PROTOCOL SYNOPSIS

Study Title	The Impact of Fluciclovine (^{18}F) PET on the Management of Participants with Prostate Cancer Following Negative or Equivocal PSMA PET Imaging at the Time of Biochemical Recurrence
Phase	Phase 4
Sponsor	Blue Earth Diagnostics
Funding Organization	Blue Earth Diagnostics
Study Design	This is a prospective, multi-institutional, Phase 4 study to assess change in management (CIM) following fluciclovine (^{18}F) imaging in participants with prostate cancer who have a negative or equivocal prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scan at the time of any biochemical recurrence (BCR).
Study Rationale	While PSMA PET has rapidly become the imaging modality of choice in men for staging of newly diagnosed prostate cancer, as well as in men with previous treatment and evidence of BCR (as evidenced by an increase in prostate-specific antigen [PSA]), not all men will have lesions detectable by PSMA PET. This is particularly evident in the BCR setting with lower PSA levels (i.e. <0.5 ng/mL), where, based on previous studies, detection rates vary between 35% and 64% (LOCAMETZ® USPI; POSLUMA® USPI; PYLARIFY® USPI) depending on which PSMA PET tracer is used (i.e. indicating that the "undetectable rate" lies between 36% and 65%). PSMA PET radiopharmaceuticals bind to PSMA, which is generally over-expressed on prostate cancer cells. Fluciclovine (^{18}F) is licensed in 35 countries worldwide under the trade name Axumin® for PET imaging in men with BCR of prostate cancer based on elevated PSA levels following primary treatment. As an amino acid analog depicting tumor amino acid uptake, its mechanism of action is very different than that of PSMA PET radiopharmaceuticals. It may, therefore, offer an alternative to assess the location and extent of recurrent disease, especially in participants where PSMA PET results are negative or equivocal. Participants with BCR following definitive management are faced with a myriad of potential salvage treatment options. Identifying the site(s) of recurrence could lead to more precise treatment planning, which has the potential to improve survival and quality of life (QoL). A recent study demonstrated a 56% detection rate using fluciclovine (^{18}F) PET imaging in participants with a recent negative or equivocal PSMA PET scan (Mallak et al, 2025; Eakin et al, 2025; data on file). This is in addition to other studies that have reported detection rates of 18% to 38% (Pernthaler et al, 2019; Calais et al, 2019) and prior published case reports (Ulaner et al, 2024; Nguyen et al, 2023). CIM in participants with BCR (agnostic of PET scan status) undergoing fluciclovine (^{18}F) scans has been previously studied and reported to be 59% to 64% (LOCATE[1], FALCON[2]); however, the clinical impact of such CIM in this specific population has not been previously studied.

[1] NCT02680041

[2] EudraCT Number: 2015-000625-37

Primary Objectives and Outcome Measures	**Objective:** To assess the impact of fluciclovine (^{18}F) PET/computed tomography (CT) imaging on participant management.	**Outcome Measure:** Percentage of participants with any recorded CIM following a fluciclovine (^{18}F) PET/CT scan.
Secondary Objectives and Outcome Measures	**Objectives:** 1. To further assess the impact of fluciclovine (^{18}F) PET/CT imaging on participant management.	**Outcome Measures:** For those participants with a CIM: • Percentage of participants with a recorded minor or major CIM following a fluciclovine (^{18}F) PET/CT scan. • Summary of the CIM groups following a fluciclovine (^{18}F) PET/CT scan.
	2. To assess the detection rates for fluciclovine (^{18}F) PET/CT.	Participant-level and region-level (prostate bed, pelvic lymph nodes [PLNs], other) detection rates.
	3. To assess the detection rates for fluciclovine (^{18}F) PET/CT stratified by PSA levels.	Participant-level and region-level (prostate bed, PLNs, other) detection rates stratified by PSA levels.
	4. To assess the impact of fluciclovine (^{18}F) PET/CT positivity/negativity on participant management.	Assess the impact of positive/negative fluciclovine (^{18}F) PET/CT on: • Percentage of participants with any recorded CIM. For those participants with a CIM: • Percentage of participants with a recorded minor or major CIM. • Summary of CIM groups.
Tertiary Objectives and Outcome Measures	**Objectives:** 1. To explore the impact of fluciclovine (^{18}F) PET/CT on initiating subsequent treatment.	**Outcome Measures:** • Time to initiation of subsequent treatment stratified by CIM group. • Time to initiation of subsequent treatment stratified by CIM group and PET/CT positivity.
	2. To explore the impact of fluciclovine (^{18}F) PET/CT on initiating subsequent systemic therapy.	• Time to initiation of subsequent systemic therapy stratified by CIM group. • Time to initiation of subsequent systemic therapy stratified by CIM group and PET/CT positivity.

