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RESEARCH**

APPLICATION NUMBER:

208054Orig1s000

MEDICAL REVIEW(S)

Clinical Review
 Phillip B. Davis, MD
 Priority Review 505(b)(2) NDA
 Axumin (¹⁸F-Fluciclovine)

CLINICAL REVIEW

Application Type	505 (b) (1)
Application Number(s)	208054
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Reviewer Name(s)	Phillip B. Davis, MD
Review Completion Date	2/26/2016
Established Name	18F-Fluciclovine
(Proposed) Trade Name	Axumin
Applicant	Blue Earth Diagnostics
Formulation(s)	Solution
Dosing Regimen	10mCi via intravenous injection
Applicant Proposed Indication(s)/Population(s)	PET Imaging men with suspected prostate cancer recurrence.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence. Axumin PET imaging may identify sites of prostate cancer.

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Glossary

AE	adverse event
BSA	Bovine Serum Albumin
BRF	Benefit Risk Framework
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OSI	Office of Scientific Investigation
PCA	Prostate Carcinoma
PrEC	Prostate Epithelial Cells
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	post-marketing commitment
PMR	post-marketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Fluciclovine F18 Injection is a new molecular entity diagnostic radiopharmaceutical developed at Emory University for use with PET imaging of men with prostate cancer

- Proposed proprietary name: Axumin
- Proposed dosing regimen: 10 mCi (370 MBq) via intravenous injection; maximum mass dose is 10 micrograms.
- Proposed indication: Axumin is a radioactive diagnostic agent for positron emission tomography (PET) imaging (b) (4) men with suspected prostate cancer recurrence. (b) (4)

(b) (4)
based (b) (4) on elevated blood prostate specific antigen (PSA) levels following (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

Benefit-Risk Summary and Assessment

Fluciclovine F18 Injection is indicated for PET imaging in men suspected of having prostate cancer recurrence based upon PSA levels. In these patients, Axumin PET imaging may identify sites of prostate cancer recurrence which will assist clinicians in selecting the most appropriate therapy for their individual patients. I recommend approving this radio-diagnostic agent for the proposed indication.

Prostate cancer is the 2nd most common cancer in men worldwide; in 2016 predictions are there will be 181,000 cases and 26,100 deaths in the United States. Workup and staging (as well as restaging) of men with prostate cancer often involves imaging tests. However, currently available imaging modalities are imperfect; this is partially supported by observations that 10% of men treated for localized prostate cancer are eventually be discovered to have biochemical disease recurrence with negative findings on conventional imaging tests.

In the submitted clinical data, the sponsor has shown with reasonable confidence that Fluciclovine will provide clinical utility in the proposed patient population by allowing clinicians to identify sites of prostate cancer recurrence. Submitted data allows us to be confident that positive Fluciclovine PET/CT imagines in these patients will likely represent true sites of prostate cancer; we have verified acceptable positive predictive values for all regions analyze, as well as acceptable sensitivity/specificity estimates for the prostate bed region. I highlight that we do not have true performance measures in the form of sensitivity and specificity for Fluciclovine in the extra-prostatic regions including the pelvic soft tissues, bones and other distant organs/soft tissues as negative image results in these regions were usually not followed by biopsy for determination of true clinical status. However, I firmly believe the data supports Fluciclovine providing added value to the available FDA approved imaging agents for use in prostate cancer patients by Fluciclovine PET/CT identifying sites of disease when other conventional imaging is negative. In such cases, Fluciclovine F18 Injection will enable clinicians to more accurately stage patients and select the most appropriate therapeutic options.

The safety profile of Axumin is very favorable based on the fact that it is a synthetic L-leucine amino acid analogue that is administered as a onetime micro-dose (10 micrograms), the drug has been shown to be well tolerated (no deaths, no serious adverse events) in clinical studies enrolling over 800 patients who fit the proposed patient population, and the estimated radiation dosimetry of 8 mSv is acceptable and consistent with other FDA approved imaging agents.

The reviewer believes the applicant has submitted sufficient evidence to support the clinical utility and safety of Fluciclovine F18 Injection for the proposed indication in men with suspected prostate cancer recurrence. The sponsor's clinical studies allow a reasonable estimation of the

