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1019 39th Avenue SE Suite 120 | Puyallup, WA 98374-2115
Office: (360) 252-2500 | **Toll Free:** (800) 562-4789
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Certificate of Approval

NOTIFICATION TO SPONSOR/CRO OF BOARD ACTION

BOARD ACTION DATE:	07/12/2017	**PANEL:**	1
WIRB PROTOCOL NUMBER:	20171334	**APPROVAL EXPIRES:**	07/12/2018
WORK ORDER NUMBER:	1-1017015-1	**CONTINUING REVIEW:**	Annually

SPONSOR: Desert Positron Imaging Center, LLC
PROTOCOL NUM: DMI Axumin-001
AMD. PRO. NUM:
TITLE:
A Phase II Study to Evaluate Axumin PET/CT for Risk Stratification for Laser Focal Therapy of Intermediate Risk Localized Prostate Cancer

APPROVAL INCLUDES:
Axumin Patient Brochure #16173555.0
Axumin™ (fluciclovine F 18) Injection Slideshow #16173560.0
Protocol

THE BOARD DIRECTED THE FOLLOWING INFORMATION BE PLACED ON THE WIRB CERTIFICATE OF APPROVAL DOCUMENT FOR ANY INVESTIGATOR APPROVED BY WIRB TO CONDUCT THIS RESEARCH:
The Board requires that all subjects must be able to consent for themselves to be enrolled in this study. This means that you cannot enroll incapable subjects who require enrollment by consent of a legally authorized representative.

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Although a participant is not obliged to give his or her reasons for withdrawing prematurely from the clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant's rights.

3. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate. (Due to the unique circumstances of research conducted at international sites outside the United States and Canada, when there is a local IRB and WIRB approved materials are reviewed by the local IRB and translated into the local language, the following requirements regarding consent forms bearing the WIRB approval stamp and regarding certification of translations are not applicable.)
    a. Use only the most current consent form bearing the WIRB "APPROVED" stamp.
    b. Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB unless other arrangements have been made and approved by WIRB.
    c. Obtain pre-approval from WIRB for use of recruitment materials and other materials provided to subjects.

4. Enrollment of limited readers and non-readers: unless consent has been waived or the protocol excludes enrollment of limited readers or non-readers, involve an impartial witness in the consent process when enrolling limited or non-readers and document the participation of the impartial witness using the designated signature lines on the WIRB-approved consent form. In the absence of designated signature lines, download the WIRB standard impartial witness form from www.wirb.com.

5. Enrollment of pregnant partners that do not have the capacity to consent for themselves and require consent be provided by a legally authorized representative: unless the protocol excludes the enrollment of pregnant partners that do not have capacity

to consent for themselves, obtain consent from the pregnant partners legally authorized representative and document consent using the pregnant partner legally authorized representative signature lines on the WIRB-approved consent form. In the absence of designated signature lines, download the WIRB standard legally authorized pregnant partner form from www.wirb.com.

6. Obtain pre-approval from WIRB for changes in research.

7. Obtain pre-approval from WIRB for planned deviations and changes in research activity as follows:
   - If the research is federally funded, conducted under an FWA, or is a clinical investigation of a drug or biologic, then all planned protocol deviations must be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].
   - However, if the research is a clinical investigation of a device and the research is not federally funded and not conducted under an FWA, then only planned protocol deviations that may adversely affect the rights, safety or welfare of subjects or the integrity of the research data should be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].

   The reason for these different requirements regarding planned protocol deviations is that the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) drug and biologic divisions have adopted the regulatory interpretation that every planned protocol deviation is a change in research that needs prior IRB review and approval before implementation; however, the FDA device division operates under a distinct regulation (See 21 CFR 812.150(a)(4).

   Deviations necessary to eliminate apparent immediate hazards to the human subjects should be reported within 10 days.

8. Report the following information items to the IRB within 5 days:
   a. New or increased risk
   b. Protocol deviation that harmed a subject or placed subject at risk of harm
   c. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
   d. Audit, inspection, or inquiry by a federal agency
   e. Written reports of federal agencies (e.g., FDA Form 483)
   f. Allegation of Noncompliance or Finding of Noncompliance
   g. Breach of confidentiality
   h. Unresolved subject complaint
   i. Suspension or premature termination by the sponsor, investigator, or institution
   j. Incarceration of a subject in a research study not approved to involve prisoners
   k. Adverse events or IND safety reports that require a change to the protocol or consent
   l. State medical board actions
   m. Unanticipated adverse device effect
   n. Information where the sponsor requires prompt reporting to the IRB

   Information not listed above does not require prompt reporting to WIRB.

