LOCATE

PROTOCOL NUMBER: BED003

Version 4.0 Date: 07 June 2017

The Impact of ^{18}F-fluciclovine (FACBC) PET/CT on Management of Patients with Rising PSA after Initial Prostate Cancer Treatment

PHASE IIIb

IND Number : 107707

Sponsor: Blue Earth Diagnostics

Blue Earth Diagnostics

Clinical Research Protocol

The Impact of ^{18}F-fluciclovine (FACBC) PET/CT on Management of Patients with Rising PSA after Initial Prostate Cancer Treatment

Protocol Number:	BED003
Version / Date:	3.0/ May 23rd 2016
Investigational Product:	Fluciclovine (^{18}F) [referred to as ^{18}F-fluciclovine in this protocol]
EUDRACT/IND Number:	
Development Phase:	Phase IIIb
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Sponsor Signature Peter Gardner Date 6 Jun 2017.

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include providing Blue Earth Diagnostics with the information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: BED003 Version 4.0

Protocol Title: The Impact of ^{18}F-fluciclovine (FACBC) PET/CT on Management of Patients with Rising PSA after Initial Prostate Cancer Treatment

Protocol Date: 07 June 2017

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Investigator Signature Date

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Print Name and Title

Site # _____

Site Name _____

Address _____

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CONTENTS

LIST OF ABBREVIATIONS

ACRIN	American College of Radiology Imaging Network
AAT	Amino acid transporters
AE	Adverse event
ADT	Androgen Deprivation Therapy
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BED	Blue Earth Diagnostics
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
C.I.	Confidence Interval
CRF	Case report form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Management Center
DR	Detection Rate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FACBC	Fluciclovine (^{18}F) [referred to as ^{18}F-fluciclovine in this protocol]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
MEq	Milliequivalent
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration

mCi	Millicurie
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mSv	Millisieverts
NPV	Negative predictive value
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography with Computerized Tomography
PI	Principal Investigator
PPV	Positive Predictive Value
PK	Pharmacokinetic
PSA	Prostate Specific Antigen
PSADT	Prostate Specific Antigen Doubling Time
SAE	Serious Adverse Experience
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOP	Standard Operating Procedure
SPECT	Single Photon Emission Computed Tomography
TNM	TNM Classification of Malignant Tumors
US	Ultrasonograph

