or incorporated into proteins.^{3,4} A key advantage to the use of fluciclovine is minimal excretion of the radiotracer into the urine, which lends itself well to imaging the pelvis without the use of pre-scan urinary bladder catheterization. Studies with fluciclovine have focused primarily on biochemical recurrence using PET/CT. Currently, data are scarce regarding the role of fluciclovine in patients undergoing initial staging, and there are virtually no data using PET/MRI.⁵ A single study examining the effectiveness of fluciclovine PET/CT for detection of nodal metastases demonstrated increased detection of sub-centimeter pelvic lymph nodes when compared to conventional imaging.⁶

Several studies have examined the use of 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) PET/CT for the evaluation and staging of prostate cancer. FDG-PET/CT has not become a mainstay in the pretreatment staging of patients due to low sensitivity and specificity. In response, a number of radiotracers have been developed to detect metastatic disease in the setting of prostate cancer. The first alternative tracer in clinical use in the United States is [¹¹C]choline. Sensitivity for staging patients using [¹¹C]choline is higher than for FDG, but remains relatively poor with studies ranging from 45-73%.⁷⁻⁹ A significant logistical problem with the use of [¹¹C]choline is the 20 min half-life of the radiotracer, thus requiring on-site production by a cyclotron.

Prostate specific membrane antigen (PSMA) is a transmembrane cellular receptor that is overexpressed in prostate cancer cells. Recently, small molecules have been developed that bind to the extracellular component of the transmembrane PSMA receptor. These agents have been tagged with both ¹⁸F and ⁶⁸Ga for imaging and ⁹⁰Y and ¹⁷⁷Lu for therapeutic purposes. Restaging accuracy of fluciclovine and PSMA-PET/CT are superior to choline compounds, particularly at low PSA levels, although no direct comparison of PSMA ligands and fluciclovine PET are currently available in the published literature.¹⁰ A limitation of PSMA ligands is that approximately 10% of prostate carcinoma and nodal metastases are PSMA negative.¹¹⁻¹⁴ PSMA ligands are currently investigational in the United States and not available for routine clinical use.

While other PET tracers remain promising, [¹⁸F]fluciclovine has several key advantages. [¹⁸F]Fluciclovine is more widely available and can be distributed to centers without onsite radiolabeling capabilities due to its ¹⁸F-label. Initial data suggest that fluciclovine is diagnostically superior to [¹¹C]choline. Although PSMA ligands are promising, fluciclovine can have much greater near-term impact for pretreatment staging because it is FDA-approved. By accurately staging high-risk patients prior to treatment, we speculate that treatment algorithms can shift, allowing better assessment of surgical eligibility and therapy planning.

PET/MRI is likely the optimal modality to image patients for pretreatment staging of prostate carcinoma. In one study, a patient can undergo a multiparametric prostate MRI for characterization of the primary lesion and the extent of regional extraprostatic disease along with a molecular imaging study to improve the accuracy of regional staging and provide whole body staging. In addition, simultaneous acquisition of PET and MRI data allows for more accurate coregistration of MRI and PET data which may be difficult to achieve with software fusion, a key to detecting non-enlarged lymph nodes and other small lesions.

We will also develop preliminary data regarding the utility of fluciclovine-PET/MRI in early assessment of treatment response in this patient population. In men treated with radiation therapy and/or androgen deprivation therapy (ADT), early detection of treatment failure may identify patients who would benefit from additional local or intensive systemic therapy much sooner than is possible with serum PSA measurement alone. The favorable properties of PET/MRI are expected to be useful for early treatment response assessment as well. Because most of the patients in this study will not undergo

surgery, many of the post-therapy studies will be in men undergoing radiation therapy and/or androgen deprivation hormonal therapy. We will measure changes in fluciclovine uptake and MR parameters at a 3-6 month imaging time point and correlate these results with clinical follow up including progression-free survival. If fluciclovine-PET/MRI has utility for early assessment of response, men at high risk for recurrence based on imaging may be offered additional local therapy and/or systemic therapy prior to progression based on serum PSA measurements.

2.0 Study Objectives

Specific Aim #1: Determine the concordance of imaging findings for fluciclovine-PET/MRI and mpMRI of the pelvis and prostate gland.

Hypothesis #1: Fluciclovine-PET/MRI will identify more regional lymph node metastases than mpMRI alone.

There have been numerous prior studies demonstrating the value of mpMRI for the locoregional staging for PCa. Prior studies in the setting of biochemical recurrence have demonstrated high sensitivity and specificity of fluciclovine-PET/CT for detection of recurrent disease in the prostate bed and extraprostatic disease.¹⁵ We expect the simultaneous acquisition of mpMRI and fluciclovine PET data to provide valuable preoperative staging information, with fluciclovine PET detecting metastatic disease in subcentimeter pelvic lymph nodes not identified with mpMRI alone. Additionally, fluciclovine-PET/MRI provides whole body staging in regions not evaluated by mpMRI and may detect additional distant metastases.