   Please go to www.wirb.com for complete definitions and forms for reporting.

9. Provide reports to WIRB concerning the progress of the research, when requested.

10. Ensure that prior to performing study-related duties, each member of the research study team has had training in the protection of human subjects appropriate to the processes required in the approved protocol.

Federal regulations require that WIRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WIRB when the expiration date is approaching.

DISTRIBUTION OF COPIES:
Contact, Company
Bernadette M. Greenwood, Desert Positron Imaging Center, LLC

INVESTIGATIONAL PLAN

Sponsor: Desert Positron Imaging Center, LLC **Study No: 1176339**

Sponsor: Pr. No: DMI Axumin-001 **Protocol. No: 20171334**

A Phase II Study to Evaluate Axumin PET/CT for Risk Stratification for Laser Focal Therapy of Intermediate Risk Localized Prostate Cancer (NCT03373006)

CONFIDENTIALITY STATEMENT

This document contains information that is privileged or confidential and may not be disclosed unless Federal or State law or regulations require such disclosure. This information may be disclosed only to those persons involved in the study who have a need to know, but all such persons much be instructed not to further disseminate this information to others. These restrictions on disclosure will apply equally to all future information supplied which is indicated as privileged or confidential.

PROTOCOL OVERVIEW

Study Title:	A Phase II Study of Axumin (Fluciclovine F 18) for Evaluation of Patients Receiving Outpatient Magnetic Resonance Image-guided Laser Focal Therapy for Intermediate Risk, Localized Prostate Cancer.
Protocol Identifiers:	Sponsor: Desert Positron Imaging, LLC IRB Study No.: 1176339 Sponsor Pr. No.: DMI Axumin-001 IRB Pr. No.: 20171334
Study Purpose:	To investigate the utility of fluciclovine F 18 for evaluation For metastatic disease in men undergoing laser focal Therapy of prostate cancer and the impact on inclusion for a focal therapy cohort.
Study Design:	Open, single center, non-randomized, uncontrolled.
Number of Subjects:	20
Study Population:	Male patients, age 45 and older with MR image-able and biopsy proven prostate cancer.
Imaging Method:	PET/CT with fluciclovine F 18 Subjects will be receiving PET/CT imaging prior to thermal ablation of MR-image-able and biopsy proven areas of prostate cancer.

Visit Schedule:	Subjects will be imaged prior to laser focal therapy and Axumin PET/CT studies will be read the same day by a trained radiologist.
Safety Variables:	Complications, side-effects.
Efficacy Variables:	Obtain data on imaging results through interpreter findings as dictated in radiology report.

INVESTIGATORS

Principal Investigator:	John F. Feller, M.D. Desert Medical Imaging Center Indian Wells, CA
Co-Principal Investigator:	Adam Brochert, M.D. Desert Medical Imaging Center Indian Wells, CA
Co-Investigators:	Bernadette M. Greenwood, BSc Desert Medical Imaging Center Indian Wells, CA

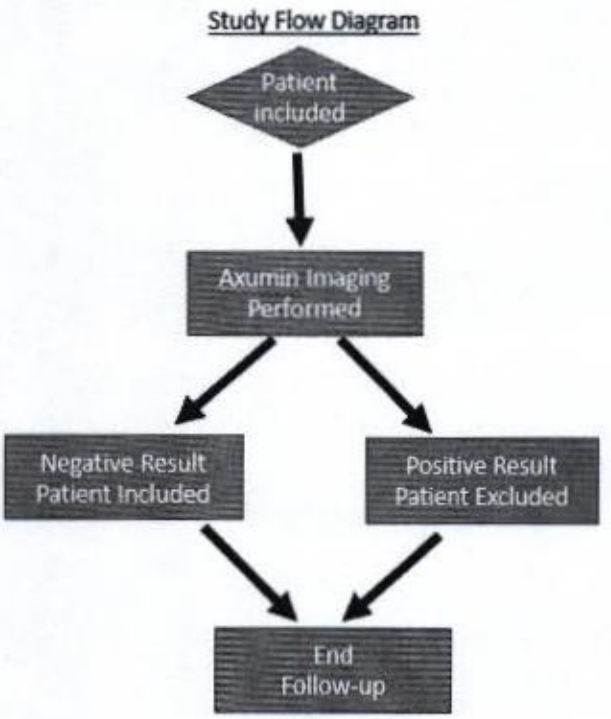
Manufacturer Representatives:

Karen E. Linder, Ph.D.