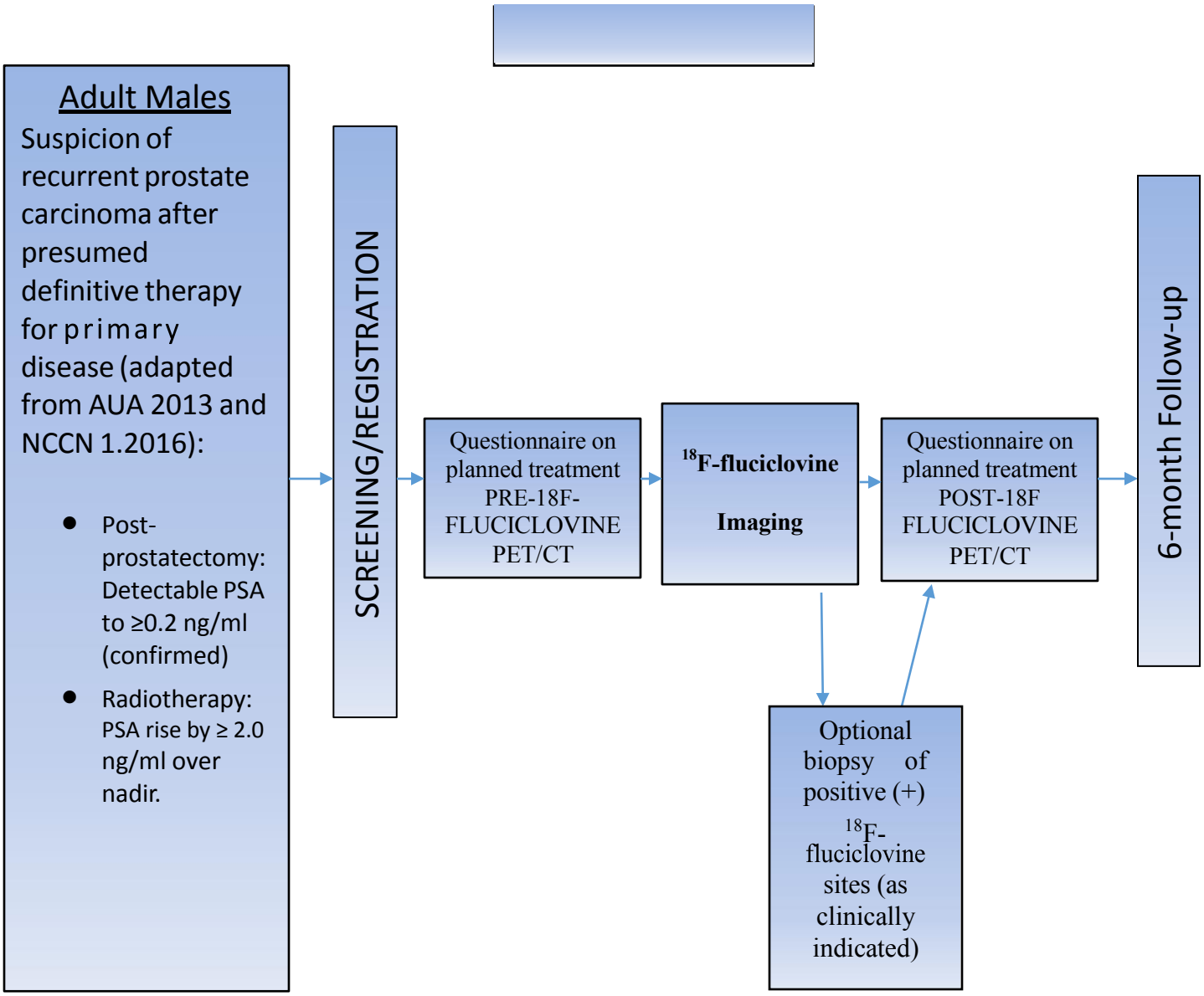
PROTOCOL SYNOPSIS

TITLE	The Impact of ^{18}F-fluciclovine (FACBC) PET/CT on Management of Patients with Rising PSA after Initial Prostate Cancer Treatment
SPONSOR	Blue Earth Diagnostics
FUNDING ORGANIZATION	Blue Earth Diagnostics
NUMBER OF SITES	20
RATIONALE	^{18}F-fluciclovine PET/CT has the potential to improve medical care and quality of life among men with prostate cancer in several ways. First, identification of disease in the prostate bed and/or regional nodes would provide evidence in support of salvage radiation treatment, and help to plan radiotherapy. In addition, the absence of distant disease by ^{18}F-fluciclovine PET/CT in patients would preserve salvage local therapy as a clinical option beyond the time typically offered. Second, identification of distant disease at the time of consideration of salvage radiation therapy would allow patients to forego radiation that would ultimately be futile. This would spare those patients radiation-induced side effects such as impaired recovery of continence, impaired recovery of erectile function, and diarrhea. Finally, the absence of disease detection on a sensitive imaging modality in patients with a rising PSA would have the potential to delay initiation of systemic androgen deprivation therapy, a treatment strategy that causes a number of morbid side effects that are detrimental to quality of life.
STUDY DESIGN	This is a prospective phase IIIb study to assess the impact on patient management of ^{18}F-fluciclovine PET/CT in patients with rising prostate specific antigen (PSA) after initial prostate cancer treatment.
PRIMARY OBJECTIVE	To measure the fraction of patients for whom ^{18}F-fluciclovine PET/CT alters intended management through detection of disease after curative-intent treatment in a population of men with elevated PSA levels indicative of persistent or recurrent prostate cancer and negative or equivocal findings on standard-of-care diagnostic imaging tests.

SECONDARY OBJECTIVES	1. To measure the fraction of patients for whom ^{18}F-fluciclovine PET/CT leads to a change of actual management by comparison with intended management plan before ^{18}F-fluciclovine PET/CT. 2. To estimate the fraction of patients in whom ^{18}F-fluciclovine PET/CT yields evidence of recurrent disease on the basis of imaging results. 3. To estimate 1) the rates of detecting regionally recurrent disease (i.e., prostatic bed-only and/or pelvic disease outside of the bed) and 2) the rate of detecting distant metastases (i.e., bone metastases, visceral metastases, or non-regional nodal metastases) with ^{18}F-fluciclovine PET/CT in the study population. 4. To determine 1) the Positive Predictive Value (PPV) of ^{18}F-fluciclovine PET/CT to detect regionally recurrent disease and 2) the PPV of ^{18}F-fluciclovine PET/CT to detect distant metastases in the study population in patients who undergo optional biopsy of ^{18}F-fluciclovine PET/CT findings or have documentation of disease status based on other imaging and/or follow-up data. 5. To explore differences in estimated cost of treatment plans determined prior to and following ^{18}F-fluciclovine PET/CT
NUMBER OF SUBJECTS	330 patients
SUBJECT SELECTION CRITERIA	Study Population Patients with suspicion of recurrent prostate carcinoma after presumed definitive therapy for primary disease Inclusion Criteria: • History of histologically confirmed adenocarcinoma of the prostate post curative-intent local treatment (radical prostatectomy, local radiotherapy, brachytherapy). • Suspicion of recurrent prostate carcinoma after previous presumed definitive therapy for primary disease defined as : o Post-prostatectomy (with/without adjuvant RT): Detectable or rising PSA level that is ≥0.2 ng/mL with a second confirmatory level of ≥0.2 ng/mL o Post radiotherapy (without RP): PSA rise ≥2ng/mL over nadir • Negative or equivocal findings on standard-of-care imaging for restaging of disease in the previous 60 days: Standard-of care imaging is defined as:

	○ Whole-body 99mTc-MDP bone scintigraphy or NaF PET-CT (dependent on standard of care at the institution) and ○ Either CT or MRI of the pelvis (or the abdomen and pelvis). • Being considered for salvage therapy • Any non-surgical local treatment such as previous cryotherapy, external beam radiation, or HiFU must have occurred at least 1 year in the past. • Previous brachytherapy treatment will have occurred at least 2 years in the past • Ability to understand and the willingness to sign a written informed consent <u>Exclusion Criteria</u>: • Ongoing treatment with any systemic therapy intended for the treatment of prostate cancer (e.g., antiandrogen or LHRH agonist or antagonist) • Androgen deprivation therapy (ADT) in the past 3 months • History of bilateral orchidectomy • Inability to tolerate ^{18}F-fluciclovine PET/CT
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	All subjects will receive a single intravenous dose of 10mCi (370MBq) $\pm$20% ^{18}F-fluciclovine immediately prior to PET scan. There will be no repeat dosing
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Patients will be imaged with ^{18}F-fluciclovine PET/CT prior to planned treatment. Follow-up for treatment outcome and results of standard-of-care investigations for up to 6 months after ^{18}F-fluciclovine PET/CT.
CONCOMITANT MEDICATIONS	<u>Allowed</u>: All treatments except for those specifically prohibited <u>Prohibited</u>: Ongoing treatment with any systemic therapy intended for the treatment of prostate cancer (e.g., antiandrogen or LHRH agonist or antagonist), including bilateral orchiectomy at time of screening or scanning
Efficacy Evaluations	
Primary endpoint	Change to management plan assessed by comparing Pre-^{18}F-fluciclovine PET/CT management plan with Post-^{18}F-fluciclovine PET/CT management plan.
Secondary endpoint	1. Per-patient impact (yes/no) of ^{18}F-fluciclovine PET/CT on pre-PET intended versus post-PET actual patient management.

	2. The rate of detection of any disease site by ^{18}F-fluciclovine PET/CT in the study population. 3. The rate of detection of 1) prostatic bed and other pelvic disease and 2) distant metastases (i.e., bone metastases, visceral metastases, or non-regional nodal metastases) with ^{18}F-fluciclovine PET/CT in the study population. 4. The PPV of ^{18}F-fluciclovine PET/CT to detect regionally recurrent disease compared to biopsy in those patients who undergo a regional disease biopsy on the basis of a ^{18}F-fluciclovine PET/CT finding or in case of bony disease a correlation with MRI or biopsy. 5. The PPV of ^{18}F-fluciclovine PET/CT to detect distant disease compared to biopsy in those patients who undergo a distant disease biopsy on the basis of a ^{18}F-fluciclovine PET/CT finding or in case of bony disease a correlation with MRI or biopsy. An independent adjudication panel will review and adjudicate ^{18}F-fluciclovine PET/CT lesions with biopsy or MRI during follow-up to assess the PPV and, where possible, NPV, sensitivity and specificity. Rates of disease detection (radiographic only and confirmed by pathology or MRI) will be described
Safety Evaluations	Monitoring for adverse events, change in EKGs and routine hematology and biochemistry evaluations taken prior to and following receipt of ^{18}F-fluciclovine
Planned Interim Analyses	An interim analysis of a subset of study results on all enrolled subjects may be submtted for potential public presentation prior to completion of all data collection and analyses. As trial design will not be modified as a result of this interim analysis, no adjustment to the type I error is required.
STATISTICS Primary Analysis Plan	For the evaluation of the primary endpoint (i.e., impact on therapy), questionnaires obtained pre- and post- ^{18}F-fluciclovine PET/CT will be compared to calculate the fraction of cases with a change in management (versus no change in planned management). The 95% confidence interval will be calculated using the Exact method for a binomial distribution.
Rationale for Number of Subjects	Assuming a prevalence rate of positive ^{18}F-fluciclovine PET/CT of approximately 40%, of which 30% will be expected to change the physician's intended management plan and binding of the 95% CI width at 0.20 (i.e., half –length at 0.10), 89 ^{18}F-fluciclovine positive patients will be needed for the assessment of our primary aim. After taking into account the random nature of the observed numbers of patients meeting the clinical criteria in a prospective study, and potential data loss, provide a 90% probability of yielding the required number of patients for the primary comparison it is planned to enroll at least 292 and up to 330 patients into the study in order to obtain 89 evaluable patients.


