

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208054Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	April 5, 2016
<b>From</b>	Nushin Todd MD, PhD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 208054 (priority review; 505 (b)(1) application)
<b>Supplement#</b>	Original
<b>Applicant</b>	Blue Earth Diagnostics
<b>Date of Submission</b>	September 28, 2015
<b>PDUFA Goal Date</b>	May 27, 2015
<b>Proprietary Name / Non-Proprietary Name</b>	Axumin / Fluciclovine 18 F
<b>Dosage form(s) / Strength(s)</b>	Injection / 370 MBq (10 mCi)
<b>Applicant Proposed Indication(s)/Population(s)</b>	Positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Axumin is indicated for PET imaging in men with suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following prior treatment

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CMC – Chemistry, Manufacturing and Controls

OSE – Office of Surveillance and Epidemiology

DMEPA – Division of Medication Error Prevention and Analysis

DRISK – Division of Risk Management

## 1. Benefit-Risk Assessment

Axumin (fluciclovine F 18) is a new molecular entity diagnostic radiopharmaceutical. It is indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated prostate specific antigen (PSA) levels following treatment. There is a clinical need for a radiopharmaceutical with good diagnostic performance in detecting sites of prostate cancer recurrence and which can be routinely used in clinical practice. Fluciclovine fulfills this need and has demonstrated to be safe and effective for its proposed use. I recommend approval of fluciclovine for use in the detection of prostate cancer in men with biochemical recurrence.

Prostate cancer is the most commonly diagnosed non-cutaneous neoplasm in men. It is estimated that in 2016 there will be approximately 181,000 new cases and 26,000 deaths from prostate cancer in the United States. Up to one third of men treated with curative intent following a diagnosis of primary prostate cancer will experience recurrent disease within 10 to 15 years post therapy.

Recurrence of disease is typically based on serial measurement of PSA. Determining the location of the recurrence is critical, as this defines optimal choice of therapy. The diagnostic accuracy of standard imaging tests for the identification of sites of recurrence, however, is low. More accurate, non-invasive imaging techniques for the detection of recurrent tumor are needed.

Currently, there are two FDA approved radiotracers for the detection of prostate cancer, but due to performance and/or production restrictions, these agents have limited clinical utility. A third radiotracer is a glucose analogue which has established utility in a wide variety of tumor settings. But this tracer is rapidly excreted into the bladder and thus obstructs visualization of the prostatic bed region. The availability of a radioactive ligand with good diagnostic performance for visualizing prostate cancer and which can be routinely used in clinical practice would be a marked advance on currently available technologies.

Fluciclovine is a synthetic L-leucine analogue radiolabeled with fluorine 18 (F 18). It has a 110 minute half-life and is actively transported into mammalian cells by amino acid transporters. It is not metabolized, nor is it incorporated into newly synthesized proteins. Following injection, fluciclovine is preferentially taken into cells that have enhanced amino acid transport, such as tumor cells that require increased amounts of amino acids to support increased metabolism and proliferation. PET imaging studies have demonstrated that fluciclovine is preferentially taken into prostate carcinoma compared with surrounding normal tissue and that visualization of the image is not obscured by bladder uptake.

The efficacy of fluciclovine was based on re-analyses of data from two prospective studies in men with suspected recurrence of prostate cancer based on rising PSA levels following radical prostatectomy and/or radiotherapy. The pivotal study evaluated 105 fluciclovine scans in comparison to histopathology obtained by biopsy of the prostate bed and biopsies of lesions suspicious by imaging. The images were originally read by on-site readers. The images were also randomized and re-read by three blinded, independent readers in the re-analysis. The results of the independent read were generally consistent with one another and confirmed the results of the on-site reads.

The performance of fluciclovine is affected by PSA levels. Among the 16 scans in patients with PSA levels less than or equal to 1 ng/mL, there were 8 false positive scans and 1 false negative scan. Among the 83 scans in patients with PSA levels greater than 1 ng/mL, there were 4 false positive scans and no false negative scans.

The second study evaluated the concordance between 96 fluciclovine and a comparator radiotracer in men with suspected prostate cancer recurrence based on rising PSA levels following treatment. The images were read on by on-site readers. The images were also randomized and re-read by three blinded, independent readers. The agreement values between fluciclovine and the comparator agent for the original on-site reads and the three blinded readers were 78%, 61%, 67%, and 77%, respectively.

In totality, the evidence supports the efficacy of fluciclovine for biochemically recurrent prostate cancer.