tracer’s performance by both comparisons to an FDA approved imaging agent with histology standard of truth and also by measuring agreement with a second FDA approved imaging agent indicated for use in prostate cancer recurrence. The performance estimates from the pivotal clinical studies are acceptable to this reviewer and support the conclusion that Fluciclovine F18 Injection will provide added value and clinical utility for clinicians in the workup of patients suspected of having prostate cancer recurrence. The clinical efficacy data in the context of 1) the need for new imaging agents with acceptable diagnostic performance for identifying prostate cancer, a potentially fatal disease, and 2) a favorable safety profile that leads the clinical team to have no significant safety concerns for the single micro-dose administration of Axumin, allows us to confidently recommend approval of this new imaging agent for use in the evaluation of prostate cancer patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> In the United States, prostate cancer is the second most commonly diagnosed cancer and cause of cancer death in men with an estimated 221,000 new diagnoses and 25,500 deaths in 2015; it is the fifth leading cause of cancer death in men worldwide. 	<p>Based upon recent statistics, prostate cancer is a common cancer and frequent cause of cancer death in men.</p>
<u>Current Workup & Treatment Options</u>	<ul style="list-style-type: none"> In patients with suspected prostate cancer recurrence, clinicians must determine the site(s) of cancer in order to select the most appropriate and beneficial treatment for these patients. Current imaging tests fall short of providing certainty to this process and most are referred to in the literature as investigational or as having debatable clinical value in this patient population 	<p>Upon review of the literature and guidelines for prostate cancer workup and treatment, it is clear to me that current imaging tests have lower than ideal performance in imaging this neoplasm. A need exists for additional non-invasive diagnostic tests with acceptable performance which add value to the current available tools for identifying and localizing prostate cancer recurrence.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	<ul style="list-style-type: none"> The clinical utility of using Axumin PET/CT was demonstrated in the proposed patient population of men with prostate cancer recurrence by comparison to histology standard of truth and two FDA approved radio-diagnostic imaging agents (1 PET and 1 SPECT agent). Axumin demonstrated acceptable diagnostic performance in terms of positive predictive value, true positives, false positives in imaging prostate cancer lesions in the prostatic bed region and outside the prostate bed. In the original published studies (Emory and Bologna data), Axumin was positive in more patients than the FDA approved imaging agents in men with suspected disease recurrence based on current standard of care laboratory testing. 	<p>Axumin will provide added clinical utility to the available approved diagnostic imaging agents in helping clinicians evaluate subjects suspected of having prostate cancer recurrence.</p>
<u>Risk</u>	<ul style="list-style-type: none"> The submitted data clearly shows there are no significant safety concerns related to the single micro-dose use of Axumin in this patient population. The radiation dosimetry estimate of 8.2 mSv is similar to other approved radio-diagnostic imaging agents and is lower than one FDA approved radio-diagnostic agent with a prostate cancer indication 	<p>The reviewer believes there is minimal risk associated with a single dose administration of Axumin in the proposed patient population; this is based on no significant adverse events seen in the submitted clinical studies and the acceptable radiation dosimetry estimates.</p>
<u>Risk Management</u>	<ul style="list-style-type: none"> In the reviewer’s opinion, the risks of a single micro-dose administration of Axumin are well described and there are no uncertainties that need further attention or investigation. 	<p>No risk management actions are recommended.</p>

2 Therapeutic Context

2.1. Prostate Cancer Overview

Background and Initial Evaluation

Prostate cancer is the 2nd most common cancer in men worldwide. In 2012, it estimated there were 1,100,000 cases and 307,000 deaths from the disease. In the United States in 2016, predictions are there will be 181,000 cases and 26,100 deaths.

“The clinical behavior of prostate cancer ranges from a microscopic, well-differentiated tumor that may never be clinically significant to an aggressive, high grade cancer that ultimately causes metastases, morbidity, and death”. Presenting symptoms may include urinary frequency, urgency, nocturia, but these are often more related to concomitant benign prostate enlargement. Most patients with early stage disease actually have no symptoms related to prostate cancer. Although an uncommon initial presentation, patients with metastatic disease may complain of bone pain from osseous involvement.

Widespread use of screening in the developed world, including the use of Prostate Specific Antigen (PSA), has helped clinicians to diagnose prostate cancer while it is still confined to the prostate bed, thus allowing improved chance for cure.¹

In newly diagnosed prostate cancer, the factors which impact therapeutic options include:

- Anatomic extent of disease (tumor, node, metastasis)
- Histologic grade (the Gleason score)
- Serum PSA level
- Potential benefits/risks of each treatment option
- The individual patient’s overall medical condition and preferences

Risk Stratification

Initial staging typically includes physical examination (digital rectal examination (DRE)), serum PSA level, and pathological evaluation (including Gleason score) of the initial biopsy. Selection of imaging studies to assist with prostate cancer staging is dependent on the initial clinical picture. Radionuclide bone scan is the current standard of care for evaluating the bones for metastatic disease. Computed tomography [CT] of the abdomen and pelvis and/or endorectal coil MRI are used in some patients to assess for extension of cancer outside the prostate bed, depending on the initial clinical presentation. As the case for the workup and staging of other cancers, imaging tests and the staging system are imperfect in nature; this is partially supported by the observation that up to 10-30% of men eventually have disease recurrence following

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radical prostatectomy for “localized” prostate cancer.