Sr. Manager, Clinical Science and Medical Affairs
Blue Earth Diagnostics Inc.
25 Burlington Mall Road
Suite 404
Burlington MA 01803

Email: k.linder@blueearthdx.com
Office: +609-751-0587
Cell: +609-608-6455

PROTOCOL FLOW-CHART



BACKGROUND

Radical prostatectomy and radiation therapy remain the gold standard therapeutic options for men with newly diagnosed prostate cancer[1,2]. However, because of increased awareness, screening, and measurement of serum PSA, prostate cancers are being detected at an earlier stage, meaning that radical whole-gland therapy is no longer considered necessary in every man with newly diagnosed prostate cancer. Renewed interest has emerged for active surveillance strategies, a concept of close observation with delayed curative intent if deemed necessary. Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program confirm the dramatic decline in downward stage migration between 1974-1985 and 1995-2000[3,4]. For this growing population of low-and intermediate- risk prostate cancer patients, active surveillance may be biologically or psychologically undesirable, yet the short- and long-term complications and co-morbidities associated with radical whole-organ therapies are still associated with a risk of treatment-related morbidity. Thus, there has been a growing interest in minimally invasive focal therapies for prostate carcinoma in select patients[3, 5-9]. As a result several minimally invasive thermal ablation methods, most prominently cryotherapy[10,11] and high-intensity focused ultrasound (HIFU)[11,12], have been developed and are currently being evaluated. As important as it is to ensure men who should be receiving focal treatment can have it, equally important is that men with high-grade or metastatic disease not receive it. Our aim is to assess the utility of Axumin for detection of metastatic disease in a population of men undergoing laser focal therapy for organ-confined prostate cancer.

Laser induced interstitial thermal therapy (laser) is a novel form of controlled targeted thermal ablation that may offer measurable advantages over other ablative therapies for focal prostate therapy. Because laser is magnetic resonance (MR) compatible, it enables an image advantage over other surgical or ablation techniques that utilize transrectal ultrasound to target and monitor treatment[13]. MR imaging provides excellent soft-tissue contrast and three-dimensional (3D) anatomical imaging in any arbitrary plane, which can help to improve treatment planning and targeting[14,15]. Additionally, MR-based temperature monitoring allows real-time feedback during MRI-guided thermal therapy[16] as both deposition of light energy and MR signal acquisition can be performed simultaneously without degradation in the MR signal. Also, being in the MR diagnostic environment allows use of post- treatment imaging to verify treatment delivery.

Because MR images clearly depict the prostate anatomy and the surrounding critical structures, MR imaging has been incorporated into planning for external- beam radiotherapy and brachytherapy of the prostate. In addition to these basic features, recently developed/emerging MR technologies, such as MR spectroscopy, MR diffusion imaging, and dynamic contrast-enhanced MR imaging, are promising technologies that may be used to identify regions of disease in the prostate and better target therapy, particularly as high-field scanners (3.0T) become available[14,15]. Clearly, there is a potential role for MR-guided ablation technology in the prostate[16]. Axumin may help further risk stratify men out of focal therapy if metastatic disease is present in men prior to undergoing focal therapy for prostate cancer.

DESCRIPTION OF DRUG

Mechanism of action:

Fluciclovine F 18 is a synthetic amino acid transported across mammalian cell membranes by amino acid transporters, such as LAT-1 and ASCT2, which are upregulated in prostate cancer cells. Fluciclovine F 18 is taken up to a greater extent in prostate cancer cells compared with surrounding normal tissues.

Pharmacodynamics:

Following intravenous administration, the tumor-to-normal tissue contrast is highest between 4 and 10 minutes after injection, with a 61% reduction in mean tumor uptake at 90 minutes after injection.