Adult Males
Suspicion of recurrent prostate carcinoma after presumed definitive therapy for primary disease (adapted from AUA 2013 and NCCN 1.2016):
Post-prostatectomy: Detectable PSA to ≥0.2 ng/ml (confirmed)
Radiotherapy: PSA rise by ≥ 2.0 ng/ml over nadir.
SCREENING/REGISTRATION
Questionnaire on planned treatment PRE-18F-FLUCICLOVINE PET/CT
18F-fluciclovine Imaging
Questionnaire on planned treatment POST-18F FLUCICLOVINE PET/CT
6-month Follow-up
Optional biopsy of positive (+) 18F-fluciclovine sites (as clinically indicated)

1 BACKGROUND

Biochemically recurrent prostate cancer is a common clinical problem. Optimal strategies for detection of persistent or recurrent disease and for management of such patients are not currently well defined. Radical therapy for prostate cancer patients without pre-treatment evidence of distant disease using standard-of-care diagnostic imaging studies improves disease-specific survival and overall survival, (1) but relapse remains a significant problem. Biochemical failure rates despite optimal therapy can be as high as 30% with intermediate-risk disease (2) and 50% with high-risk disease. (3) Some of these relapses are attributable to distant metastases not detected by standard imaging modalities. Others are attributable to locally persistent disease in the region of the prostate or proximate nodes. Management of recurrent disease after curative-intent local therapy optimally requires disease localization.

Standard-of-care staging imaging for prostate cancer as recommended by the current National Comprehensive Cancer Network guidelines includes ^{99m}Tc-MDP bone scintigraphy and pelvic imaging with CT or MRI. (4) In the setting of early biochemical relapse after prostatectomy, although used to help define the extent of disease, these studies are generally uninformative. As a result, clinicians must often decide for or against further local therapy (e.g., salvage external beam radiation therapy for biochemical recurrence after prostatectomy) as guided by nomogram-based probabilities rather than anatomic localization. A more sensitive imaging modality that could offer anatomic localization within the clinical setting of early PSA relapse would better inform treatment decisions and improve the management of patients with apparent recurrence based on PSA levels.

Prostate cancer functional imaging with PET is presently used on a limited basis. Widely available, PET or PET/CT with ^{18}F-fluorodeoxyglucose (FDG) is not standard as FDG uptake is usually low in prostate cancer prior to the development of castration-resistant disease. ^{18}F-sodium fluoride PET is more sensitive than standard ^{99m}Tc-MDP bone scintigraphy, but both methods are non-specific and do not image cancer outside of the skeleton. Acetate- and choline-based PET tracers have been the subject of study but are not broadly approved and available. PET or PET/CT with the experimental L-leucine analog ^{18}F-fluciclovine has demonstrated promise and is the subject of this experimental protocol.

1.1 Overview of Clinical Studies

Published data from single-institution studies of ^{18}F-fluciclovine PET have preliminarily demonstrated its operating characteristics in over one hundred study subjects with recurrent prostate cancer after curative-attempt primary therapy (see Figure) (5,6,7). Dosimetry has previously been described and is notable for a favorable pelvic imaging profile because of low levels of uptake within the urinary bladder. ^{18}F-fluciclovine PET/CT has demonstrated approximately 90% sensitivity and 40-67% specificity for detection of cancer in the prostate bed. It has demonstrated 55-100% sensitivity and more than 95% specificity for the detection of disease outside of the prostate bed. Multi-center study is needed to determine the clinical impact of localization of suspected prostate cancer recurrence by ^{18}F-fluciclovine PET/CT, specifically the impact on patient management.

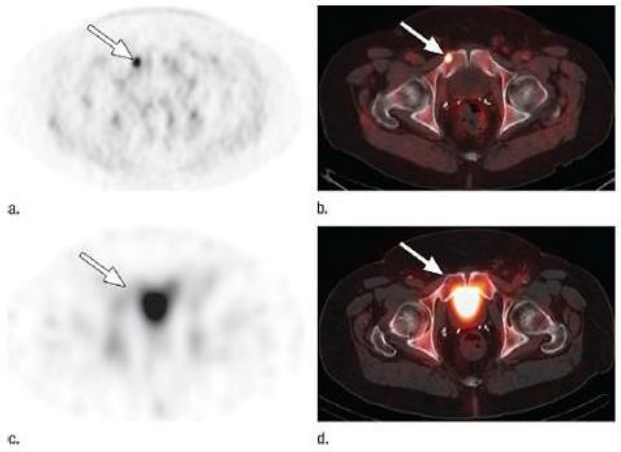


Figure: Restaging images for a patient who is status post radical prostatectomy with a serum PSA of 2.97 ng/mL. (a) Transverse anti-3-^{18}F-FACBC PET, (b) fused anti-3-^{18}F-FACBC PET/CT images, (c) ^{111}In-capromab pendetide SPECT, and (d) fused ^{111}In-capromab pendetide SPECT/CT. The arrow points to a lytic bone lesion in the right pubic ramus that was subsequently biopsy proven to contain prostate cancer. The lesion was not identified by ^{111}In-capromab pendetide SPECT. Schuster et al, Radiology, 2011.