The safety database was sufficient to adequately characterize the safety profile of fluciclovine. Safety information was reviewed for 837 patients exposed to fluciclovine in seven clinical trials. There were no deaths, no serious adverse events, and no significant safety issues identified that was attributed to fluciclovine administration. The observed adverse events and radiation dosimetry estimate of 8.2 mSv per dose are similar to other radiodiagnostic imaging agents, including those with FDA approval for use in prostate cancer patients. The safety profile of fluciclovine is acceptable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"> <li>• In the United States, prostate cancer is the most commonly diagnosed non-cutaneous neoplasm in men, with an estimated 181,000 new diagnoses and 26,000 deaths in 2016. It is the second leading cause of death from cancer in men.</li> <li>• Up to one third of men treated for prostate cancer will experience recurrent disease within 10 to 15 years following primary treatment.</li> </ul>	<p>Prostate cancer is common and the second highest cause of cancer death in men.</p>
<a href="#">Current Treatment Options</a>	<ul style="list-style-type: none"> <li>• Biochemical recurrence is recognized by rising serum PSA levels post treatment. In men with suspected prostate cancer recurrence, identifying the site of tumor recurrence is paramount as this defines optimal choice of therapy. The imaging evaluation of a patient with a biochemical recurrence usually consists of CT, MRI, and bone scan. However, the diagnostic accuracy of standard imaging tests for the identification of sites of recurrence is low.</li> </ul>	<p>More accurate, non-invasive diagnostic imaging tests for the detection and localization of recurrent prostate cancer are needed.</p> <p>The availability of a radioactive ligand with good diagnostic performance for visualizing prostate cancer and that can be routinely used</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• In recent years, nuclear imaging and PET scans have been utilized. Currently, there are only two FDA approved radioactive ligands for the detection of sites of recurrent prostate cancer. One product is a SPECT agent approved in 1999, but the detection rate of this agent is low and the procedure has been largely superseded by PET. In 2012, FDA approved a radiotracer with an acceptable diagnostic performance in prostate cancer. However, the short half-life of this isotope (20 minutes) limits its use to medical centers with on-site production capability.</li> <li>• More recently, PET imaging using radiolabeled fluorine 18 has made substantial contribution to clinical oncology practice. Its ability to be taken up by cells with high glucose metabolism, such as cancer cells, permits imaging differentiation of tumors from normal tissue. Additionally, its 110 minute half-life allows for efficient commercial distribution. However, this PET tracer is not ideal for imaging prostate cancer. Because of the rapid excretion of the tracer into the bladder, visualization of the prostatic bed region is obstructed.</li> </ul>	<p>in clinical practice would be a marked advance on currently available technologies.</p>
<u>Benefit</u>	<ul style="list-style-type: none"> <li>• The clinical utility of fluciclovine was demonstrated in the proposed patient population by comparison to histology standard of truth and two FDA approved radiodiagnostic imaging agents.</li> <li>• Fluciclovine demonstrated acceptable diagnostic performance in imaging prostate cancer lesions both within and outside the prostate bed region. In the submitted published studies (Emory and Bologna data), fluciclovine detected more lesions in men with suspected disease recurrence than FDA approved imaging agents for the same indication.</li> </ul>	<p>The totality of evidence supports the efficacy of fluciclovine for the detection of prostate cancer recurrence in men with elevated PSA levels post therapy.</p>
<u>Risk</u>	<ul style="list-style-type: none"> <li>• Safety information was reviewed for 837 patients exposed to fluciclovine in seven clinical trials. No significant safety concerns were identified in the review of this application.</li> <li>• The radiation dosimetry estimate of 8.2 mSv is similar to other approved radiodiagnostic imaging agents and is lower than one of the FDA approved radiodiagnostic agents with a prostate cancer</li> </ul>	<p>No significant safety concerns were identified and radiation dosimetry estimates are comparable to approved radiodiagnostic agents.</p>

<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
	indication.	
<a href="#"><u>Risk Management</u></a>	<ul style="list-style-type: none"><li>• There were no significant safety concerns identified in the review of the application that would warrant consideration for Risk Evaluation and Mitigation Strategy (REMS).</li></ul>	No safety issues were identified to warrant a Medication Guide, pharmacovigilance in the postmarketing setting, or REMS consideration.

## 2. Background

On September 28, 2015, Blue Earth Diagnostics, Ltd (applicant) submitted a New Drug Application (NDA) for Axumin (fluciclovine F 18) for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on prostate specific antigen (PSA) levels. The applicant seeks licensure to market the product under Section 351 of the PHS Act and approval under section 505(b)(1) of the Federal Food, Drug and Cosmetic Act.

Axumin (fluciclovine F 18) is a new molecular entity (NME) and is not marketed in the United States. It is a synthetic L-leucine analogue radiolabeled with fluorine 18 (F 18). Fluciclovine has a 110 minute half-life and is actively transported into mammalian cells by amino acid transporters (AAT). It is not metabolized, nor is it incorporated into newly synthesized proteins. Following injection, fluciclovine is preferentially taken into cells that have enhanced amino acid transport, such as tumor cells that require increased amounts of amino acids to support increased metabolism and proliferation. PET imaging studies have demonstrated that fluciclovine is preferentially taken into prostate carcinoma compared with surrounding normal tissue and that visualization of the image is not obscured by bladder uptake.

The applicant has requested priority review of the NDA for fluciclovine based on: the indication (detection of prostate cancer in men with elevated blood PSA levels following prior treatment); the seriousness of the condition (prostate cancer recurrence); and, for providing a significant improvement in the safety or effectiveness of the diagnosis of a serious condition. The FDA reviewed the request and granted a priority review designation.

- *Therapeutic context*

In 2015, an estimated 221,000 men in the United States were diagnosed with prostate cancer, making it the most commonly diagnosed non-cutaneous neoplasm in men in this country. The average age at diagnosis is 66 years and the age-adjusted incidence rate is 1 case per 7 men per year, with 6 of 10 cases occurring in men older than age 65. The American Cancer Society estimates that in 2016, over 27,000 men will die of prostate cancer.