Pharmacokinetics:

Distribution: Following intravenous administration, fluciclovine F 18 distributes to the liver (14% of administered activity), pancreas (3%), lung (7%), red bone marrow (12%) and myocardium (4%). With increasing time, fluciclovine F 18 distributes to skeletal muscle.

Excretion: Across the first four hours post-injection, 3% of administered radioactivity was excreted in the urine. Across the first 24 hours post-injection, 5% of administered radioactivity was excreted in the urine.

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION All subjects will receive a single IV dose of 10mCi (370MBq) ±20%18F-fluciclovine immediately prior to PET scan.

Administration: Prior to PET/CT, 10mCi ±20% of 18F-fluciclovine will be administered as an IV bolus injection followed by a 10 mL saline flush, with the subject lying in a supine position. The dose will be injected into 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, including start of administration, injection site, date, prescription number, total volume and total radioactivity.

Packaging, Labeling and ordering: Fluciclovine F 18 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 18F-fluciclovine injection is not less than 95% during the shelf life of the product. The order for a specific patient at a specific date and time must be made to PETNET Solutions Centralized Scheduling Team (Tel: 1 877 473

8638) and will be delivered from the radiopharmacy to the imaging site by courier. Indian Wells PET/CT Center will keep records of all shipments of fluciclovine F 18 received, dispensing and disposal/destruction performed on site in accordance with ACR and NCRP guidelines (See Appendix C).

Imaging protocol.

1. The recommended dose is 370 MBq (10 mCi) administered as an intravenous bolus injection.
2. Begin PET scanning 3 to 5 minutes after completion of the Axumin injection
3. Proximal thigh to skull base x 5min/bed position caudocranial direction
4. Recon: Iterative
5. Iterations – 2, Subsets - 8
6. Filter Gaussian

Image interpretation: Image interpretation will be based on guidelines outlined in and derived from an international 18F-fluciclovine Reader Consensus Meeting held in June 2014 and will follow processes similar to those outlined on the on-line Axumin™ (fluciclovine F 18) Image Interpretation Training (https://www.snmmilearningcenter.org/Activity/4521746/ . Reader has undergone training in interpretation of 18F- fluciclovine PET/CT scans, and has a training set available for reference.

1. Non-Significant Risk Study

   Desert Positron Imaging has identified this investigation as a Non-Significant Risk (NSR) study.

PRELIMINARY WORK

1. CLINICAL STUDIES: The safety and efficacy of Axumin were evaluated in two studies (Study 1 and Study 2) in men with suspected recurrence of prostate cancer based on rising PSA levels following radical prostatectomy and/or radiotherapy.

Study 1 evaluated 105 Axumin scans in comparison to histopathology obtained by biopsy of the prostate bed and biopsies of lesions suspicious by imaging. PET/CT imaging generally included the abdomen and pelvic regions. The Axumin images were originally read by on-site readers. The images were subsequently read by three blinded independent readers. Table 4 of the package insert for Axumin shows the performance of Axumin in the detection of recurrence in each patient scan and, specifically, within the prostate bed and extra-prostatic regions, respectively. The results of the independent read were generally consistent with one another and confirmed the results of the on-site reads.

In general, patients with negative scans had lower PSA values than those with positive scans. The detection rate (number with positive scans/total scanned) for patients with a PSA value of less than or equal to 1.78 ng/mL (1st PSA quartile) was 15/25, of which 11 were histologically confirmed as positive. In the remaining three PSA quartiles, the detection rate was 71/74, of which 58 were histologically confirmed. Among the 25 patients in the first PSA quartile, there were 4 false positive scans and 1 false negative scan. For the 74 patients with PSA levels greater than 1.78 ng/mL, there were 13 false positive scans and no false negative scans. Study 2 evaluated the concordance between 96 Axumin and C11 choline scans in patients with median PSA value of 1.44 ng/mL (interquartile range = 0.78 to 2.8 ng/mL). The C11 choline scans were read by on-site readers. The Axumin scans were read by the same three blinded independent readers used for Study 1. The agreement values between the Axumin and C11 choline reads were 61%, 67% and 77%, respectively.

STUDY DESIGN

Purpose/Objectives

The primary purpose of this study is to evaluate the utility for use of Axumin to exclude men from laser focal therapy.