The goal of the proposed study is to further evaluate the impact of ^{18}F-fluciclovine PET/CT of prostate cancer in a multi-institution study. We hypothesize that by identifying disease in or outside of the prostate bed—either in regional lymph nodes or distant disease sites, ^{18}F-fluciclovine PET/CT will impact the approach to patient management. This typically involves prostate bed irradiation in patients with prior prostatectomy, and a combination of additional focal therapy such as radiotherapy, cryotherapy, and/or systemic therapy in patients treated initially with local radiotherapy or brachytherapy. We propose a study of men who have undergone definitive treatment of localized prostate cancer (e.g. by prostatectomy, local radiotherapy, brachytherapy) and are presenting with rising PSA levels indicative of recurrent or persistent disease. We have chosen to study patients without evidence of disease (or with equivocal findings) by standard imaging (bone scintigraphy and CT or MRI) and with PSA levels in the range where imaging findings outside the prostatic bed would be expected to have a significant impact on treatment. Study participants with negative or equivocal conventional staging studies (^{99m}Tc-MDP bone scintigraphy /NaF PET-CT (dependent on standard of care at the institution) and abdominal-pelvic CT or MRI) will undergo ^{18}F-fluciclovine PET/CT.

2 STUDY RATIONALE

This study has the potential to improve management of a common disease state (biochemically recurrent prostate cancer) within the most common cancer among men. If successful, it will establish an imaging strategy that is demonstrated to appropriately modify care compared to current standard imaging approaches. Single center experience of a similar study was reported at the SNMMI meeting in 2015 (11). They reported initial findings from an ongoing randomized study in which 24/54 patients with rising PSA and negative pelvic MRI and ^{99m}Tc-MDP bone scan were randomized to receive ^{18}F-fluciclovine PET/CT before definitive treatment. In these patients 6/23 had changes made to their radiation fields as a result of the PET/CT; 1 had the offer of radiotherapy withdrawn. Overall in these early results 7/24 patients (29.2%) had the radiotherapy decision modified by the results of the PET/CT scan. If these results can be confirmed in a multi-center study there is the potential to improve medical care and quality of life among men with prostate cancer in several ways. First, identification of disease in the prostate bed and/or regional nodes would provide evidence in support of salvage radiation treatment, and help to plan radiotherapy. In addition, the absence of distant disease by ^{18}F-fluciclovine PET/CT in patients with a PSA $\geq$ 1 ng/mL would preserve salvage local therapy as a clinical option beyond the time typically offered. Second, identification of distant disease at the time of consideration of salvage radiation therapy would allow patients to forego radiation that would ultimately be futile. This would spare those patients

radiation-induced side effects such as impaired recovery of continence, impaired recovery of erectile function, and diarrhea. Finally, the absence of disease detection using a sensitive imaging modality in patients with a rising PSA would have the potential to delay initiation of systemic androgen deprivation therapy, a treatment strategy that causes a number of morbid side effects that are detrimental to quality of life.

This prospective study will enroll up to 330 men with PSA-persistent or PSA-recurrent prostate cancer after curative-intent primary therapy and negative or equivocal findings on standard-of-care imaging (see enrolment criteria for details of eligibility). Consenting participants will be imaged with ^{18}F-fluciclovine PET/CT. Site clinicians will manage study subjects per standard practices and will document any change in treatment based on review of ^{18}F-fluciclovine PET/CT findings. Rates of disease detection (radiographic-only, and pathologically confirmed) will be described.

2.1 Risk-Benefit Assessment

Benefits

The research scans may provide further clinical information regarding the patient's disease status that may not have been appreciated using other standard of care tests. If such information arises, this will be reported back to the responsible clinician to help direct the patient's further management. This may provide a direct benefit to the subject.

Risks

The risks from the imaging studies to subjects mainly relate to the intravenous injection and the radiation emitted by the radiopharmaceutical and CT. Intravenous injection carries a small risk of infection and hematoma.

The mean effective dose per unit administered activity of ^{18}F-fluciclovine is 22.1μSv/MBq (8). An administered activity of 10mCi (370 MBq) will result in an effective dose of 8.2mSv. The maximum effective dose due to the CT transmission scan will vary from site to site, but as a guide a dose of 7 mSv would be expected (details of scanner-specific CT effective doses will be given in the Study Imaging Manual). The effective dose due to the CT acquisition will be in accordance with ALARA (As Low As Reasonably Achievable) principles. The total dose of 15.2mSv is in line with other common nuclear medicine procedures.

As with all imaging techniques there is the risk that the PET/CT scan may provide a false positive image (giving the appearance of cancer) in sites where it is not present, due to other events in the body such as inflammation or false negative (failing to detect a nidus of cancer). Thus patients should continue to be reviewed and may require other investigations, including biopsy, to confirm scan findings.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to measure the fraction of patients for whom ^{18}F-fluciclovine PET/CT alters patient treatment through detection of disease after curative-intent treatment in a population of men with elevated PSA levels indicative of persistent or recurrent prostate cancer and negative or equivocal findings on standard-of-care diagnostic imaging tests.

3.2 Secondary Objectives

1. To measure the fraction of patients for whom ^{18}F-fluciclovine PET/CT leads to a change of actual management by comparison with the intended management plan before ^{18}F-fluciclovine PET/CT.
2. To estimate the fraction of patients in whom ^{18}F-fluciclovine PET/CT yields evidence of recurrent disease on the basis of imaging results.
3. To estimate 1) the rates of detecting regionally recurrent disease (i.e., prostatic bed-only and/or pelvic disease outside of the bed) and 2) the rate of detecting distant metastases (i.e., bone metastases, visceral metastases, or non-regional nodal metastases) with ^{18}F-fluciclovine PET/CT in the study population.
4. To determine 1) the PPV of ^{18}F-fluciclovine PET/CT to detect regionally recurrent disease and 2) the PPV of ^{18}F-fluciclovine PET/CT to detect distant metastases in the study population in patients who undergo optional biopsy of ^{18}F-fluciclovine PET/CT findings or have documentation of disease status based on other imaging and/or follow-up data. For soft tissue disease these calculations will be limited to those patients who undergo a confirmatory biopsy and for bone disease those with confirmatory findings on MRI any time during the 6-month follow up. The denominator for the analysis will be [lesions biopsied + bone lesions].
5. To explore differences in estimated cost of treatment plans determined prior to and following ^{18}F-fluciclovine PET/CT.