Clinical staging of primary prostate cancer staging is based on the American Joint Committee on Cancer (AJCC) recommendations which evaluates and describes the extent of disease including the primary tumor (T), lymph nodes (N), and distant metastases (M). In 2010, pretreatment serum PSA and Gleason score were included in the staging schema to help place patients in prognostic categories. This information is then combined with patient characteristics (age, life expectancy, overall medical condition, symptoms, and patient preferences) to select the best therapy based on the individual patient. It should be noted that the clinical staging system is definitely imperfect and prone to errors in its individual parts, including inaccuracies with DRE, variability in Gleason grade, and prostate biopsy sampling errors.

Following radical prostatectomy, the resected prostate tissue is evaluated to determine the pathologic stage. This may yield additional information missed during clinical staging (higher Gleason grade, extension outside the prostate capsule, regional node involvement) which can change treatment plans for individual patients.^{2,6}

Clinical Workup for Recurrent Disease

Following prostatectomy, PSA should be undetectable as PSA is both sensitive and specific for prostate tissue. Patients discovered to have serum PSA ≥ 0.2 ng/mL (with positive repeats) following prostatectomy are presumed to have disease recurrence and must be evaluated for recurrent disease (AUA guidelines). Following radiation therapy, patients with a serum PSA ≥ 2.0 ng/mL above nadir (with positive repeats) are also assumed to have residual/recurrent disease and require further evaluation. The main prognostic parameters in patients with rising PSA following definitive therapy include the PSA level, PSA velocity, Gleason score on the original biopsy, and tumor stage at the time of original definitive treatment. If recurrent disease is confirmed to be localized, aggressive therapy can achieve prolonged disease-free survival.

The review notes that a low percentage of patients presenting with only a PSA rise following definitive therapy will be found to have metastatic disease, thus imaging is often reserved for higher risk patients. Imaging in these patients allows ruling out bone metastases, extensive pelvic disease or other metastatic deposits which will eliminate the option for local salvage therapy and necessitate systemic chemotherapy. This highlights the value of diagnostic imaging agents that can accurately detect local, regional and distant prostate cancer lesions in patients at risk for metastatic disease.

Available imaging modalities include CT, MRI, PET/CT, radionuclide bone scan, and TRUS for the prostate bed. CT appears to be of limited value unless PSA levels are above 10 ng/mL. One study in 86 men post prostatectomy with biochemical recurrence showed that CT of the pelvis provided new information in only 9% of subjects; average PSA values in subjects with positive scans were 27.4 versus 4.9ng/mL for negative scans.

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Technetium 99 radionuclide is still considered the standard of care for evaluating the bones, although it is described as having “limited sensitivity”. In a study of 93 men who were evaluated for a PSA-only recurrence post radical prostatectomy, the lowest serum PSA associated with a positive bone scan (in the absence of adjuvant ADT) was 46 ng/mL. A logistic regression model showed the chance of a positive bone scan was less than 5% percent unless serum PSA was > 40 ng/mL. Up To Date states that “bone scans are probably unnecessary unless there are symptoms referable to bone or the PSA is greater than 10 ng/mL”.

The clinical use of MRI in men with biochemical recurrence is not established, but is being investigated as a tool in patients with prior radiation therapy to identify seminal vesicle invasion or extra-prostatic extension prior to decisions regarding salvage prostatectomy. Studies are small for this purpose with widely variations in the reported sensitivity and specificity for identifying seminal vesicle involvement. Some investigators believe MRI may also complement treatment planning by outlining the prostatic bed and/or localizing small foci of recurrent disease in men undergoing salvage radiation therapy following radical prostatectomy.

FDG-18 PET/CT for the evaluation of recurrent prostate cancer is a topic of debate and is currently investigational; this test is not currently covered by Medicare. One of the challenges is background activity in the bladder obscuring the prostate bed and pelvic structures. The overall usefulness has been described as limited, especially in men with lower PSA values, but some clinicians use this tracer for evaluating for local recurrences and imaging the bones and soft tissues (including lymph nodes) for metastases.

Newer PET tracers including ¹⁸F- Sodium Fluoride and ¹¹C-Choline may offer improved diagnostic performance for imaging prostate cancer recurrence. ¹¹C-Choline PET/CT is approved for use in patients with suspected prostate cancer recurrence when conventional imaging is “non-informative”, and the label states positive findings should be biopsied for histologic confirmation. The diagnostic accuracy as described in the ¹¹C-Choline approved drug label has not been defined in terms of sensitivity or specificity, but imaging findings were correlated with histology and there were acceptable numbers of true positives and false positives in the two prospective studies reviewed. ¹⁸F- Sodium Fluoride is approved for imaging altered osteogenic activity, and is being investigated as a tool for identifying sites of osseous metastatic disease in prostate cancer recurrence.⁴

Reviewer Comment: *The reviewer notes that the literature indicates that imaging prostate cancer recurrence is a very imperfect science; the above mentioned imaging tests have debatable diagnostic performance in this disease. I believe new agents with acceptable performance for detecting metastatic deposits, particularly in the pelvic soft tissues, lymph nodes and distant organ systems (lungs, liver, brain), are needed to assist clinicians evaluating men with prostate cancer.*