Up to 33% of men treated for prostate cancer will experience recurrent disease within 10 to 15 years following primary treatment. In a vast majority of cases, evidence of recurrent disease is based on serial measurement of prostate specific antigen (PSA) alone and is referred to as biochemically recurrent (BCR) prostate cancer. In patients with BCR prostate cancer, it is critical to determine the location of the recurrence, as this helps guide the optimal choice of therapy.

Currently, the available imaging modalities include CT, MRI, PET/CT, radionuclide bone scans, and TRUS for the prostate bed\*. The diagnostic accuracy of these imaging tests for the identification of sites of prostate cancer recurrence is suboptimal. In the literature, it is estimated that almost 90% of the standard battery of imaging tests, including CT/MR and bone scintigraphy, may be negative. More accurate, non-invasive imaging techniques for the detection of recurrent tumor are therefore needed.

\*CT=computed tomography; MRI=magnetic resonance imaging; PET/CT=positron imaging tomography/CT;  
TRUS=transurethral ultrasonography

Nuclear imaging techniques have been utilized in this population for a number of years. ProstaScint (<sup>111</sup>Indium capromab pendetide), a single photon emission computerized tomography (SPECT) agent, was approved in 1999 for the diagnostic imaging of post-prostatectomy patients with a rising PSA, but this procedure is difficult to use with perceived inadequate diagnostic performance and is therefore no longer widely adopted.

The most widely used PET agent is the glucose analogue F 18 fludeoxyglucose (FDG) which has established utility in a variety of tumors. FDG is not generally used in prostate cancer because of low glucose uptake due to indolent growth of many prostate cancers and the high urinary excretion of FDG, making good quality diagnostic imaging difficult.

PET imaging with C-11 choline was approved for clinical use in 2012 and has been shown to improve detection of cancer recurrence in men with BCR prostate cancer. However, the 20 minute half-life of C-11 limits the use of this agent only to medical centers with on-site C-11 production capability.

- *Regulatory background*

The development of fluciclovine was conducted under Investigational New Drug (IND) application number 107707, which was initially submitted to the FDA on April 1, 2010. Key aspects of the regulatory history of fluciclovine and the interactions between the applicant and FDA are summarized below:

<b>Date</b>	<b>Regulatory Activity</b>	<b>Meeting Results</b>
March, 2014	Transfer of ownership	Applicant notified FDA of the change in sponsorship of IND 107707 from GE Healthcare to Blue Earth Diagnostics Ltd.
June, 2014	Type C guidance meeting	Applicant agreed to submit the full protocol of the pooled analysis study with case report forms, an imaging charter for the re-read study, and statistical analysis plans for major studies
July, 2014	Advice letter	Discussions held regarding clinical and statistical issues on completed clinical studies
Feb & May, 2015	Type C meetings	Continued discussions for planned analyses of clinical and statistical results of clinical studies
August, 2015	Pediatric waiver requested	FDA has agreed to waive pediatric studies
September, 2015	Submission of NDA and request for priority review	Application was accepted and given priority review designation

### 3. Product Quality

Chemistry, Manufacturing and Controls (CMC) recommends approval of the application once clearance of selected manufacturing facilities is finalized. At the time of completion of the product quality reviews, three of the four designated facilities had been inspected and determined to be in acceptable status. The fourth facility, however, was pending classification of compliance status. During the CDTL review, report of the acceptable status of the last facility was submitted. I concur with the approval recommendation provided by CMC.

- *General product quality considerations*

The drug substance, fluciclovine ( $^{18}\text{F}$ ), is produced as an aqueous solution (b) (4)

The quality of the drug substance is controlled during the manufacture and testing of the drug product. Due to the short half-life of the  $^{18}\text{F}$  fluorine radioisotope, each batch is prepared on the day of clinical use.

Both, the drug substance and drug product, are manufactured using (b) (4)  
The final drug product sterilization is assured by (b) (4)  
subsequently tested for integrity.

Review of the commercial manufacturing process demonstrated consistent and acceptable drug product batches. The control strategies employed during the entire manufacturing process, from controls used for in-process materials (b) (4) to the finished product, adequately assured quality of the PET drug product. Assurance of the final product was also demonstrated through bacterial endotoxin and sterility testing.

Stability testing to determine the shelf-life and storage conditions of fluciclovine was assessed. Radiochemical purity, a crucial parameter when evaluating degradation of a radioactive molecule, was demonstrated to remain within the acceptance criteria over the shelf-life of fluciclovine, independent of the storage temperature. Fluciclovine has been granted a 10 hour shelf-life under controlled room temperature (20 to 25 °C) storage conditions.

- *Facilities review/inspection*

Four manufacturing facilities were inspected. All were four sites were determined to be acceptable for the operations proposed in the submission.

- *Other notable issues*

During the review process, three noteworthy CMC issues came to prominence requiring further discussions with the applicant. The issues were the following: 1) high level of drug product impurity; 2) pH of final product; and, 3) technical information for the container closure system of the drug product from one of the manufacturers.