4 STUDY DESIGN

4.1 Study Overview

This prospective study will enroll up to 330 men with PSA-persistent or PSA-recurrent prostate cancer after curative-intent primary therapy and negative or equivocal findings on standard-of-care imaging (see enrolment criteria for details of eligibility). Consenting participants will be imaged with ^{18}F-fluciclovine PET/CT. Site clinicians will manage study subjects per standard practices and will document any change in treatment based on review of ^{18}F-fluciclovine PET/CT findings. Additionally, as clinically indicated, optional biopsy will be performed. All participants will be followed for up to 6 months, with clinical data collected for this study: PSA measurement from scan for 6 months. An expert reader will provide guidance to local readers on request. The final reporting of the PET/CT scan will be a single report by the local reader following any such discussion.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

For the primary objective, the change of management will be based on referring physician questionnaires completed pre- and post- ^{18}F-fluciclovine PET/CT (Intended v Revised Management Plans). Management options on referral will include prostatic bed radiotherapy (±hormone treatment), prostatic bed plus regional radiotherapy, cryoablation, surgery. Post PET/CT scan additional options include, inter alia no therapy, treatment of oligometastatic disease, hormonal and other systemic therapies).

5.2 Secondary Efficacy Endpoints

1. Per-patient impact (yes/no) of ^{18}F-fluciclovine PET/CT on pre-PET intended versus post-PET actual patient management (assessed at 6 months post scan)

2. The rate of detection of any disease site by ^{18}F-fluciclovine PET/CT in the study population;
3. The rate of detection of 1) prostatic bed and other pelvic disease and 2) distant metastases (i.e., bone metastases, visceral metastases, or non-regional nodal metastases) with ^{18}F-fluciclovine PET/CT in the study population;
4. The PPV of ^{18}F-fluciclovine PET/CT to detect regionally recurrent disease compared to biopsy in those patients who undergo a regional disease biopsy on the basis of a ^{18}F-fluciclovine PET/CT finding or in case of bony disease a correlation with MRI or biopsy.
5. The PPV of ^{18}F-fluciclovine PET/CT to detect distant disease compared to biopsy in those patients who undergo a distant disease biopsy on the basis of a ^{18}F-fluciclovine PET/CT finding or in case of bony disease a correlation with MRI or biopsy.

5.3 Safety Evaluations

1. Change from baseline QTc intervals and any clinically significant alterations in EKG after ^{18}F-fluciclovine PET/CT scanning
2. Change from baseline values in hematology and biochemistry profiles after ^{18}F-fluciclovine PET/CT scanning
3. Incidence of adverse events occurring after the ^{18}F-fluciclovine injection

6 SUBJECT SELECTION

6.1 Study Population

Eligible patients that meet inclusion and exclusion criteria will have suspicion of recurrent prostate carcinoma after presumed definitive therapy for primary disease.

6.2 Inclusion Criteria

1. History of histologically confirmed adenocarcinoma of the prostate post curative-intent local treatment (radical prostatectomy, local radiotherapy, brachytherapy)
2. Suspicion of recurrent prostate carcinoma after presumed definitive therapy for primary disease, defined as
    a. Post-prostatectomy (with/without adjuvant RT): Detectable or rising PSA level that is $\geq$0.2 ng/mL with a second confirmatory level of $\geq$0.2 ng/mL
    b. Post radiotherapy (without RP): PSA rise $\geq$2ng/mL over nadir
3. Negative or equivocal findings on standard-of-care imaging for restaging of disease in the previous 60 days consisting of:
    a. Whole-body ^{99m}Tc-MDP bone scintigraphy or NaF PET-CT (dependent on standard of care at the institution) and
    b. Either CT or MRI of the pelvis (or the abdomen and pelvis).
4. Being considered for salvage therapy
5. Previous cryotherapy, external beam radiation, or HiFU must have occurred at least one year in the past.
6. Previous brachytherapy treatment will have occurred at least 2 years in the past

7. Ability to understand and the willingness to sign a written informed consent

6.3 Exclusion Criteria

1. Ongoing treatment with any systemic therapy intended for the treatment of prostate cancer (e.g., antiandrogen or LHRH agonist or antagonist)
2. Androgen deprivation therapy (ADT) in the past 3 months.
3. History of bilateral orchiectomy.
4. Inability to tolerate ^{18}F-fluciclovine PET/CT.

7 CONCURRENT MEDICATIONS

7.1 Allowed Medications and Treatments

All standard and approved treatments are permitted except for those specifically prohibited in section 7.2.

7.2 Prohibited Medications and Treatments

The following medications and treatments are prohibited prior to the ^{18}F-fluciclovine PET/CT. Any administration of ^{18}F-fluciclovine during treatment with these will be considered a protocol violation.

- Treatment with any systemic therapy intended for the treatment of prostate cancer (e.g., antiandrogen or LHRH agonist or antagonist)
- Bilateral orchiectomy

8 STUDY TREATMENTS

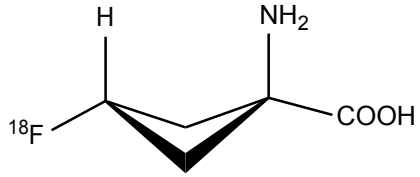
8.1 Formulation of Test Product

^{18}F-fluciclovine is a radiolabelled synthetic amino acid. The radioactive isotope ^{18}F decays with a half-life of approximately 110 minutes.

Chemical formula

$C_5H_8{}^{18}FNO_2$

Chemical structure



Chemical name

(anti)-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid.

Physiological effects

Biodistribution and radiation dosimetry studies have demonstrated physiological uptake of ^{18}F-fluciclovine to be highest in the liver and pancreas, with rapid biological clearance. (9) There is low albeit prolonged uptake in skeletal muscle and bone marrow, with clearance dominated by the tracer half-life. (9)

8.2 Packaging and Labeling

The investigational agent is supplied as a unit dose for injection in a syringe with a radioactive concentration at a reference date and time that is stated on the container label. Each syringe is supplied in a container providing appropriate radiation shielding. Information will be provided with the shipment giving the confirmation number, radioactive concentration of injection (mCi/mL) at a stated time and date, shelf life information, protocol number and a unique prescription number. The radiochemical purity of ^{18}F-fluciclovine injection is not less than 95% during the shelf life of the product

8.3 Supply of Study Drug at the Site

Sites will be provided with instructions for ordering the ^{18}F-fluciclovine injections for use in the study. The order for a specific patient to be scanned at a specific date and time must be made to PETNET Solutions Centralized Scheduling Team (Tel: 1 877 473 8638). The ^{18}F-fluciclovine will be delivered from the radiopharmacy to the imaging site by courier. Each syringe is supplied in a container providing appropriate radiation shielding. The site must keep records of all shipments of ^{18}F-fluciclovine received, dispensing and disposal/destruction performed on site as is appropriate to each facility.

8.4 Dispensing

When the study site receives the dose and prior to administration, the activity in the syringe will be measured in a dose calibrator. Should the activity be less than 8mCi or the volume required exceed 5 mL undiluted material or the administration be more than 10 hours from manufacture the scan should not be performed.