2.2. Prostate Cancer Treatment Options

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Primary Prostate Cancer

Based on recommendations from the American Urological Association (AUA) and the National Comprehensive Cancer Network (NCCN), seen below are the basic treatment options for treating primary prostate cancer based on clinical staging, pathologic staging and individual patient characteristics (age, overall medical condition, preferences, etc).^{2,3}

Very Low Risk/Low Risk:

- Active Surveillance,
- Radiation Therapy, or
- Radical Prostatectomy

Clinically Localized, Intermediate Risk:

- Radiation Therapy ± Androgen Deprivation Therapy (ADT) , or
- Radical Prostatectomy with Pelvic Lymph Node Dissection ± post-operative radiation therapy (depending on pathological findings)

Clinically Locally Advanced/Very High Risk:

- External source Radiation Therapy plus extended ADT, or
- Radical Prostatectomy with extended Pelvic Lymph Node Dissection ± post-operative radiation therapy (depending on pathological findings)

Lymph Node Involvement (Stage 4):

- Definitive Radiation Therapy plus ADT

Disseminated Metastases (Stage M1):

- Androgen Deprivation Therapy (Gonadotropin Releasing Hormone or Bilateral Orchiectomy)

Disease Recurrence

In patients with suspected prostate cancer recurrence, the key question is location(s) of cancer recurrence which will play a key role in determining optimum therapy. The two main treatment options include radiation therapy and ADT.⁵

Table 1. Available Imaging Options for Prostate Cancer.

Product (s) Name	Relevant Indication	Year of Approval	Dosing	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Diagnostic Radiopharmaceuticals						
¹¹ C-Choline	Suspected	2012	10-20 mCi as	Acceptable True	None	Indicated in

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	prostate cancer recurrence		a bolus intravenous injection	Positives and False Positives for identifying recurrent disease in the pelvic soft tissues. Sensitivity and Specificity not defined.		patients with non-informative conventional imaging
Prostascint (¹¹¹In-Capromab Pentetide)	Newly diagnosed prostate cancer and patients with suspected disease recurrence	1996	5 mCi intravenous injection over 5 minutes	The approved drug label shows the "Sensitivity" as 49% and "overall accuracy" as 63%.	Prostascint is generally well tolerated.	Indicated in patients with non-informative conventional imaging, the diagnostic performance and clinical utility of Prostascint is debatable.

Reviewer Comments: *FDG-18 and Sodium Fluoride PET/CT are sometimes used in this patient population, although the diagnostic performance of both tracers is uncertain and they are considered investigational for this purpose. The reviewer also notes that CT, MRI and ultrasound are additional imaging modalities that can be used in prostate cancer staging and re-staging. However, the clinical usefulness and diagnostic accuracy of these agents has not been fully characterized.*

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fluciclovine F18 Injection is a new molecular entity (NME) and is not currently marketed in the U.S. or any other country.

3.2. Summary of Pre-submission/Submission Regulatory Activity

Drug development of Axumin was carried out under IND 107707 which was initially submitted on 4/01/2010. Key interactions with the sponsor prior to the NDA submission included:

6/26/2014: IND 107707 Type C Face to Face Guidance Meeting

- The sponsor noted that primary prostate cancer is “often indolent and limited amino acid uptake, limiting potential use of the product in initial staging of prostate cancer”.
- The sponsor shared their plans for a pooled analysis of data they have obtained the rights to including the Emory and Bologna studies. DMIP recommended that histopathology be the truth standard for determination of cancer status of lesions.
- DMIP stated that false positives and false negatives need to be evaluated.
- The sponsor confirmed a blinded, independent, centralized re-read study would be conducted on the images following standardization of image read methodologies.
- The sponsor shared [REDACTED] (b) (4)
[REDACTED] The DMIP stated that the [REDACTED] (b) (4) statistical analysis plan should be submitted to the division for review.
- In conclusion, the sponsor 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 plan [REDACTED] (b) (4)

7/31/2015 FDA Preliminary Meeting Responses

- These responses were to the sponsor’s 7/05/2015 meeting package submission. Please see DARRTS submission dated 7/31/2015 filed by Thuy Nguyen for details.

8/03/2015: IND 107707 Type C Guidance Teleconference

- During this teleconference, the discussion focused on the 7/31/2015 FDA preliminary meeting responses to the sponsor’s 7/05/2015 meeting package.
- The Sponsor explained that Fluciclovine appears useful for patients with high PSA values undergoing scanning for the detection of metastatic disease after prostate cancer biopsy confirmation before treatment. The Sponsor stated the use of Fluciclovine for [REDACTED] (b) (4) diagnosis does not seem appropriate as there is no means to distinguish benign prostate hypertrophy from prostate cancer. The DMIP stated this will be a review issue during the review of the NDA submission since it will depend on the patient population and data.
- DMIP asked about the possibility of a food effect. The Sponsor stated that patients had been fasting 4 hours prior to a Fluciclovine scan. The Sponsor will perform a literature review regarding the possible food effect for Fluciclovine.
- The DMIP statistical team provided an attachment with comments and formulas describing the [REDACTED] (b) (4) endpoint analyses. The reviewer notes the statistical team stated that their focus would be upon the region level analyses; [REDACTED] (b) (4) endpoint discussions included sensitivity and specificity calculations in comparison to histology standard of truth, as well as Kappa calculations for the Bologna data which only utilized a comparator (¹¹C-Choline), not a truth standard. Please see the meeting minutes in DARRTS for additional details.