- 1) A large component of the chemical content of the final product is a structurally related substance to fluciclovine. This main related substance observed in the final product is (b) (4)

[REDACTED]

The CMC review team expressed concerns that the limits proposed for the structurally related impurity, (b) (4) was much higher than the amounts found in the batches used in the clinical trials. There was also concern that (b) (4) may compete with fluciclovine for receptor binding sites and thus impede fluciclovine's performance.

Discussions were held with the applicant regarding the impurity content of the product. On January 11, 2016, the applicant made a commitment to investigate reducing the amount of (b) (4) impurity in the drug product. The applicant conveyed that preliminary work will start soon and a report of the development work will be provided to the FDA, along with discussions and agreements of future steps, within 12 months of NDA approval.

- 2) The second product quality issue necessitating further discussion and information from the applicant related to the pH limits for the final product. The applicant had proposed pH range of (b) (4) to 6. The lower limit of the proposed pH was considered by the CMC review team to be (b) (4) for intravenous injection. The CMC team requested justification for the lower pH limit of (b) (4) and recommended the applicant consider raising the lower pH limit. On January 11, 2016, the applicant agreed to change the pH range to 4 to 6 from the originally proposed range of (b) (4) to 6.
- 3) Technical information from the drug product container closure system from (b) (4) was not provided in the NDA. The applicant was asked to provide this information before the review deadline. In an email dated March 10, 2016, (b) (4) submitted the necessary information showing that the container closure system is acceptable for use.

#### 4. Nonclinical Pharmacology/Toxicology

The Pharmacology Toxicology review team recommends approval of the NDA. I concur with their recommendation.

- *General nonclinical pharmacology/toxicology considerations*

The nonclinical safety of fluciclovine has been assessed in single dose acute studies in the rat and dog, repeat dose 14 day studies in the rat, dog and rabbit, and *in vitro* and *in vivo* genotoxicity assays. Local tolerance has been assessed in the rabbit. (b) (4) is the largest related

substance to fluciclovine present in drug product and a series of studies have been specifically conducted to assess its safety. Definitive studies were all performed in accordance with GLP. Acute toxicity studies in rat and dog, and rat only for (b) (4), did not reveal specific target organs of toxicity. Intravenous dosages up to 1000 µg/kg were administered and it was concluded that the maximum non-lethal dose is greater than this. Similarly, repeat dose studies in rats, rabbit and dogs of 14 days duration at intravenous dosages up to 1000 µg/kg did not indicate target organ toxicity.

Acute toxicity and repeat dose toxicity indicate that a dosage up to 1000 µg/kg fluciclovine represents a no observed adverse effect level (NOAEL). This represents a human dose equivalent of (b) (4) for studies in the rat and (b) (4) for studies in the dog. Based on a maximum human dose of 2 µg/mL fluciclovine and a maximum volume of 5 mL to a 70 kg person, the human dose is approximately (b) (4). The NOAEL in the rat is over 1000 times the human dose and the dog NOAEL is almost 4000 times the human dose.

*In vivo* micronucleus tests at dosages up to 1000 µg/kg and *in vitro* mutagenicity studies at high concentrations with and without metabolic activation indicate fluciclovine and (b) (4) are neither clastogenic nor mutagenic.

Carcinogenicity, reproductive and developmental toxicity studies have not been performed.

- *Other notable issues*

Intravenous and paravenous irritancy was evaluated in rabbits. Based on histopathological evaluation, fluciclovine was not an irritant by either route of injection. However, review of the study revealed that vigorous struggling was noted in 3 of 6 rabbits when the product was injected subcutaneously. The vigorous struggling has been attributed to pain caused by the low pH (3.12) and high osmotic pressure of the formulation (1.8 times that of saline).

After discussions with the applicant during the review of the NDA, the acceptance criteria for the lower limit of the pH range was increased to 4 (from originally proposed (b) (4)). The new pH range of 4 to 6 for the final drug product is expected to be physiologically more compatible for intravenous injection and therefore less irritating.

## 5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology information provided in the application and recommends approval. I concur with their recommendation.

- *General clinical pharmacology considerations*

No clinical pharmacology studies were conducted by the applicant. Information pertinent to the pharmacological assessment of fluciclovine came from data from the Emory University study and published literature. Biodistribution data came from GE Healthcare and (b) (4).

### *Dose*

The recommended dose of fluciclovine is 10 mCi by intravenous injection in a total volume not exceeding 5 mL. The mass dose is 2 ug/mL (max of 10 ug). No dose finding studies were conducted by the applicant or apparent in the literature. Fluciclovine doses used in clinical trials ranged from 162 to 485 MBq (4.4 to 13.1 mCi). In a clinical study from Oslo University, investigators used a dose of 200 MBq and found that the images obtained were suboptimal. Other studies used higher doses of fluciclovine with better image resolution. While the clinical pharmacology team realizes that an optimal dose of fluciclovine has not been identified, they conclude the proposed microdose of 370 mBq (10 mCi) is effective with an acceptable safety profile. Optimization of fluciclovine dose, therefore, is not necessary.