8.5 Administration Instructions

Prior to PET/CT, 10mCi ±20% of ^{18}F-fluciclovine will be administered as an IV bolus injection followed by a 10 mL saline flush. ^{18}F-fluciclovine will be injected through a cannula (or indwelling catheter) with the subject lying in a supine position and in an antecubital vein or another vein that will provide access. The administration site will be evaluated pre- and post- administration for any reaction (e.g. bleeding, hematoma, redness, or infection). Documentation of administration to a subject will be recorded according to standard of care and on the appropriate eCRF, including date, prescription number, total volume, start/stop time of administration, and injection site.

8.6 Study Drug Accountability

An accurate and current accounting of the dispensing and disposal of ^{18}F-fluciclovine for each subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify this document throughout the course of the study.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

9.1 Informed Consent

The participant must sign and date the local site IRB-approved version of the Informed Consent form before any study-specific procedures are performed.

Written and oral versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, his referring physician or other independent parties to decide whether he will participate in the study. Written Informed Consent will then be obtained by means of the participant's dated signature and the dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, trained in GCP and informed consent procedures. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

9.2 Clinical Assessments

Data from the following assessments and procedures should be documented in the Subject's medical records and recorded in the eCRF

1. **Concomitant Medications**

   All concomitant medication and concurrent therapies will be documented at Screening and at all Visits and at End of Follow up. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

2. **Demographics**

   Demographic information will include age, gender, race and ethnicity.

3. **Medical History**

   Include history of prostate cancer and prostate cancer treatments, and other clinically significant diagnoses. Prostate cancer history should include the date of initial diagnosis, initial tumor stage and Gleason score, dates of definitive therapy and adjuvant treatment (if given), and date of diagnosis of biochemical recurrence.

4. **Imaging Studies**

   Imaging data will include all imaging results (including relevant bone scans, CT etc) from 60 days before screening so the final follow-up and all prostate cancer imaging results available from the Subject's file

5. **Vital Signs**

Blood pressure and pulse rate will be performed after resting for 5 minutes.

6. **12 lead Electrocardiogram (EKG)**

EKG will be recorded as indicated in Section 10. Original EKGs are to be anonymized and forwarded to Clinical Research, Blue Earth Diagnostics, Magdalen Centre, Oxford Science Park, Oxford OX4 4GA, United Kingdom and copies maintained in the Subject's medical record.

7. **PSA Levels**

PSA levels will be recorded from the Subjects medical records

8. **Management Plan**

The Intended Management Plan. The treating physician will complete the Management Plan Questionnaire to document his/her intended treatment including planned radiation fields, intended resection limits of surgery, use of brachytherapy, cryotherapy or HiFU, intended use of adjuvant therapy.

The Revised Management Plan. Where an additional diagnostic procedure (e.g., imaging or biopsy) is performed in light of the PET/CT findings, the results of these should be considered prior to recording the revised management plan. Any such diagnostic procedures do not qualify as a "change" to clinical management. The treating physician will complete the Management Plan Questionnaire to document changes to the Pre-scan Management Plan. Changes include such responses as change to radiation or surgical fields. The patient may enter another clinical trial as part of the Revised Management Plan.

Actual Management Plan. At the final follow up visit any deviations or changes to the Revised Management Plan will be documented

9. **Biopsy**

Biopsy is not required by the protocol; however patients with PET/CT positive findings in soft-tissue supported by anatomical abnormalities on CT or MRI may have a biopsy performed per standard practice where the procedure is deemed clinically feasible and safe. Biopsies completed within 4 months after imaging will contribute to the aim of the study.

1. Biopsy results of suspected bone metastases conducted per standard practice will also be collected. Bone lesions may be followed up through imaging where biopsy is not practical.
2. Based on local-radiologist/nuclear medicine physicians assessment of ^{18}F-fluciclovine PET/CT-positive findings supported by anatomic abnormalities, conduct imaging-guided biopsy of soft-tissue ^{18}F-fluciclovine -enhancement region per institutional standard of care;
3. Submit pathology report(s) to the ACR Core Laboratory. The address is given in the Imaging Manual.

10. Blood Chemistry Profile

Blood will be obtained and sent to each site's clinical chemistry lab for determination of serum sodium, potassium, calcium, chloride, BUN, creatinine, glutamic oxaloacetic transaminase (SGOT/AST), glutamic-pyruvic transaminase (SGPT/ALT), alkaline phosphatase, creatine kinase (CK), lactate dehydrogenase (LDH), albumin, total protein, total bilirubin.

11. Hematology

Blood will be obtained and sent to each site's clinical hematology lab for a complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count determinations).

12. Urinalysis

Prior to the ^{18}F-fluciclovine dosing a midstream sample of urine will be obtained and tested by dipstick for leukocytes, nitrite, pH, protein, ketones, glucose, bilirubin, urobilinogen, and blood. This will not be repeated following scanning unless clinically indicated.

13. Adverse Events

See Section 12.

10 EVALUATIONS BY VISIT

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is given in Appendix 1

10.1 Visit 1 - Screening

1. Review the study with the subject and obtain written informed consent and HIPAA authorization
2. Record demographics data and current medication being taken.
3. Obtain medical history including treatment history.
4. Confirm negative or equivocal findings on baseline imaging studies (note: baseline imaging studies must be within 60 days prior Visit 1).
5. Measure vital signs
6. Obtain blood sample for:
    - PSA testing
    - Hematology
    - Biochemistry evaluations
7. Obtain 12-lead EKG
8. Obtain urine sample for dipstick urinalysis (may be collected and tested at any time between screening and the scan date)

10.2 Enrollment and PET/CT Preparation

Subjects who have provided informed consent and who meet all eligibility criteria will be enrolled into the study. At the time the Subject is determined to be eligible, the following activities will be performed:

1. Register the Subject via eCRF
2. Schedule the ^{18}F-fluciclovine PET/CT imaging study within 30 days of Visit 1
3. The treating physician must complete the Management Plan Questionnaire. A copy of the Questionnaire must be maintained in the Subject's medical record.
4. PET/CT Preparation:

    Subjects will be required to fast for at least 4 hours prior to the scan, drinking only sips of water within 4 hours of the scan if needed for administration of medications and not exercise from the day before the scan through to the time of the scan. Optionally, if it is the standard practice at the site, one hour prior to scanning, the patient may drink 500 mL of oral contrast (e.g. 1.2%, Readi-Cat) over 1 hour to maximize conspicuity of abdomen and pelvic structures. No IV CT contrast will be used.