Specific Aim #2: Determine the correlation between organ-confined disease, lymph node metastases, extraprostatic extension, and seminal vesicle invasion on fluciclovine-PET/MRI with the expected frequencies of these metastases based on established nomograms and risk-prediction models as well as follow up fluciclovine-PET/MRI.

Hypothesis #2: Fluciclovine-PET/MRI will demonstrate metastases in the expected frequencies for patients with high-risk PCa and will regress with effective therapy.

For pretreatment patients with PCa, several clinical risk-predictors (including nomograms and Partin tables) utilize serum prostate-specific antigen (PSA), Gleason score, and clinical stage to predict organ-confined disease, the presence of extraprostatic extension, seminal vesicle invasion, and lymph node metastases.² Because majority of the high-risk prostate cancer population in this study will not undergo prostatectomy, nomograms and risk-prediction models combined with follow up fluciclovine-PET/MRI after therapy will be used as a surrogate for accuracy. If successful, this research plan will provide key data for further studies that will use histopathological confirmation as the reference standard.

Specific Aim #3: Measure changes in fluciclovine-PET/MRI at 6-12 weeks after initiation of therapy and correlate with serum PSA.

Hypothesis #3: Fluciclovine-PET/MRI parameters including fluciclovine uptake and fluciclovine-defined metabolic tumor volumes will change with effective therapy.

Resolution of fluciclovine-PET/MRI findings after therapy will also be used to help confirm true lesions on the pre-treatment imaging. If successful, this research plan will provide key data for further studies in for initial staging and monitoring therapy response that will use histopathological confirmation and patient outcomes as the reference standards.

For the post-treatment imaging, a repeat fluciclovine-PET/MRI study will be performed at 6-12 weeks months after initiation of therapy. The fluciclovine-PET and MR measurements will be compared between the pre- and post-treatment studies. Early detection of men at high risk for early treatment failure might undergo additional treatment prior to PSA rise from nadir. In the small number of patients in this study who undergo prostatectomy, the follow up fluciclovine-PET/MRI has the potential to detect residual disease that could then be treated with additional local therapy.

3.0 Investigational Plan

3.1 Study Design

- Prospective IRB-approved study enrolling patients with biopsy-proven high-risk prostate cancer for pretreatment fluciclovine-PET/MRI prior to the initiation of treatment and at three month follow-up
- All patients will undergo standard-of-care clinical evaluation and imaging workup with nuclear medicine bone scan and either CT of the abdomen and pelvis or MRI pelvis
- Majority of patients will be non-operative due to high-risk status, but participation in study does not exclude operative intervention
- Treatment team will initially be blinded to results of PET/MRI, but will be unblinded following standard-of-care imaging and formation of the initial treatment plan
- If study PET/MRI demonstrates a suspicious finding that may preclude a patient from operative intervention (in a patient being considered for surgery) or alter locoregional treatment (e.g. radiation therapy), the treatment team will be alerted to potentially investigate the finding further (i.e. additional imaging or biopsy)
- Findings on PET/MRI relayed to the clinical team may prompt further investigation on standard-of-care imaging and discussion in the genitourinary tumor board. If additional imaging and/or tumor board consensus indicates the need for biopsy, the biopsy can be billed to insurance as standard-of-care.
- A repeat fluciclovine-PET/MRI study will be performed at 6-12 weeks weeks after initiating therapy (typically radiation therapy, prostatectomy, and/or androgen deprivation therapy) at the time when serum PSA values are initially checked to establish response

3.2 Study Population

- Patients with high-risk biopsy-proven treatment-naïve prostate cancer

3.3 Inclusion Criteria

- High-risk biopsy-proven treatment-naïve prostate adenocarcinoma (Gleason score ≥ 8 and/or serum PSA > 20)

3.4 Exclusion Criteria

- Inability to tolerate or undergo PET/MRI
- Previous or current hematologic or lymphatic disorder (including leukemia, lymphoma, Castleman's disease, etc.)
- Recurrent prostate adenocarcinoma
- Known visceral, osseous, or extrapelvic metastases prior to fluciclovine-PET/MRI
- Known allergy to glucagon or gadolinium-based contrast

3.5 Withdrawal Criteria

- Given that enrollment in this study will involve two imaging exams, no withdrawal criteria will be used

3.6 Replacement of Patients

- Given that enrollment in this study will involve two imaging exams, no replacement of patients will be used

3.7 Study Duration

- Study enrollment and imaging will take place over 12 months

3.8 Safety Monitoring

3.8.1 Data and Safety Monitoring Plan

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. PET/MRI scans will be loaded into a separate password-protected image storage system that will not appear on the PACS utilized in clinical practice.