PET scanning should begin from 3-5 minutes after completion of the injection administration (target 4 minutes), imaging should start from proximal thigh and proceed to the base of the skull, while typical total scan time is between 20-30 minutes, increasing the duration of acquisition over the pelvis may increase the sensitivity of detection of disease (e.g. acquire for 5 minutes for the first two bed positions over the pelvis and  $\geq 3$  minutes per bed position for the remaining bed positions).

### *Biodistribution*

Fluciclovine is rapidly distributed throughout the body, with uptake being highest in organs with high levels of amino acid uptake, particularly the liver, pancreas, and bone marrow. There is very little brain uptake. With increasing time post injection, uptake in skeletal muscle increases. No clinically significant differences in the biodistribution of fluciclovine were noted between men and women.

### *Metabolism, Elimination and Food Effect*

There is no evidence of any significant metabolism of fluciclovine from *in vitro* and *in vivo* studies. Fluciclovine and (b) (4) do not bind to plasma proteins. The principle route of elimination is renal. Urinary excretion, however, appears to be slow with <5% of the dose eliminated within the first 6 hours of administration in normal individuals. On the basis of activity washout from the liver and the pancreas, and assuming that all of this activity enters the duodenum through hepatobiliary and pancreatic transport, fluciclovine excretion via the GI tract is estimated to be less than 10 %. However, it should be noted that it is difficult to accurately assess the excretion profile of fluciclovine as excretion is only measurable by estimating radioactivity; fluciclovine has a half-life of approximately 110 minutes and the product is no longer detectable within 24 hours.

Radioluminography data indicate the radioactivity in plasma and urine is predominantly in the form of unmetabolized drug. The vast majority of the population studied was elderly men with reduced renal function. Based on a comparison of data from this population to safety reported in studies involving the small number of younger men and women, there was no obvious effect on renal function. It appears reasonable to use the product, if indicated, regardless of renal function.

Although fluciclovine is exclusively for intravenous administration, there is a theoretical possibility of a food effect as the drug is transported by amino acid transporters. While there can be an increase of plasma amino acids (by approximately 25%) 1 to 2 hours post high protein

ingestion, it is very unlikely that such an increase in total circulating amino acids would have any significant effect on fluciclovine transport and resulting image quality.

- *Drug-drug interactions*

No drug interaction studies were conducted by the applicant or reported in the literature. Fluciclovine is not subject to metabolism and is not a substrate for renal drug transporters and therefore drug interactions would not be expected. Additionally, because only a single microdose is administered, fluciclovine is unlikely to have an impact on drug interactions.

- *Intrinsic factors*

Sub-group analyses revealed no obvious impact of age, race, or prior cancer treatment on fluciclovine performance. No dose adjustments are recommended.

- *ECG and QTc*

Fluciclovine is administered only once and in a microdose amount, therefore, the likelihood of QT or QTc prolongation is remote. Review of ECG and QTc information of patients in the clinical studies revealed no abnormalities or trends indicative of a safety signal for fluciclovine.

- *Other notable issues*

None

## **6. Clinical Microbiology**

Not applicable.

## **7. Clinical/Statistical- Efficacy**

The efficacy of fluciclovine was evaluated in re-analyses of data from two prospective studies in men with suspected recurrence of prostate cancer based on rising PSA levels following radical prostatectomy and/or radiotherapy. The clinical and statistical review teams have determined the applicant has provided substantial evidence of effectiveness of fluciclovine for the proposed indication. I concur with their recommendation.

- *Pivotal Studies*

### Emory Study (R01)

Prospective, open label, single center, and single dose study comparing fluciclovine to comparator (<sup>111</sup>Indium capromab pendetide) in men with biochemical recurrence of prostate cancer. The standard of truth (SOT) was histology. Pathological evaluations of the prostate bed and tumor deposits outside the prostate bed were used as a reference standard to establish truth. Images were read on-site by two readers (consensus if disagreement). Analysis of histology was

also on-site. The study was conducted at Emory University and the results were published in *The Journal of Urology* (Schuster et al, volume 191; pages 1446-1453), in May, 2014.

#### BED001 (Emory Data)

This was a re-analysis of the imaging data from the previously conducted R01 study at Emory University. The applicant obtained ownership of the data, developed a statistical analysis plan, and re-analyzed the diagnostic performance of fluciclovine as compared to histology (SOT). The primary objective was to assess the performance of fluciclovine for detecting recurrence of prostate carcinoma in the prostate bed validated by histology of prostate bed biopsies and patient follow up. Original on-site image interpretations were re-evaluated. Comparisons were made of image results to histology (SOT). No comparisons were made with <sup>111</sup>In capromab pendetide.

#### BED002 (Emory Data)

This study was as a re-read of images obtained from the R01 study at Emory University. The applicant, having obtained ownership of the R01 data, developed a reader training program, statistical analysis plan and compared the performance of fluciclovine as compared to histology SOT following independent, blinded, centralized reads of the R01 study images. The primary objective was to describe the performance of fluciclovine for detecting recurrence of prostate carcinoma in the prostate bed validated by pathologic analysis of prostate bed biopsies and patient follow up. No comparisons were made with <sup>111</sup>In capromab pendetide.