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Reviewer Comments: *I was not present for this teleconference, nor did I review the July 2015 meeting package or provide written responses to the sponsor's questions. Another reviewer was assigned to this product in 2015 leading up to the NDA submission. I was previously assigned to this IND product and involved in the 2014 discussions, but not the 2015 guidance discussions and teleconference.*

3.3. Foreign Regulatory Actions and Marketing History

Axumin is not currently marketed in any country.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review team determined OSI audits were not necessary; no treatments were administered for the sponsor's BED001 and BED002 studies.

4.2. Product Quality

Summary of Quality Assessments

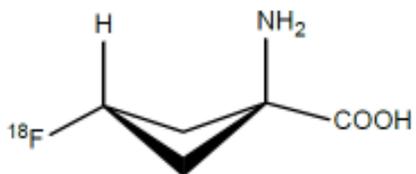
The proposed proprietary name for the product is Axumin. Fluciclovine (18F) is the International Non-proprietary Name (INN) for the active substance *anti*-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid. Fluciclovine F 18 is the proposed United States Approved Name (USAN).

The drug substance, fluciclovine (18F), is produced as an aqueous solution (b) (4)

[REDACTED]

[REDACTED] The quality of radioactive fluciclovine (18F) drug substance is controlled during the manufacture and testing of the drug product. Due to the short half-life of the 18F-fluorine radioisotope, each batch is prepared on the day of clinical use.

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Molecular Formula: C₅H₈¹⁸FNO₂
Molecular Weight: 132.1 (b) (4)

CMC Reviewer Recommendations

The application may be approved from chemistry, manufacturing and controls (CMC) perspective, once the final acceptable recommendation is received regarding the manufacturing facilities.

The various quality aspects, i.e., the drug substance, the drug product, the manufacturing process, the microbiological aspects and the environmental assessment have been reviewed by the review team and are adequate to support approval of the application. The review of the manufacturing facilities is not complete at the time of this review and the application may only be approved once the final acceptable recommendation is received regarding the manufacturing facility. The drug product, Axumin, is granted a 10 hour shelf-life (from the end of synthesis or manufacture) under controlled room temperature (USP) storage conditions.

The applicant has made a commitment (11-Jan-2011 amendment) to investigate the feasibility of reducing the amount of (b) (4) impurity in the drug product. Preliminary work will start soon and the company will aim to report the results of the development work to the Agency, and discuss and agree future steps, within 12 months of NDA approval.

4.3. **Clinical Microbiology**

The microbiology reviewer recommended approval on the basis of sterility assurance.

4.4. **Nonclinical Pharmacology/Toxicology**

The following is taken from the non-clinical review:

Pharmacology

In vitro pharmacology studies demonstrated that [14C]-FACBC1 uptake was rapid with peak uptakes at 5 to 30 minutes in human prostate adenocarcinoma (PCa) cell lines. The uptake by PCa cell lines was higher than that by normal human prostate epithelial cell line at early time points (1.62 to 8.56 times higher at 5 and 15 minutes and significantly higher in 4 of the 5 PCa lines at 30 minutes). In vivo pharmacology studies demonstrated that ¹⁸F-anti-FACBC was rapidly distributed in tumor tissue in mice with the highest or near the highest tumor/tissue ratios at 5 minutes post dosing.

Safety Pharmacology

No remarkable adverse effect on CNS, CVS and respiratory functions were observed

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and high safety margins were achieved [human dose multiples (HDM) ≥ 18 based on body surface area (BSA)].

General toxicology

Fourteen day intravenous toxicity studies were conducted in rats (0, 22, and 43 mcg anti-FACBC/kg/day) and dogs (0, 5.4, and 10.8 mcg anti-FACBC/kg/day). The NOAELs are established at 22 mcg/kg/day in rats and 10.8 mcg/kg/day in dogs based on no significant drug-related finding, establishing adequate HDM (21X or 35X based on BSA).

Genetic toxicology

Anti-FACBC was negative in in vitro reverse mutation assay in bacterial cells (Ames), in vitro chromosomal aberration assay in cultured mammalian cells, and in vivo micronucleus assay in rats.

Special toxicology

Vigorous struggling was noted in rabbits (3/6) when the FACBC formulation was injected subcutaneously, which was attributed to pain caused by low pH (3.12) and high osmotic pressure (1.8 X of saline) of the formulation.