3.8.2 Ethical Considerations

Given that the study involves two imaging sessions with PET/MRI and the expected age of the enrolled adult patients, ethical concerns regarding additional radiation exposure are minimal. The only ethical consideration was the availability of the results of the study PET/MRI to the clinicians. Given that the PET tracer used (fluciclovine) is FDA-approved for a similar indication in the setting biochemical recurrence, it is highly likely that the tracer will behave in a similar fashion in these patients prior to therapy given similarities in tumor biology. Therefore, a suspicious lesion on the study PET/MRI is expected to correlate with metastatic disease. Therefore, if the PET/MRI demonstrates a suspicious finding, the treating clinician (including urology and radiation oncology) will be alerted, and the decision to pursue biopsy and/or alter the patients treatment plan will be based on standard of care imaging and consensus after presenting the case at the GU tumor board.

4.0 Study Procedures

4.1 Informed Consent Procedure

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 IRB-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.

4.2 Patient Registration

Enrollment in the study will be available after the patient has been seen by their treating physician at UAB. The majority of these patients are expected to be seen in Urology clinic. However, all patients that meet enrollment criteria are eligible. Registration in the study will be performed by a research coordinator from the UAB Department of Radiology. Participation in the study is voluntary and choosing not to participate will not affect patient care in any way.

4.3 Initiation of Study

The PET tracer [^{18}F]fluciclovine is FDA-approved for biochemically recurrent prostate cancer and readily available from commercial production sites. Additionally, UAB currently is performing clinical PET/MRI scans, including [^{18}F]fluciclovine-PET/MRI. Therefore, the study can be initiated immediately following institutional and IRB approval.

4.4 Drug Information

[^{18}F]fluciclovine is a non-natural amino acid radiotracer that is currently FDA-approved PET imaging agent for use in patients with biochemically-recurrent prostate cancer. The radiotracer targets both the LAT1 and ACST2 transporters, both of which are upregulated in prostate cancer cells. The dosage of radiotracer administered to the patient is 370 MBq (10 mCi) intravenously. This results in an effective dose of 8 mSv (800 mrem) to the patient, which is equal to 2.7 years of natural background radiation exposure (3 mSv/yr).

4.5 Patient Assessment

Identification and workup of patients prior to potential enrollment in the study will follow standard-of-care procedures per the treating physician (urology, radiation oncology, etc.). For initial staging of high-risk prostate cancer, this will include a nuclear medicine bone scan and either a CT abdomen and pelvis or MRI of the pelvis per NCCN guidelines. If a patient is determined to be eligible for the, the research coordinator in this study will be asked to come to the clinic to discuss potential enrollment in the study.

4.6 Imaging Information

4.6.1 [¹⁸F]Fluciclovine PET Preparation and Injection

The injected dose will be 370 MBq (10 mCi) of [¹⁸F]fluciclovine. The patient will be instructed to avoid strenuous exercise for 24 hours prior to injection and to avoid caloric intake for 4 hours prior to injection. PET/MRI imaging will begin immediately following injection. Intramuscular injection of glucagon 1 mg will be performed immediately prior to the prostate MRI portion of the PET/MRI.

4.6.2 [¹⁸F]Fluciclovine PET/MRI Protocol

Whole body imaging

Positron Emission Tomography Acquisition: The patient will be placed on the PET/MRI scanner in the supine position. Initial localizer images will be obtained. Dynamic images of the pelvis will be acquired for the first 8 min after fluciclovine injection with framing of 3 sec x 20, 10 sec x 12, 20 sec x 6, 180 sec x 1. Subsequently, static whole body images will be acquired from pelvis to skull base utilizing approximately eight 14 cm detector beds for 5 minute acquisitions per bed position. Correction for randoms, scatter, attenuation and reconstructions will be performed per the manufacturer's recommendations.

Whole Body MRI: Sequences performed will include MR attenuation correction (MRAC), axial and coronal T2 single shot fast spin echo, sagittal T1 turbo spin echo for skeletal evaluation, and whole body Dixon-derived sequences.

Following whole body PET imaging, a routine multiparametric MRI of the prostate gland will be performed at UAB in the PET/MRI scanner per institutional protocol, which includes high b-value diffusion-weighted imaging (b2000), small field-of-view T2 imaging, and dynamic contrast enhanced T1 images. An additional static pelvic PET acquisition will be performed concurrently.