- *Supportive Studies*

#### Bologna Study: Re-analyses of Bologna Data to BED001 and BED002

The applicant submitted additional studies in support of the proposed indication. The bulk of these data originate from the University of Bologna. Results were published in *Clinical Nuclear Medicine* (Nanni et al, volume 48; pages 1017-1020), in 2015.

The Bologna study compared fluciclovine to an FDA approved imaging agent, C-11 choline, for detecting prostate cancer recurrence in patients presumed positive for disease. The applicant re-analyzed the Bologna data and included the results to the BED001 study. The applicant also conducted an independent, blinded, re-read of the images from the Bologna data and provided those results to the BED002 study.

The Bologna data is being considered as supportive because there was no truth standard employed in the study.

- *Study Results and Assessment of Effectiveness*

#### Approach to Assessing Efficacy

The investigation of prostate cancer recurrence in men with elevated PSA post-treatment, which is the primary objective of the application, consists of histological evaluation of lesions detected through test images, control images, other techniques, or agreement between test images and control images. Since patient management is largely dependent on whether recurrence is limited to the prostate bed or is additionally or exclusively outside this area (extra-prostatic), lesion detections are assigned a location, (prostate bed; extra-prostatic region), and test efficacy then consists of correctly evaluating recurrence for these two regions, and also at patient level.

For the SOT and at patient level: if all lesions gathered through biopsies and evaluated by histopathology are negative, the patient has disease negative status for the primary analyses. If any lesion is positive by histology, then the patient is positive for recurrence. Likewise, the histological status of lesions in the prostate bed or extra-prostate region determines the SOT for those regions. The critical element here is that there is no SOT that evaluates the patient's status independent of histological evaluations of lesions detected by test, control, or other images or methods that direct biopsies. Therefore, it is not possible to measure the standard performance characteristics such as sensitivity and specificity of fluciclovine.

The applicant chose positive predictive value (PPV) as the primary endpoint, which can be defined at several levels: lesion/region/patient. The statistical review team chose the patient level as the critical and clinically meaningful level relevant to efficacy considerations. The clinical review team focused on two measures at patient level, namely PPV and modified sensitivity. They chose these measures for two reasons: 1) PPV is the applicant's primary endpoint (which is affected by prevalence of 70% in this study); and 2) some measure that acts as a corrective to the stand-alone PPV is necessary, and modified sensitivity is meaningful here. Modified sensitivity is defined as proportion among patients with SOT positive lesions who were SOT positive for fluciclovine.

Evaluations relevant to the proposed indication of fluciclovine require a truth standard. The Emory study (R01) data source was determined to have an SOT for the primary statistical analyses, which provided both a comparator diagnostic and histological confirmation for image findings. One significant limitation of the Emory results was the absence of blinded reads of the data.

Emory (R01) Study:

This study was conducted under Investigational New Drug application (b) (4). Please refer to Dr. Davis's review for details of the study. Summary results of the Emory study are presented in Table 1.

**Table 1: Emory R01 Published Results with Histology Truth Standard**

	<b>Fluciclovine</b>	<b><sup>111</sup>In Capromab Pentetide</b>
<b>Prostate Bed</b>		
True Positives	55	41
True Negatives	12	17
False Positives	18	13
False Negatives	6	20
<b>Extra-Prostatic Region</b>		
True Positives	22	4
True Negatives	29	26
False Positives	1	4
False Negatives	18	36

The number of false negative fluciclovine scans totaled 24 as compared to 56 false negative scans with <sup>111</sup>In capromab pendetide. This is noteworthy given that every patient scanned was known to have prostate cancer recurrence based on elevated PSA levels. Thus, with perfect imaging test, every patient would have a lesion identified. Given the imperfect nature of prostate cancer imaging tests, the fact that more sites of recurrence were identified with the investigational tracer (more true positives, less false negatives) compared to the approved imaging test (with histology truth standard) supports the added clinical utility of in this population.

BED001 and BED002 Emory Data

The patient population consisted of men with a mean age of 67 years. Approximately 19% of the group was African American and the remainder being predominantly white. PSA values prior to scan ranged from 0.05 to 45 ng/mL (mean 6 ng/mL). PSA doubling time, where calculable (N=98), averaged 12 months (median 8.7 months). All patients had negative bone scans prior to fluciclovine imaging. Of note, the results of the scans and biopsy analyses were available to the study team during the study period.

Analyses of the applicant’s data for both the BED001 (on-site reads) and BED002 (centralized re-reads) clinical studies were conducted by the statistical and clinical review teams. The data compare favorably with each other which support the integrity and accuracy of the data from the original published Emory study (R01), showing that the original on-site image interpretations are very similar to the blinded, independent, centralized applicant interpretations (Table 2).

**Table 2: Efficacy Analyses for Prostate Bed Region**

	<b>On-Site (BED001)</b>	<b>Reader 1 (BED002)</b>	<b>Reader 2 (BED002)</b>	<b>Reader 3 (BED002)</b>
<b>N (Regions)</b>	97	98	97	96
<b>True Positive</b>	57	58	56	47
<b>False Positive</b>	27	29	26	15
<b>True Negative</b>	12	10	12	24
<b>False Negative</b>	1	1	3	10
<b>Sensitivity</b>	98%	98%	95%	83%
<b>Specificity</b>	31%	26%	32%	62%
<b>PPV (positive predictive value)</b>	68%	67%	68%	76%
<b>NPV (negative predictive value)</b>	92%	91%	80%	71%

BED001 re-analysis and BED002 re-read data for the extra-prostatic sites was also verified by the primary statistical reviewer (Table 3). These data also compare favorably with each other and further support the integrity and accuracy of data from the published Emory study (R01).