10.3 Visit 2 – ^{18}F-fluciclovine PET-CT

Prior to the dose of ^{18}F-fluciclovine and the PET/CT scan, the following assessments will be performed:

1. Review and update the Subject's medical history to check for new health-related events and changes to concomitant medications since the Screening visit.
2. Ensure treatment plan has been documented prior to ^{18}F-fluciclovine PET/CT;
3. Obtain vital signs.
4. Obtain blood sample for:)
   - Hematology)
   - Biochemistry) Unless obtained at screening
5. 12-lead EKG)
6. Obtain a urine sample and perform dipstick analysis.)
   - If the results are abnormal these are to be recorded and the Subject is to proceed to having the fluciclovine PET/CT

Dosing and PET/CT Procedure: A venous cannula will be inserted and the Subject will receive one dose of ^{18}F-fluciclovine. Subjects will be imaged starting 4 minutes after injection from proximal-thigh to skull base. The duration of the scan is approximately 25 minutes on the PET/CT scanner.

Following the scan, Subjects will be encouraged to drink water to encourage hydration and frequent voiding to reduce radiation dose from ^{18}F-fluciclovine excretion. The following assessments will be performed

1. Obtain blood sample for:)
   a. Hematology)
   b. Biochemistry) Unless to be obtained in the next 7 days
2. 12-lead EKG)
3. Obtain vital signs immediately post scan and at 60 (± 5) minutes, and 120 (±5) minutes post-injection.
4. Assess the Subject for adverse events at 30 minutes, 60 minutes, and 120 minutes post-injection.

10.4 Visit 3 - Telephone Consultation at 24 - 72 (+/- 4) hours after dosing

An adverse event evaluation will be performed at **24 - 72 hours** (± 4 hours) after ^{18}F-fluciclovine administration via telephone consultation.

10.5 Documentation of Management plan revision post ^{18}F-fluciclovine PET/CT Scan (2-22 days following the scan)

The treating physician will complete the Management Plan Questionnaire to document changes to the Pre-Scan Management Plan. A copy of the Questionnaire must be maintained in the Subject's medical record.

10.6 End of Study (26+/-4 weeks post scan)

The treating physician will complete the Management Plan Questionnaire to document the actual treatment given, including any changes to radiation, surgery, or medications given.

The following data from Visit 2 through to 6 months after the ^{18}F-fluciclovine PET/CT will be abstracted from the Subject's medical record:

1. All PSA results.
2. All biopsy results and reports.
3. Restaging procedure results (e.g. bone scan or CT/MRI scans).
4. Current prostate cancer status and date of recurrence if applicable.
5. Adverse events reported by the patient
6. Date and cause of death if applicable.

10.7 Off Study Criteria

Subjects will not continue with the study based on the following criteria:

- Subject withdraws consent.
- Subject does not complete ^{18}F-fluciclovine PET/CT imaging

10.8 Discontinuation/Withdrawal of Subjects

Each Subject has the right to withdraw from the study at any time without giving a reason and without prejudice. In addition, a Subject may be discontinued from the study at any time for any of the following reasons:

- Ineligibility (recognized/arising after registration and prior to ^{18}F-fluciclovine administration)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of consent
- Loss to follow up
- Investigator discretion

Withdrawal from the study will not result in exclusion of the data for that Subject from analysis provided all baseline study measures have been completed.

The reason for withdrawal, if known, will be recorded in the eCRF.

10.9 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced

11 IMAGING PROTOCOL

11.1 PET/CT Scanner

A dedicated hybrid PET/CT scanner is mandatory. The selected PET/CT scanner must be qualified by the study management team and be capable of performing both emission and CT transmission images in order to allow for attenuation-corrected PET/CT images. The ability to calculate SUVs is also mandatory. PET/MR scanners are not approved for use on this study.

11.2 ^{18}F-fluciclovine injection administration

A venous cannula will be inserted, preferably in the right arm, and the participant will receive 10 mCi ±20% ^{18}F-fluciclovine injection diluted up to 10mL injected via the cannula with arms down, as an IV bolus injection followed by 10mL flush with normal saline solution. The participant will then be positioned supine in the scanner, with the arms above the head (if possible), and will be scanned in the direction of proximal-thigh to skull base. The time from end of injection of ^{18}F-fluciclovine injection to the start of imaging should be 3 to 5 minutes with a goal of 4 minutes.

11.3 ^{18}F-fluciclovine PET/CT acquisition

For the PET acquisition, participants will be imaged for approximately 25 minutes. For the CT acquisition, an unenhanced (no IV contrast) CT will be employed. Further details on the PET/CT acquisition are given in the Study Imaging Manual.

11.4 Image Transfer

Following the completion of PET/CT imaging at the study site, the scan data will be sent to the ACR Imaging Core Laboratory using either the ACR TRIAD software, by uploading anonymized files via an sFTP server, or on physical media by courier. Full details are in the Study Imaging Manual.

11.5 ^{18}F-fluciclovine image analysis

Image interpretation will be based on guidelines derived from an international ^{18}F-fluciclovine Reader Consensus Meeting held in June 2014 (10). All readers will undergo training in interpretation of ^{18}F-fluciclovine PET/CT scans, and will have a training set available for reference.

Primary evaluation and reporting of the PET/CT scan will be site-based (as per standard of care). Support for the local reader can be provided on request by contacting the Study Chair or Co-Chairs as listed in the protocol. The report provided to the treating physician and recorded in the eCRF will be that of the Site Investigator. The revised treatment decision will be made on the report of the Nuclear Medicine physician.

12 ADVERSE EVENT REPORTING AND DOCUMENTATION

12.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in

nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient eCRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.3 (June 14, 2010) will be used to assess and grade event severity, including laboratory abnormalities judged to be clinically significant. The severity grading is provided below (Table 1).

Table 1. CTCAE (V4.03) AE Severity Grading

Severity (Toxicity Grade)	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate daily activities. *
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care. **
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

*Daily activities refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

If the experience is not covered in the modified criteria, the guidelines shown in Table 2 below will be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe event is not necessarily serious.

Table 2. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

Death (5)	Death related to AE

Adverse Event Relationship to Study Drug

The relationship of an AE to study drug will be assessed using the following guidelines in Table 3.