Fluciclovine PET/MRI scans will be performed at two time points:

- Prior to initiation of treatment
- At 3-6 months following treatment initiation when routine clinical practice is to begin assessing PSA values for response

The study protocol has been submitted to, reviewed, and approved by the UAB Radiation Safety Committee.

4.6.3 PET/MRI Imaging Interpretation and Storage

Images from the PET/MRI will be stored and reviewed using a commercially available software package (MIM Encore, Cleveland, OH) and not be available for viewing in the institutional PACS or patient's medical record. This is in an effort to blind the treating physicians from making clinical decisions on an experimental imaging technique. The prostate MRI images will be sent to clinical PACS and the medical record as part of standard-of-care imaging and can be used in the clinical-decision making process. No formal interpretation will be generated for the [^{18}F]fluciclovine-PET portion of the PET/MRI study, but the prostate MRI will have a clinical interpretation by a dedicated abdominal radiologist who will also be blinded to the patient enrollment in the study. Dedicated study readers from both abdominal imaging and molecular imaging will interpret first the prostate MRI alone, and then the fused PET/MRI to assess potential added value from the PET/MRI. The study readers will be blinded to the results of any additional standard-of-care imaging and clinical evaluation and will only have knowledge that the patient has biopsy-proven prostate cancer.

mpMRI images acquired from the fluciclovine-PET/MRI study will be scored initially without access to the fluciclovine-PET portion of the study using the method described below. Once the results of the MR only portion of the study have been recorded, the same reader will be given access to the entire study and provide a second set of scores for the combined PET/MRI images. The concordance for metastases in lymph node stations will be determined from these scores. At least two readers will score each study, and discrepancies will be recorded and resolved through a consensus read after finalizing individual scoring.

MRI Data Analysis: The MRI images will be qualitatively analyzed.

Qualitative analysis: A visual evaluation of the pelvic lymph nodes with suspected metastatic disease will be performed. The number of positive metastatic lymph nodes and their nodal stations will be recorded. Nodal stations that will be examined include right and left common iliac, internal iliac, external iliac, obturator, inguinal, and retroperitoneal (total of 11 stations per patients).

T1/T2 Images

0 = Normal lymph nodes

1 = Mild prominence not meeting RECIST criteria for adenopathy (low suspicion)

2 = Definitely abnormal size or morphology, possible metastasis (intermediate suspicion)

3 = Markedly abnormal size and morphology, likely metastasis (high suspicion)

DWI Images

0 = Normal diffusion

1 = Low level of diffusion restriction when compared to adjacent normal appearing lymph nodes (low suspicion)

- 2 = Slightly higher level of diffusion restriction when compared to adjacent normal appearing lymph nodes (intermediate suspicion)
3 = Definitely higher level of diffusion restriction when compared to adjacent normal appearing lymph nodes (high suspicion)

Note: In cases of nonhomogenous intensity on DWI and ADC images, the grade will be determined on the basis of the most suspicious area.

PET Data Analysis: The PET images will be qualitatively and quantitatively assessed. The scoring will be based primarily on the PET data, but the reader will have access to the MRI data for anatomic correlation and characterization of lymph node morphology. For PET data analysis, a lymph node positive based on MRI criteria but negative based on fluciclovine-PET criteria will be scored as negative.

Qualitative analysis: A visual evaluation of the pelvic lymph nodes with suspected metastatic disease will be performed. As per manufacturer guidelines, lymph nodes measuring less than 1 cm in short-axis dimension will be compared to blood pool tracer activity. For lymph nodes measuring greater than 1 cm, comparison of activity will be made to the activity in the bone marrow of the L3 vertebral body. The number of positive metastatic lymph nodes and their nodal stations will be recorded.

- 0 = No uptake or uptake lower than appropriate reference (blood pool vs. L3 marrow)
1 = Uptake equal to reference (low suspicion)
2 = Uptake slightly greater than reference (intermediate suspicion)
3 = Uptake definitely greater than reference (high suspicion)

Quantitative analysis: Nodes scored as intermediate or high suspicion based on MRI and/or PET will undergo further quantitative analysis.

Standardized uptake values (SUVs): The maximum SUV will be measured. Additionally, the mean SUV and metabolic tumor volume will be measured based on a 40% isocontour.

Lesion to blood pool and marrow ratios: Tissue SUV is a simple uptake ratio of activity in an area of interest compared to a normalized tissue background level. As stated in section B, activity in lymph nodes measuring less than 1 cm in short-axis dimension will be compared with activity in the blood pool and a lesion:blood pool activity ratio will be calculated. For lymph nodes measuring greater than 1 cm in short-axis dimension, activity will be compared to activity in the L3 vertebral body marrow and a lesion:marrow activity ratio will be calculated..