**Table 3: Efficacy Analyses for Extra-Prostatic Regions**

	<b>On-Site (BED001)</b>	<b>Reader 1 (BED002)</b>	<b>Reader 2 (BED002)</b>	<b>Reader 3 (BED002)</b>
<b>N (Subjects)</b>	29	28	28	25
<b>True Positive</b>	27	25	26	22
<b>False Positive</b>	2	2	2	2
<b>True Negative</b>	0	0	0	0
<b>False Negative</b>	0	1	0	1
<b>Sensitivity</b>	27/27 (100%)	25/26 (96%)	26/26 (100%)	22/23 (96%)
<b>Specificity</b>	0/2	0/2	0/2	0/2
<b>PPV (positive predictive value)</b>	27/29 (93%)	25/27 (93%)	26/28 (93%)	22/24 (92%)
<b>NPV (negative predictive value)</b>	0/0	0/1	0/2	0/1

Subgroup Analyses

There were no significant differences in efficacy observed in subpopulation analyses including age, gender, or race. Differences, however, were observed for PSA quartiles, as shown in the table below.

**Table 4: Results of PSA Quartile on a Subject Level**

<b>PSA Value (ng/mL)</b>	<b>≤ 1.05</b>	<b>&gt; 1.05 to ≤ 3.98</b>	<b>&gt; 3.98 to ≤ 8.9</b>	<b>&gt; 8.9</b>
<b>Subjects (N=99)</b>	16	31	25	27
<b>True Positive</b>	3	23	20	23
<b>True Negative</b>	4	5	4	4
<b>False Positive</b>	8	3	1	
<b>False Negative</b>	1	0	0	
<b>PPV</b>	27%	88%	95%	100%
<b>NPV</b>	80%	100%	100%	100%

In these re-analyses, among the 13 subjects (not counting any subject twice) with false positive or false negative images, 9 belonged to  $PSA \leq 1.05$ . These data suggest that fluciclovine imaging performance may not be reliable among subjects with lower blood PSA levels.

#### Re-analyses BED001 and BED002: Bologna Data

The applicant collected subject level data from 88 patients enrolled in the C-11 choline comparison study conducted at Bologna University into the BED001 and BED002 database. Several of these subjects underwent repeat scans giving a total of 96 scan pairs for analysis. As this is a within subject dataset, there was complete overlap of subject demographic features in this group. Subjects were white men, mean age of 67 years, and a PSA level ranging from 0 - 23 ng/mL (mean 2.9 ng/mL). PSA doubling time (N=70) averaged 6.4 months. Patients underwent scanning using C-11 choline within 1 week of fluciclovine scan.

No SOT was employed, therefore, the true sensitivity and specificity of the test and comparator imaging agents in this population is not known. Therefore, for purposes of this review, the Bologna data are considered supportive.

The raw agreement values of on-site reads and 3 blinded reads were 78%, 61%, 67%, and 77%, respectively. A “spread” in agreement was noted between blinded and on-site reads (61% to 78%). The applicant justified this spread by calling the Bologna images difficult to read. The applicant’s results were not verified by the statistical review team.

The results indicate acceptable agreement rates with the comparator. Similar to the Emory published study, the Bologna publication showed that fluciclovine was positive in more patients than the comparator FDA approved imaging agent.

- *Conclusions on the Substantial Evidence of Effectiveness*

The applicant’s submitted clinical data meets regulatory standards with regards to evaluating the drug in the intended patient population for the proposed indication. The controlled clinical studies, BED001 Emory and BED002 Emory, allow for the reasonable conclusion that fluciclovine has sufficient accuracy in identifying prostate cancer in the proposed patient population. These studies compared fluciclovine PET imaging results to both a truth standard (histology) and an FDA approved imaging agent indicated for use in prostate cancer patients. Results indicate favorable positive predictive value for the drug when compared to histology for identifying sites of disease recurrence in the prostate bed, pelvic region and distant soft tissues. The consistency of favorable results among the initial study publication, the BED001 re-analysis study and the BED002 re-read study provide confidence that fluciclovine perform as well or better than the two approved radio-diagnostic agents indicated for use in prostate cancer patients.

In addition, the supportive studies, BED001 Bologna and BED002 Bologna, compared the investigational agent to another FDA approved imaging agent and estimated agreement of fluciclovine to this approved agent for detecting prostate cancer recurrence in subjects presumed positive for disease (no truth standard). These results show acceptable agreement rates with the comparator. And similar to the original Emory publication, the original Bologna published paper showed that fluciclovine was positive in more patients than the FDA approved imaging agent.

The applicant also submitted data on exploratory studies of fluciclovine performance in primary prostate cancer. The information provided was preliminary, limited in scope, and was outside the proposed indication sought for approval. The efficacy review, therefore, focused on data relegated to fluciclovine performance for imaging detection in prostate cancer recurrence.