	3. To explore the impact of fluciclovine (^{18}F) PET/CT on the diagnosis of subsequent distant metastatic disease.	• Time to diagnosis of subsequent distant metastatic disease stratified by CIM group. • Time to diagnosis of subsequent distant metastatic disease stratified by CIM group and PET/CT positivity.
	4. To explore the impact of fluciclovine (^{18}F) PET/CT on participant QoL.	• Changes in patient-reported outcomes (PROs) assessed by Functional Assessment of Cancer Therapy – Prostate (FACT-P) and EuroQol five-dimensional questionnaire (EQ-5D-5L) stratified by CIM group. The PROs will be measured from baseline up to the end of study: – Change from baseline in FACT-P total score. – Proportion of participants with improvement in the FACT-P total score. – Change from baseline in EQ-5D-5L index score. – Proportional of participants with improvement in the EQ-5D-5L index score. • Change in PROs assessed by FACT-P and EQ-5D-5L stratified by CIM group and PET/CT positivity.
Safety Objectives and Outcome Measures	**Objectives:** 1. To assess treatment-emergent adverse events (TEAEs).	**Outcome Measures:** • Incidence of TEAEs.
Study Sites	This study will be conducted at up to 10 sites in the United States (US).	
Investigational Product(s), Including Control Products	The investigational product for this Phase 4 study is fluciclovine (^{18}F), which is licensed in the US under the trade name Axumin®. It will be administered at 10 mCi ± 2 mCi (370 MBq ± 74 MBq) as a bolus intravenous (i.v.) injection as per the United States Prescribing Information (USPI). There is no control product in this single-arm study.	
Study and Participant Duration	**Study Duration:** up to 6.5 years, including an 18-month enrollment period and post-enrollment follow-up period of up to 5 years. **Participant Duration:** Screening period of up to 45 days, then 6-monthly Standard of Care (SoC) follow-up post-fluciclovine (^{18}F) PET/CT for up to 5 years.	
Planned Primary and Post-hoc Analyses	The primary analysis will be performed after enrollment is complete and data are available for all primary and secondary endpoints. Further analyses for the tertiary objectives will be completed every 6 months after the primary analysis for up to 5 years.	

STATISTICS Primary Analysis Plan	Comparisons between the intended management plan and the revised management plan will be categorized as 'no change', 'minor change', or 'major change', with a recorded CIM including both minor and major changes. The primary analysis will describe the number, percentage, and exact 95% confidence intervals (CIs) of participants with any CIM after the fluciclovine (^{18}F) scan.
Rationale for Number of Participants	Based on the aforementioned studies (see Study Rationale), the detection rate of fluciclovine (^{18}F) in this participant population with negative or equivocal PSMA PET scans has been described to be between 18% and 56%. CIM in participants with BCR (agnostic of PET scan status) undergoing fluciclovine (^{18}F) scans has been previously studied and reported to be 59% to 64% (LOCATE[1], FALCON[2]), with differing rates of CIM between positive and negative scans. For the primary objective of CIM, a minimum of 127 participants with complete primary endpoint data will be required to allow for a width of ±8% in a two-sided 95% CI. This is based on the conservative assumption that 30% of participants will have a treatment change, given the aforementioned detection rates of fluciclovine (^{18}F) PET/CT in this scenario and the anticipation that positive fluciclovine (^{18}F) scans are more likely to drive CIM. The aim is to recruit 142 participants for this study, based on an anticipated primary endpoint drop-out rate of 10%.

6 PARTICIPANT SELECTION

6.1 Study Population

Participants with suspected BCR of prostate cancer following prior curative intent treatment and a negative or equivocal PSMA PET scan (with any FDA-approved PSMA PET tracer) will be eligible for participation in this study provided that they fulfill all of the inclusion criteria and none of the exclusion criteria.

Given the nature of the disease under investigation, only adult male participants will be included in this study. Participants of all races and ethnic groups are eligible for this study.

6.2 Inclusion Criteria

1. Participants must be males aged ≥18 years at Screening.
2. Participant with suspected BCR of prostate cancer (see Inclusion Criterion #3 below) following prior curative intent treatment and a negative or equivocal PSMA PET scan with any FDA-approved PSMA PET tracer (must be within 45 days prior to Visit 2 [fluciclovine (^{18}F) PET/CT scan]), regardless of findings on conventional imaging.
3. Participants suspicious for a biochemically recurrent prostate cancer with a detectable or rising PSA after definitive therapy on the basis of:
   - Post-radical prostatectomy (with or without adjuvant or salvage radiation therapy): PSA that is ≥0.2 ng/mL (completed >6 weeks after surgery) or
   - Post-radiation therapy (with or without ADT): Increase in PSA level that is ≥2.0 ng/mL above the nadir PSA level and rising PSA is confirmed on consecutive PSA determinations.
4. Men who are sexually active with women of childbearing potential (WOCBP), must agree to use a highly effective method(s) of contraception for 24 hours post-fluciclovine (^{18}F) injection (see Appendix 2).
5. Participant must provide written informed consent before any study-specific procedures or interventions are performed.
6. Ability of the participant to comply with planned study procedures.

6.3 Exclusion Criteria

1. Participants with known metastatic castrate resistant prostate cancer.
2. Participants with any medical condition (including intercurrent illness and uncontrolled serious infection) or circumstance (including receiving an IP) that the investigator believes may compromise the data collected or lead to a failure to comply with the study requirements.
3. Participants who are planned to have an x-ray contrast agent or any other PET radiotracer within five physical half-lives of the first PET radionuclide prior to the study fluciclovine (^{18}F) PET/CT scan.
4. Participants participating in an interventional clinical trial within 30 days and having received an IP five physical half-lives prior to the study fluciclovine (^{18}F) PET/CT scan.

5. Participants with known hypersensitivity to the active substance or to any of the excipients of fluciclovine (^{18}F).
6. Participants who have received salvage therapy for the current episode of BCR.
7. Participants who initiate cancer treatment (systemic or radiation therapy) or who have started any supplements or herbal medications intended to treat cancer between the PSMA PET and fluciclovine (^{18}F) PET/CT scans.