Dynamic PET analysis: Time-activity curves (TACs) will be generated for pelvic lymph nodes scored as intermediate or high suspicion on visual analysis. Additionally, TACs will be generated for three reference pelvic lymph nodes scored as normal. The maximum SUV at peak fluciclovine uptake, the time to peak, and the shape of the TACs over the 8 min dynamic acquisition (rising, plateau, washout) will be recorded. This analysis is exploratory as the role of dynamic fluciclovine-PET for the initial staging of prostate cancer is not established.

KEY ANALYSIS FOR SPECIFIC AIM 1

Based on the consensus PET and MRI scoring, the total percentage of nodal scoring discrepancies will be calculated. Although the total number of patients is small, a total of 165 pelvic nodal stations will be examined. In this pilot study, a discrepancy between MR-only and fluciclovine-PET/MR greater than 10% would motivate a larger study with more rigorous references standards including histopathology.

KEY ANALYSIS FOR SPECIFIC AIM 2

This study will use the nomograms routinely used by the UAB urology service in assessing newly diagnosed prostate cancer. The use of nomograms is necessary, as we will not routinely obtain histopathological verification in these high-risk, nonoperative patients in this study. Expected frequencies of lymph node metastases based on patient risk factors will be compared to observed frequencies of lymph node metastases in specific aim 1 on mpMRI alone, fluciclovine-PET/MRI, and assuming that discrepant nodes between imaging modalities (i.e. positive on one, negative on other) will be counted as positive, a combination of the two modalities that includes discrepant nodes. The assessment that most closely matches the expected frequency based on the nomogram will be considered most accurate, although small sample size will require larger studies for confirmation.

As stated previously, although most patients enrolled in the study will not be surgical candidates, participation in the study does not preclude a patient from surgery. However, given the known value of [^{18}F]fluciclovine in the setting of biochemically recurrent prostate cancer and the similar biological tumor profile between treatment-naïve and recurrent prostate cancer, suspicious extraprostatic findings will be reported to the referring physician due to the high likelihood of representing true positive metastatic disease. In these cases, further imaging or biopsy may be indicated prior to proceeding with surgery. The treating physician will initially be blinded to the results of the PET/MRI until a treatment plan is established through the use of standard-of-care imaging, which may include the prostate MRI portion of the PET/MRI but not the fused PET/MRI. Following the treatment decision, the physician will be unblinded to the results of the PET/MRI. Changes in treatment plan based on the PET/MRI will be tracked.

4.6.4 Safety Monitoring

Vital signs will be assessed immediately before and after injection of [¹⁸F]fluciclovine (HR and supine BP). Patients will be monitored for adverse events during injection and after completion of the imaging study. Additionally, patient's vitals (HR and supine BP) will be checked at the completion of the imaging study prior to leaving the imaging center.

4.6.5 Patient Follow-Up

Patients will be instructed to contact the UAB Department of Radiology Advanced Imaging Facility if there are any concerns about delayed side effects related to the study radiotracer. Patients will be seen in the clinic if there are any concerning study related adverse events requiring further evaluation.

5.0 Study Parameters

5.1 Primary Endpoints

- [¹⁸F]fluciclovine PET/MRI results for primary lesion and regional nodal metastases
- Concordance between [¹⁸F]fluciclovine PET/MRI results and multiparametric prostate MRI results
- Detection of organ-confined disease, regional nodal metastases, extracapsular extension, and seminal vesicle invasion [¹⁸F]fluciclovine PET/MRI in expected frequencies based on risk-predictor models and nomograms

5.2 Secondary Endpoints

- Potential added value in additional metastases detected on [¹⁸F]fluciclovine PET/MRI versus prostate MRI alone
- Use of follow up [¹⁸F]fluciclovine-PET/MRI after initiating therapy to confirm initial suspicious findings on the initial pretreatment study

5.3 Exploratory Endpoints

- Use of [¹⁸F]fluciclovine PET/MRI at 3-6 months following initiation of treatment to evaluate response to therapy at the time when serum PSA is routinely checked following treatment initiation
- Correlate disease burden at 3 month follow up with serum PSA values
- Dynamic radiotracer uptake by the primary lesion and if this changes on the posttreatment [¹⁸F]fluciclovine-PET/MRI
- Changes in signal characteristics of primary intraprostatic lesion on posttreatment mpMRI
- Changes in initial treatment plan with added information provided by fluciclovine PET/MRI versus standard-of-care imaging alone

5.4 Study Termination

The study will stop enrolling patients once the target number has been reached.