4.5. Clinical Pharmacology

The following are excerpts from the Clinical Pharmacology Review:

“There are no clinical or clinical pharmacology studies conducted by the applicant. No dose finding studies were conducted by the applicant or in any published literature. The applicant received data from Emory University (Study RO1) for safety and efficacy of ¹⁸F Fluciclovine, and cites additional data from published literature. Bio-distribution data was received from GE Healthcare and (b) (4).”

4.5.1. Mechanism of Action

¹⁸F-Fluciclovine is a synthetic L-leucine analogue which is actively transported into mammalian cells by amino acid transporters (AAT). The principle transporters involved in the uptake of ¹⁸F-Fluciclovine are LAT1 and ASC2, which have been shown to be upregulated in cancer cells. ¹⁸F-Fluciclovine are LAT1 and ASC2, which have been shown to be upregulated in cancer cells.

4.5.2. Pharmacodynamics

Clinical trials from various institutions (Oslo University, Bologna University, Emory University and Aleris, Norway) studied doses of ¹⁸F-Fluciclovine varying from 162 - 485 MBq (4.4 to 13.1 mCi). The investigators from Oslo University used a dose of 200 MBq and concluded that ineffective images were obtained. The basis for selecting doses does not appear in the submission or in the literature. No dose finding studies appeared in the literature or were

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conducted by the applicant. The proposed package insert recommends a dose of 370 MBq or 10 mCi by intravenous injection in a total volume not exceeding 5 mL. The mass dose of ¹⁸FFluciclovine is 2 ug/mL (max of 10 ug). While there is no assurance that an optimal dose has been identified, this is not an unresolved regulatory issue if the proposed dose is effective.

Regarding effects on QT intervals, the drug is injected only once and the clinical pharmacology team determined the likelihood of QT or QTc prolongation is remote. There were no significant effects of ¹⁸FFluciclovine injection on ECG interval changes in mean values or shifts from baseline in ECG parameters. There were no ECG abnormalities or trends indicative of a safety signal detected in subjects with prostate cancer or HIV. There were no clinically significant or non-clinically significant ECG findings or QTc intervals >500 msec at any time point during the study.

4.5.3. Pharmacokinetics

Pharmacokinetic studies have not been performed. The drug is administered as a micro-dose (approximately 10 ug) intravenous injection.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Please see the following 2 pages for the table of clinical studies.

Table 2. Clinical Trials Relevant to this NDA Submission

Study	Population, N	Design, Dose	Endpoints	Reference Standard	Image Reviews	Comments
Key Efficacy/Safety						
Emory Study R01	Prostate Cancer Recurrence	Prospective, single center open label, single dose study	Described as “sensitivity”, “specificity”, PPV, NPV, and “accuracy.	On site Histology Analysis & FDA approved comparator (¹¹¹ In-Capromab Pendetide)	On site interpretations by 2 reviewers (consensus if disagreement)	Positive performance of Fluciclovine reported against comparator using histology standard of truth. On site image reads used as well as on site pathology analysis; FDA did not verify all results.
BED001 Emory	Prostate Cancer Recurrence	Re-analysis of R01 data	Positive Predictive Value	On site Histology Analysis	Original on site interpretations	Positive performance of Fluciclovine compared to histology; original on site image interpretations used.
BED002 Emory	Prostate Cancer Recurrence	Re-read of BED001 images	Positive Predictive Value	On site Histology Analysis	3 blinded, centralized, independent readers	Positive results for Fluciclovine compared to histology; original on site pathology reads used.

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Supportive Efficacy/Safety Studies	Population, N	Design, Dose	Endpoints	Reference Standard	Image Reviews	Comments
Bologna Paper	Recurrent Prostate CA	Prospective, single center, open label study	Agreement and Detection Rates	None-comparator study (¹¹ C-Choline)	On site readers	Positive reported performance compared to FDA approved imaging agent; on site reads used, no FDA verification of results.
BED001 Bologna	Recurrent Prostate CA	Re-analysis of Bologna data	Agreement	¹¹ C-Choline comparator	On site reads	No truth standard employed.
BED002 Bologna	Recurrent Prostate CA	Re-read of Bologna Fluciclovine scans	Agreement	¹¹ C-Choline comparator	Blinded, Independent re-reads	No truth standard employed.
Exploratory Efficacy/Safety Studies	Population, N	Design, Dose	Endpoints	Reference Standard	Image Reviews	Comments
GE148-001	Primary Prostate CA; N= 6 HV, 6 Prostate Ca Pts	Open label, single dose;	Safety		On site reads	Exploratory
GE148-002	Primary	Open label,	Safety, dose		On site reads	