In totality, the evidence supports the efficacy of fluciclovine imaging in detection of prostate cancer in men with biochemical recurrence.

## 8. Safety

Dr. Phillip Davis conducted the safety review for fluciclovine. Please refer to his clinical review for detailed information regarding the safety data.

- *Safety database*

Safety information was reviewed for 837 patients exposed to fluciclovine in seven clinical studies and comprised of the following:

- 12 healthy volunteers, 9 men and 3 women
- 596 men diagnosed with recurrent prostate cancer
- 201 men diagnosed with primary prostate cancer
- 28 patients diagnosed with other types of cancer (breast cancer, n=9; parathyroid adenoma, n=3; glioma, n=14; and other, n=2).

The doses of fluciclovine administered ranged from 94 to 485 MBq, with most subjects receiving the target dose of approximately 370 MBq. The vast majority of subjects received a single dose and 50 subjects received more than one scan.

Overall, the size of the safety database was sufficient to adequately characterize adverse events.

- *Data integrity and submission quality*

Safety evaluations performed varied by institution but included reporting of treatment emergent adverse events (TEAEs), pre and post treatment changes in laboratory hematology, biochemistry and urinalysis, pre and post treatment ECGs and vital signs. Procedures for recording and reporting adverse events (AEs) were defined in the data safety monitoring plans and fulfilled local IRB requirements and FDA regulations. No issues were identified concerning the integrity or quality of the safety data.

- *Key safety results*

No deaths were reported in any of the clinical studies. There were no serious AEs that were considered to be related to fluciclovine. There were no reported dropouts or discontinuations for any of the studies due to adverse drug effects.

### *AEs*

Adverse events considered to be related to fluciclovine included: dysgeusia, injection site reactions (such as pain and redness at injection site), nausea, malaise, constipation, and headache. These events were reported occurring in  $\leq 0.2\%$  of patients exposed to fluciclovine. There were no reports of hypersensitivity reactions in the safety database.

### *Laboratory findings*

Although small changes in laboratory evaluations were noted in several cases, there was no consistent or clinically significant change in laboratory values following fluciclovine administration in either healthy volunteers or patients with prostate cancer. Changes observed were mostly fluctuations of small magnitude within the laboratory normal range. In some patients with prostate cancer, transient increases in serum creatinine were noted. These were attributed to dehydration of patients prior to the scan period rather than to an effect of fluciclovine on renal function.

### *Vital signs and ECG*

There were no significant effects noted on vital signs or ECG variables reported in the safety data collection.

- *Submission-specific safety issues*

The effective radiation dose resulting from the administration of 370 MBq for an adult weighing 75 kg is about 8.2 mSv. The estimated radiation dosimetry is comparable to numerous approved radiodiagnostic agents and nuclear medicine procedures.

- *Safety summary*

The safety database was sufficient to adequately characterize the safety profile of fluciclovine. Safety information was reviewed for 837 patients exposed to fluciclovine in seven clinical trials. There were no deaths, no serious adverse events, and no significant safety issues identified that was attributed to fluciclovine administration. The observed adverse events and radiation dosimetry estimate of 8.2 mSv per dose are similar to other radiodiagnostic imaging agents, including those with FDA approval for use in prostate cancer patients. The safety profile of fluciclovine is acceptable.

## **9. Advisory Committee Meeting**

No Advisory Committee was necessary or convened for this drug product.

## **10. Pediatrics**

The applicant requested a full waiver from the requirements of the Pediatric Research Equity Act (PREA) on the basis that prostate cancer does not occur in pediatric patients and therefore

necessary studies would be impossible or highly impractical. The Agency's Pediatric Review Committee (PeRC) discussed the application and agreed with the requested waiver.

## **11. Other Relevant Regulatory Issues**

No substantive regulatory issues remain to be resolved at the time of writing this CDTL review.

## **12. Labeling**

Proposed product labeling was reviewed by all disciplines involved in the review of this application as well as by the Labeling Development Team (LDT).

The proposed proprietary name, Axumin, was found acceptable by the Division of Medication Error Prevention Analysis (DMEPA) and the review team. Changes were made to carton and container labeling to minimize risk of medication error. Every section of the prescribing information (PI) was revised in order for labeling to align with regulations, guidances and best labeling practices.

The review team's labeling edits and comments were conveyed to the applicant. Final agreement on product labeling was pending at the time of this CDTL review.

## **13. Postmarketing Recommendations**

No safety concerns were identified in the review of this product that necessitates the implementation of a Risk Evaluation and Management Strategies (REMS) plan. The Division of Risk Management (DRISK) and DMIP have independently derived at the conclusion that a REMS is not needed to ensure the benefits of Axumin outweigh its risks. The risks associated with the use of Axumin are adequately addressed in labeling.

Likewise, Postmarketing Requirements (PMRs) and Commitments (PMCs) are not necessary. The available clinical data adequately characterizes the safety profile of Axumin and additional postmarketing studies are not likely to reveal new concerns.

## **14. Recommended Comments to the Applicant**

None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NUSHIN F TODD  
04/05/2016