6.0 Statistical Considerations

6.1 Study Design

This is a prospective pilot trial to determine the potential use of [^{18}F]fluciclovine PET/MRI in the pretreatment staging and post-therapy follow-up of patients with high-risk prostate adenocarcinoma. The primary objective of this study is to determine the concordance of imaging findings for fluciclovine-PET/MRI and mpMRI of the pelvis and prostate gland. The secondary objective is to determine the correlation between organ-confined disease, lymph node metastases, extraprostatic extension, and seminal vesicle invasion on fluciclovine-PET/MRI with the expected frequencies of these metastases based on established nomograms and risk-prediction models.

6.2 Sample Size Determination

This is a pilot study that may warrant a larger study with increased power to determine statistical significance if expected results are observed. We plan to enroll 15 patients, primarily determined by budgetary constraints and feasibility of patient recruitment in one year. No formal power calculations were used in the generation of the sample size. The primary end point of the study is to estimate percentage of high-risk prostate cancer patients whose metastasis can be detectable early by using [^{18}F]fluciclovine-PET/MRI comparing using standard care of mpMRI imaging. According to risk-prediction models and nomograms used in routine clinical practice, approximately 20-30% of patients with high-risk prostate adenocarcinoma will be diagnosed with nodal metastases. We expect that using [^{18}F]fluciclovine PET/MRI will achieve similar results, e.g. 30% for early detection of metastasis without invasive procedures, and using mpMRI will result in less of detection of metastasis, e.g. 20%-25%. A size of 15 will provide a two-sided 95% confidence intervals (CI) for point estimate (% of metastasis) from 9.7% to 58.4% when the true estimate is 30% using Clopper-Pearson method. Table below shows the 95% CI when the true estimate varies.

Proportion (%)(estimate of metastasis)	Sample size	95% CI Lower limit	95% CI Upper limit
20	15	4.3	48.1
25	15	6.9	53.4
30	15	9.7	58.4

6.3 Definition of Analyzed Study Population

Study population is adult males with high-risk treatment-naïve prostate adenocarcinoma who meet the inclusion criteria listed above.

6.4 Analysis

Since this is a single arm exploratory pilot study, where no formal power calculations were performed for the study's sample size, this study will largely be exploratory and descriptive. For all clinical and histological evaluations, as well as imaging parameters (SUV), we will generate summary tabulations of the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the frequency and percentage for categorical variables. Analyses will be primarily descriptive and graphical in nature whereas the proposed sample size for the study limits the distributional assumptions of certain analyses. Therefore, non-parametric approaches will

be considered. For specific aim 1, in order to correlate imaging parameters between imaging modalities our correlation analysis will be performed using Spearman's Rank correlation and Wilcoxon signed-rank sum tests. In order to address specific aim 2, to compare observed frequencies of metastases and expected frequencies, a Chi-squared analysis will be performed. Given the small sample size, a Yates' correction may be utilized. Due to the small sample size and potential for sparse data, we may use Firth's penalized likelihood approach. Data transfer, management, and analyses will be performed using Excel and SAS v9.4.

6.4.1 Analysis for Primary Endpoints and Specific Aim 1: The imaging data from [¹⁸F]fluciclovine PET/MRI or mpMRI will be categorized from 0 to 3 indicating likelihood of having metastasis as '0' indicating no sign of metastasis and >0 indicating there is sign of metastasis. The number and percentage of metastasis identified by either [¹⁸F]fluciclovine PET/MRI or mpMRI will be calculated along with exact 95% CI using Clopper-Pearson method. The agreement and concordance of using these two imaging results will be evaluated with McNemar test due to correlated results from same patients when the result is dichotomized as yes or no, or using Spearman's Rank correlation analysis when the result is measured as 0-3.

6.4.2 Analysis for Secondary Endpoints and Specific Aim 2: Serum prostate-specific antigen (PSA) will be measured for each patient as a clinical risk-predictor as a validated measure to identify PCa and monitor response to treatment. Patients will be identified if they have PCa metastases and response to treatment determined by PSA level (expected) and by using [¹⁸F]fluciclovine PET/MRI (observed) at baseline and 3 months after treatment. To compare observed frequencies of metastases and expected frequencies, a McNemar test will be performed at baseline and 3 month after treatment separately. Further, a generalized estimation equation (GEE) method will be used to examine the association of two diagnosis methods accounting for correlation between baseline and 3 months measurements. Sensitivity, specificity, and accuracy of using [¹⁸F]fluciclovine PET/MRI will be estimated along with 95% CI. Due to the small sample size and potential for sparse data, we may use Firth's penalized likelihood approach. Data transfer, management, and analyses will be performed using Excel and SAS v9.4.

6.5 Data and Safety Monitoring Plan

6.5.1 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.

6.5.2 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 UAB IRB. Prior to obtaining IRB approval, the protocol must be approved by the UAB Comprehensive Cancer Center Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

6.5.3 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 IRB-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.