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	Prostate CA; N=21	single dose;	ranging			
NMK36-PC-201	Primary Prostate CA; N=10	Open label, single dose;	Safety		On site reads	Exploratory
NMK36-PC-202	High Risk Primary Prostate CA; N=68	Multi-center, open label, single dose;	Safety, Efficacy	CT/Bone Scan comparators	On site reads	Exploratory
Emory University Schuster, 2007	Primary and Recurrent Prostate CA; N=15	Open label, single dose	Uptake in tumors vs normal tissue		On site reads	Exploratory
Emory University Schuster, 2013	Primary Prostate Ca; N=10	Open label, single dose	Uptake compared to histology specimens post prostatectomy		On site reads	Exploratory

5.2. Review Strategy

In vitro pharmacology studies demonstrated Axumin uptake in human prostate adenocarcinoma cell lines was higher than normal human prostate epithelial cells, and in vivo pharmacology studies showed acceptable Axumin uptake in mouse tumor tissues. For the efficacy evaluation (demonstration of accuracy and reliability in the proposed clinical setting), this review concentrates on the data obtained from the Emory study (R01) and Bologna study. The clinical usefulness of a test that helps identify prostate cancer in this population is accepted.

I present the original primary endpoints and results for these studies and focus on data comparing Fluciclovine to a reference standard of tissue pathology (Emory data) as primary support for the sponsor's proposed indication and utilize the data with only a comparator (Bologna study) as secondary support in order to characterize the performance characteristics of this tracer and validate the proposed clinical usefulness in patients with suspected prostate cancer recurrence. The clinical review team worked alongside the statistics team to conduct its own analysis of the data, which is presented following the sponsor's results for the BED001 and BED002 studies. Our analyses of the data allow verification of the sponsor's results and added confidence in our interpretation of the sponsor's analyses.

For the review of safety, data was evaluated from all submitted phase 1 study phase 2 studies phase 3 studies. The total number of patients included in the safety analysis was 837 subjects.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Emory Study (R01)

6.1.1. Study Design

Overview and Objective

Study R01 was an open label, single dose comparative study of ¹⁸F-Fluciclovine vs. ¹²³I-Prostascint with histology as a standard of truth and was performed at Emory University; it was published in 2014 in *The Journal of Urology* (Vol. 191, 1446-1453, May 2014).

Trial Design

- **Basic Design:** Open label, single center, non-randomized, comparative study of ¹⁸F-Fluciclovine PET imaging vs. ¹²³I-Prostascint SPECT imaging in prostate cancer patients

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in order to determine site(s) of disease recurrence post therapy.

- **Reference Standards:** The sponsor chose to compare Fluciclovine to ¹¹¹In SPECT, which is an approved diagnostic agent (initial approval 1996; NDA 103608) for prostate cancer therapy. More importantly, on site pathological evaluations of the prostate bed and tumor deposits outside the prostate bed were used as a reference standard to establish truth.
- **Diagnostic criteria:** The sponsor enrolled subjects who had undergone previous definitive treatment for prostate cancer with suspicion of recurrence based on American Society for Radiation Oncology (ASTRO) criteria of 3 consecutive PSA rises and/or ASTRO/Phoenix criteria of PSA nadir above 2.0 ng/ml after radiotherapy or cryotherapy and/or greater than 0.2 ng/ml after prostatectomy. The reviewer agrees with this choice of diagnostic criteria and believes it is consistent with clinical practice.
- **Inclusion/exclusion criteria:** The key enrollment criteria included 1) an original diagnosis of stage T1c, T2 or T3 prostate carcinoma with prior definitive therapy, 2) suspicion of recurrence based on ASTRO criteria, and 3) bone scan negative for metastatic disease. Patients were excluded who did not have both Proscint and Fluciclovine scans with 90 days of each other.
- **Dose selection:** *Please see section 4.5.2*
- **Study treatments:** Anti-3-[¹⁸F]-FACBC (Fluciclovine) was prepared as reported in IND (b) (4). Patients fasted 4 to 6 hours prior to receiving 161.7 to 484.7 MBq (4.4 to 13.1 mCi) Fluciclovine via intravenous injection. After injection of study drug, there was a 3 minute delay to allow blood pool clearance prior to performing the abdomen and pelvis PET/CT scan.
- **Assignment to treatment:** All enrolled subjects received both ¹⁸F-Fluciclovine and ¹²³I-Proscint scanning within 90 days of each other. TIMING OF EACH SCAN....
- **Blinding:** Fluciclovine scans were read by a nuclear medicine radiologist and a nuclear medicine physician. Each reader was blinded to the other's interpretation, as well as to other imaging results and reference standard findings. The original study manuscript states that "Disagreement was resolved by consensus." The "¹¹¹In-capromab pentetide images were co-interpreted in a blinded fashion using well described criteria." The reviewer notes these do not represent ideal image interpretation methods for clinical trials, as "consensus" reads and "co-interpreted" scans make it difficult to describe performance characteristics across individual readers.
- **Dose modification:** From the publication, each patient received between 161.7 and