Table 3. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

12.2 Serious Adverse Event (SAE)

An SAE is defined as any adverse event occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) on an SAE Report Form. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

All SAEs following ^{18}F-fluciclovine PET/CT must be reported on the SAE reporting form within 24 hours of the Site Study Team becoming aware of the event. All SAE information must be recorded on an SAE form and faxed, or scanned and emailed to:

Blue Earth Diagnostics

SAE E mail: Drugsafety@pharsafer.com

Tel: +44 (0) 1483 212155

Fax: +44 (0) 1483 212178

Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and faxed/emailed to the same address.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

12.3 Medical Monitoring

Dr Peter Gardiner MB ChB, MRCP, FFPM should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: +1-978-502-9098

E-mail: p.gardiner@blueearthdx.com

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Use of a camera which is not validated for the study or using an imaging technique different to that described in Section 11

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.
When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

14.1 Analysis of Primary Endpoint

For the evaluation of the primary endpoint (i.e., impact on therapy), questionnaires obtained pre- and post-^{18}F-fluciclovine PET/CT will be compared to calculate the fraction of cases with a change in management (versus no change in planned management). The 95% confidence interval will be calculated using the Exact method for a binomial distribution.

14.2 Analysis of Secondary Endpoints

For the evaluation of the secondary endpoint examining actual impact on therapy, questionnaires obtained pre-FACBC will be compared to treatment executed post-^{18}F-fluciclovine PET/CT to calculate the fraction of cases with a change in management (versus no change in planned management). For the estimation of detection rate, the proportion of the ^{18}F-fluciclovine -PET/CT positive results, 95% confidence interval will be calculated using the Exact method for a binomial distribution.

For each patient a comparison will be made of the results of the 18F-fluciclovine PET/CT results, any histopathology results, results of any other imaging and also for the clinical response to treatment(s) (standard of truth) by an Adjudication Panel. The PPV, NPV, sensitivity and specificity will be calculated, where possible, at lesion or regional or patient level. The PPV will be calculated separately for patients undergoing optional biopsy for (1) regional disease and (2) distant disease. The 95% confidence interval will be calculated using the Exact method for a binomial distribution. The Adjudication Panel will follow the Adjudication Manual that will prospectively document the processes to be used to determine a decision concerning the result of the 18F-fluciclovine PET/CT scan vs standard of truth.

Rates of disease detection (radiographic only and confirmed by pathology or MRI) will be described

14.3 Interim Analysis

When the study recruits the required number of 18F-fluciclovine -PET/CT positive patients, accrual will be stopped. A corresponding interim analysis for the primary aim will be planned and the study results will be submitted for potential public presentation prior to completion of all data collection and analyses. As subject recruitment will have been completed and the trial design will not be modified as a result of this interim analysis, no adjustment to the type I error is required.

14.4 Sample Size and Randomization

The primary objective of this study is to measure the fraction of patients for whom ^{18}F-fluciclovine -PET/CT alters intended management plan. The sample size consideration will be primarily based on binding the width of its 95% confidence interval, i.e., precision analysis. The prevalence rate of positive ^{18}F-fluciclovine -PET/CT findings in this population is assumed to be approximately 40%. About 30% of positive scans will be expected to change the physician's intended management plan. (11). The goal is to accurately assess the fraction of change in intended management in these FACBC positive patients. The table below lists the calculated sample sizes with respect to binding different 95% CI widths at the proportion of 30%. The Clopper-Pearson Exact method was used in PASS 12 (Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Confidence Level	Sample Size (N)	Target Width	Actual Width	Proportion (P)	Lower Limit	Upper Limit	Width if P = 0.5
0.950	341	0.100	0.100	0.300	0.252	0.352	0.109
0.950	**89**	**0.200**	**0.199**	**0.300**	**0.207**	**0.406**	**0.216**
0.950	40	0.300	0.300	0.300	0.166	0.465	0.324

If the goal is to bind the 95% CI width at 0.20 (i.e., half –length at 0.10), then 89 FACBC positive patients will be needed for the assessment of our primary aim. Since the positivity rate is assumed to be around 40% in the study population, we need to enroll 223 patients. Due to the random nature of the observed numbers of patients meeting the clinical criteria in a prospective study, a sample size correction technique attributed to (12) was applied. Our calculation shows that after adding 25 extra patients (i.e., 248 in total), we can be 90% sure to yield the required numbers of patients meeting the criteria. After taking 15% of potential data loss into consideration, we will need 292 patients in this study. This number

will be 1,059 for binding the 95% CI width at 0.10, and 138 for binding the 95% CI width at 0.30. If the bandwidth of 95% CI remains at 0.20, but the prevalence rate of positive ^{18}F-fluciclovine scans is lower than 0.40, it is estimated that we may need to enrol up to 330 patients into the study in order to obtain 89 evaluable patients.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.
Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials.

If a correction is required for an eCRF, the time and date stamp tracks the person entering or updating eCRF data and creates an electronic audit trail. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will be provided to the Investigator's site at the completion of the study.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archiving of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived. All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Monitoring and Auditing

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet.

Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the Sponsor. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to Blue Earth Diagnostics Ltd prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.
A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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Appendix 1: Schedule of Events

	Visit 1 - Screen up to 30 days before **Visit 2**	**Document Initial Management Plan**	**Visit 2 - Day of ^{18}F-fluciclovine PET/CT**				**Visit 3**	**Document Post 18F-Fluciclovine PET/CT Management Plan**	**End of Study**
			Pre-dose/ pre-scan	Immed. post scan	60 min post dose	120 min post dose			
Study Day	-30 to **Visit 2**	Prior to **Visit 2**	1				2	2-22	180 ± 28 days
Visit Location/Type	Treating Physician Office	NA	PET/CT Imaging Center				Phone Call	NA	NA
Assessments/Procedures									
Informed consent	X								
Inclusion/ exclusion criteria	X		X						
Medical history	X		X						
PCa history, including treatment	X								
Record PSA levels [1]	X								X
Record imaging studies [2]	X								X
Vital signs (heart rate and blood pressure)	X		X	X	X	X			
Height, weight			X						
Serum chemistry and hematology	X			X [3]					
Serum PSA	X								
Urinalysis, dipstick	X[4]								
EKG			X	X [3]					
Record biopsy results, if applicable									X
Injection site assessment			X	X	X	X	X		
AE assessment				X	X	X	X		X
Concomitant medication assessment	X		X						X
Document management/plan		Plan						Revised	Actual
Treatment response assessment									X

1 - Record all available PSA levels obtained prior to Visit 1 through End of Study; for non-prostectomy subjects, the PSA nadir and 2 times over nadir result must be documented in the record.
2 - Record all available imaging studies performed prior to Visit 1 through End of Study; negative or equivocal imaging within 60 days of Visit 1.
3 - Post-dose blood tests and EKG may be performed at the Imaging Center or within 7 days of the scan at another laboratory/site. [4]May be collected and tested at any time between screening and scan date