6.5.4 Changes in the Protocol

Once the protocol has been approved by the UAB IRB, 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 the IRB 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 IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

6.5.5 Adverse Event Reporting

As with many IV administered agents, [¹⁸F]fluciclovine could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in limited human exposure to date. Reasonable precautions should be taken, consistent with normal radiologic and clinical facility practice. The patient should be monitored until the PET procedure is completed, and trained personnel and emergency equipment should be available per facility standards.

Qualifying Adverse Events (AEs), including Serious Adverse Events (SAEs), as defined herein, will be reported via the FDA Adverse Event Expedited Reporting System (AERS). For the [¹⁸F]fluciclovine IND we will report adverse events based on the FDA final rule for IND safety reporting requirements under 21 CFR part 312 published on September 29, 2010 and implemented on March 28, 2011. This investigational study is not a BA or BE study so 21 CFR part 320 is not applicable. Adverse events will also be reported to the UAB IRB according to their requirements.

Reporting of Serious Adverse Events (SAEs) to Blue Earth Diagnostics (BED): In addition to reporting of SAEs to the responsible IRB and Health Authority, the Principal Investigator or designee will document all SAEs that occur following receipt of [¹⁸F]fluciclovine (whether or not related to study drug) to BED. Such SAEs must be reported within 24 hours of Principal Investigator or designee becoming aware of the event. All SAE information must be recorded and faxed or scanned and emailed to:

Blue Earth Diagnostics SAE E mail:	Drugsafety@pharsafer.com
Tel:	1-855-AXUMIN1 (1-855-298-6461)
Fax:	+44 (0) 1483 212178

Additional and further requested information (follow-up or corrections to the original case) will be detailed and faxed/emailed to the same address and must include the following minimum information: The name and contact information of the reporter, the name of the study drug(s), a description of the reported SAE, with the subject identified by one or more of the following (subject initials, subject number age, sex), an investigator assessment of study drug causality, and any additional data which would aid the review and causality assessment of the case including but not limited to the date of onset, severity, the time from administration of study drug(s) to start of the event, the duration and outcome of the event, any possible etiology for the event, and the final diagnosis or syndrome, if known. If BED receives any individually identifiable health information collected or produced in the study, BED shall use and disclose only for the purpose of complying with applicable laws, provided that all such uses are disclosed in the IRB-approved informed consent form. BED will use all reasonable efforts to protect the privacy and security of individually identifiable health information and will require its business partners to do so also. BED will not contact any study subjects, unless permitted by the informed consent form.

6.5.5.1 General Definitions (from 21 CFR 312.32 (a))

Adverse Event (AE): An Adverse Event is an untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related. For this study, the drug is [¹⁸F]fluciclovine and adverse events would include any events experienced by a study participant during the Adverse Event reporting period defined in Table 1 whether or not it was considered to be related to the [¹⁸F]fluciclovine. At the conclusion of the imaging study, the imaging technologist will observe the patient and also inquire if they are back to their usual state of health. If a negative answer is received, then the physician will be called to investigate this report as a possible adverse reaction.

Adverse Reaction: An Adverse Reaction is any adverse event caused by a drug. In this study, the drug is [¹⁸F]fluciclovine.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the IND drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means 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 adverse reaction, which means any adverse event caused by a drug.

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure 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.

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, a 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 functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be 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.

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.

Investigational Agent: An investigational agent is any agent held under an Investigational New Drug (IND) application. For purposes of this study, [¹⁸F]fluciclovine is the investigational agent.

6.5.5.2 AE Reporting Requirements

The investigators on this protocol will report any suspected adverse events that occur after [¹⁸F]fluciclovine administration and within the specified follow-up period to Dr. Galgano and they will work together to determine whether there was an adverse event or adverse reaction and the severity of the adverse event or reaction.

All AEs will be followed by the investigators until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology is achieved, or until subject is lost to follow up.

6.5.5.3 CAEPR/ASAE for [¹⁸F]Fluciclovine

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. The Agent Specific Adverse Event List (ASAE) would include the expected adverse events associated with the use of [¹⁸F]fluciclovine. At this time, there have rare reported AEs associated with the use of a [¹⁸F]fluciclovine in clinical studies ($\leq 1\%$ of patients). The most common adverse reactions were injection site pain, injection site erythema, and dysgeusia. We will continue to update our CAEPR and ASAE lists as this study progresses, including by reviewing the literature and our in-house data safety monitoring. If any are found, we will begin an ASAE list. Any information on reported AEs for [¹⁸F]fluciclovine will be provided by the sponsor to all of the investigators on this protocol.

6.5.5.4 Potential but Unexpected AE for [¹⁸F]Fluciclovine

There have rare reported AEs associated with the use of a [¹⁸F]fluciclovine in clinical studies ($\leq 1\%$ of patients). The most common adverse reactions were injection site pain, injection site erythema, and dysgeusia.