<u>Specific objectives:</u>

1. Primary Objectives – detection of metastases
2. Secondary Objectives – since fluciclovine will show positive uptake in regions of BPH and prostatitis in the intact prostate gland, prior mpMRI findings will be correlated to areas of uptake using Pi-RADS descriptors for likelihood of malignancy, prostatitis or benign prostatic hypertrophy

Potential Risks and Benefits of Axumin scanning.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The clinical trial database for Axumin includes data from 877 subjects including 797 males diagnosed with prostate cancer. Most patients received a single administration of Axumin, a small number of subjects (n = 50) received up to five administrations of the drug. The mean administered activity was 370 MBq (range, 163 to 485 MBq). Adverse reactions were reported in ≤1% of subjects during clinical studies with Axumin. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.

Study Population

Total target accrual will be 20 patients meeting the following criteria:

Inclusion Criteria

1. Male, 45 years of age or older.
2. Diagnosis of prostate adenocarcinoma.
3. Clinical stage T1a, T1b, T1c, T2a, T2b orT2c.
4. Gleason score of 7 (3+4 or 4+3).
5. PSA density less than 0.375.
6. One, two, or three tumor suspicious regions identified on multiparametric MRI.
7. Negative radiographic indication of extra-capsular extent.
8. Karnofsky performance status of at least 70.
9. Estimated survival of 5 years or greater, as determined by treating physician.
10. Tolerance for anesthesia/sedation.
11. Ability to give informed consent.

Exclusion Criteria

1. Presence of any condition (e.g., metal implant, shrapnel) not compatible with MRI.
2. Severe lower urinary tract symptoms as measured by an International Prostate Symptom Score (IPSS) of 20 or greater. ((http://www.urospec.com/uro/Forms/ipss.pdf)
3. History of other Primary non-skin malignancy within previous three years.
4. Diabetes.
5. Smoker.

Each subject will participate in the study the day of their PET/CT imaging procedure.

1. Subject Withdrawal and Loss to Follow-Up

Patients will be advised that they may withdraw from the study at any time and for any reason. In addition, the subject may be withdrawn from the study if the investigator deems the withdrawal of the subject to be medically necessary. If necessary, appropriate medical care will be provided. The reason for withdrawal must be recorded on the appropriate part of the case report form.

2. Methods Utilized to Assess Objectives

Methods Utilized to assess Primary Objectives

Evaluating procedural success with Axumin will be evaluated through expert radiologist interpretation and generation of PET/CT radiology report findings negative or positive for metastatic disease for the purpose of exclusion from focal therapy in an intermediate risk prostate cancer cohort.

3. Study Events

Study Events are defined as any negative events a patient experiences during the study (e.g., complications, treatment emergent signs and symptoms, new intercurrent illnesses). An intercurrent illness is defined as a disorder or other pathologic condition not reasonably associated with the drug under study. Data collected on each study event that occurs during the course of this clinical study, whether anticipated or not, will be recorded on the subjects' case report form. Every study event will be characterized according to the following: onset, duration, severity, relation to therapy, treatment of the event, and the outcome associated with the event.

The Investigator must report to the drug manufacturer, within 24 hours of becoming aware, any adverse experience that is associated with the use of the drug that is either serious and/or unexpected.

Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the study.

For this study, a serious adverse experience is one that suggests a significant hazard, contraindication, side effect, or precaution. It includes any experience that is fatal, life-threatening, permanently disabling, requires inpatient hospitalization or prolongation of hospitalization, or results in persistent or significant disability/incapacity. An unexpected adverse experience is one that is not identified in nature, severity, or frequency in Section 5.2.1 Potential Risks.

If an unanticipated adverse drug effect occurs, the investigator will immediately contact drug manufacturer.

To report suspected adverse reactions to Axumin, site will call 1-855-AXUMIN1 (1-855-298-6461)

In addition, sponsor will contact manufacturing representative

Karen E. Linder, Ph.D.
Sr. Manager, Clinical Science and Medical Affairs
Blue Earth Diagnostics Inc.
25 Burlington Mall Road
Suite 404
Burlington MA 01803

Email: k.linder@blueearthdx.com

Office: +609-751-0587
Cell: +609-608-6455

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1. APPENDIX A: Prescribing information for Axumin