Other general risks for PET/MRI imaging include:

- The injection site may become infected.
- The dose might be extravasated into tissues surrounding the vein catheter leading to localized pain/discomfort.

Radiation risks: [¹⁸F]fluciclovine injection contributes to lifetime radiation accumulation. The smallest dosage for imaging and safe handling are used for these protocols. The organ and total body doses associated with [¹⁸F]fluciclovine imaging are comparable to those associated with other widely used clinical nuclear medicine procedures.

6.5.5.5 Review of Safety Information

As required by 21 CFR 312.32(b), the physician investigators will promptly review all information relevant to the safety of the drug. The physician investigators will also be providing much of this information to the local IRB as well for data safety and review monitoring. The review will include determining whether there is a safety event over time and the causality. Reporting will be as described in Table 1.

Characterization of the severity of an Adverse Event: Adverse events will be graded as below.

Grade: Grade denotes the severity of the AE. An AE is graded using the following categories:

- Mild
- Moderate
- Severe
- Life-threatening or disabling
- Fatal

NOTE: Severity is graded on the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) based scale for each adverse event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal hemoglobin values. “Severity” is NOT the same as “Seriousness.” All appropriate clinical areas should have access to a copy of the most current CTCAE and a copy of the CTCAE can be downloaded from (<http://ctep.cancer.gov>).

Attribution of cause: The physician investigators will determine whether an adverse event was related to a medical treatment or procedure. Definitions taken from our work with CTEP and NIH give the following definitions for “Attribution” that we will adopt for this IND study: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure
- **NOTE:** Attribution is part of the assessment of an adverse event. Determining that an event is ‘unlikely related’ or ‘unrelated’ to a study agent or procedure does NOT make the event unreportable, or disqualify the event as an AE. As defined above, an AE is reportable as specified herein if it occurred: **“during the Adverse Event reporting period defined in the protocol, or by applicable guidance, regulation, or policy.”**

6.5.5.6 Adverse Event Reporting

Expedited AE reporting for this study will be done through the Cancer Consortium, IRB and FDA and as required by FDA MedWatch. These requirements are briefly outlined in the table below.

Table 1. Reporting Requirements.

	Unexpected		Expected
	Adverse Reaction (known or suspected attributable to the use of	AE not attributable to	AE, AR

	[¹⁸F]Fluciclovine		[¹⁸F]Fluciclovine	
	Serious including life-threatening (or death)	Nonserious	Life-Threatening or serious or not serious	None are expected for [¹⁸ F]Fluciclovine
Reporting Time Requirement to the FDA	Report to FDA ASAP and within 7 days of discovery of event	Annual Continuation Review submission	Annual Continuation Review submission	Not applicable to [¹⁸ F]Fluciclovine
Reporting Form for the FDA	IND Safety report of potentially serious risk	Annual Reports / Case reports	Annual Reports / Case reports	Not applicable to [¹⁸ F]Fluciclovine
Reporting Time Requirement to the local IRB	Report to IRB ASAP within 10 days of discovery of event (suspected is defined as 50% probability attributable to [¹⁸ F]Fluciclovine study) this also includes any increased risks with the study even without an AE	At continuation review time	At continuation review time	Not applicable to [¹⁸ F]Fluciclovine
Reporting form for the IRB	Expedited Reporting Form for Unanticipated Problems or Noncompliance and Adverse Event Reporting Form	Form for Unanticipated Problems or Noncompliance, Case reports on continuation form, Data Safety Monitoring Reports	Form for Unanticipated Problems or Noncompliance, Case reports on continuation form, Data Safety Monitoring Reports	Not applicable to [¹⁸ F]Fluciclovine

6.5.5.7 Expedited Adverse Reaction Reporting Guidelines

Life-threatening (or fatal) adverse reactions must be reported within 7 days to the FDA. The FDA should be notified as soon as the adverse reaction is discovered by telephone or fax or email. The instructions and forms are available at <http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>. The report should be sent ASAP by mail and followed with a follow-up report. Individual IND safety reports to FDA are submitted on the Medwatch FDA Form 3500A as an "IND Safety Report". The form should be sent to The Director, Office of Generic Drugs in the Center for Drug Evaluation

and Research at FDA. The address and phone numbers are available at: <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm119100.htm>.

All life threatening adverse reactions reports are submitted to the FDA, THE UAB IRB and to all investigators. A copy of the report is kept on file.

6.5.6 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.

6.6 Data Management

All patient data will be anonymized and stored on encrypted password-protected computers with access only given to members of the research team. Standard precautions regarding HIPAA will be taken to avoid any breach in patient privacy.

7.0 References

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