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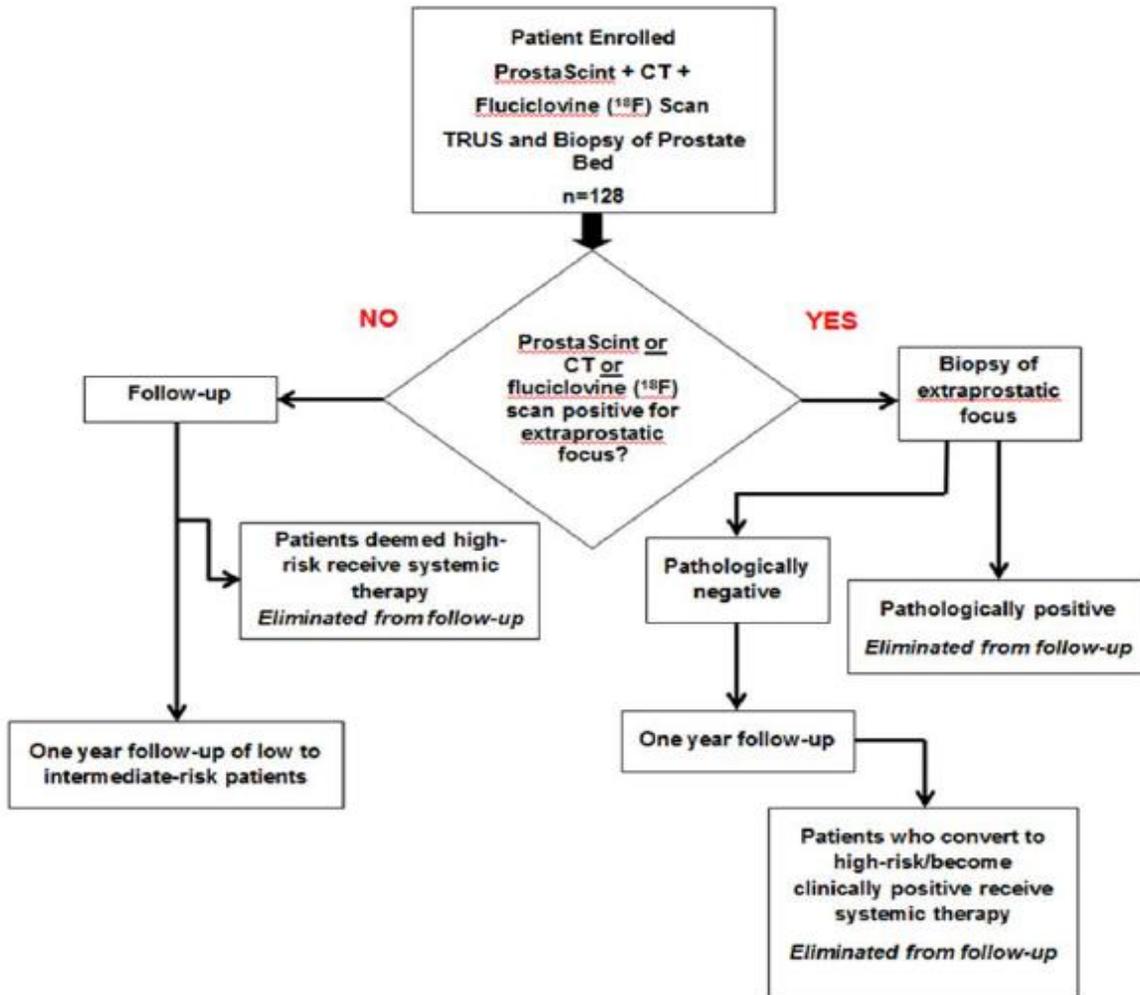
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483.7 MBq of Fluciclovine. However, the median and mean dose is not provided. The reviewer knows based on an information request that the median dose was 366 MBq (~ 10 mCi) and the mean dose was 353.8 MBq (9.6 mCi). The reviewer notes that although the published range appears wide, it is apparently due to a small number of subjects receiving a lower and higher dose than planned as the mean and median doses are acceptable with regards to the intended clinical use.

- **Administrative structure and reference standards:** A multidisciplinary consensus panel composed of a nuclear radiologist, 2 urologists and 2 radiation oncologists met regularly and communicated via e-mail to adjudicate the reference standards for the presence or absence of disease. Standard of truth in the original paper included either 1) histopathology or 2) “other truth standards” (other imaging results or response to therapy and clinical follow up over 12 months post enrolment) reached by consensus decision among the panel and the subjects’ treating physicians/surgeons (91 for prostate/prostate bed and 70 for extra-prostatic disease). Based on the sponsor’s response to an information request, the reviewer is aware that eight of the 91 subjects in this study did not have histopathology results, thus were subject to the “other truth standards” mentioned above. In the sponsor’s BED-001 re-analysis of this data, these eight subjects were excluded from the analysis and only subjects with histopathology standard of truth were included.
- **Procedures and schedule:** Please see the below figure 1 from the sponsor submission that depicts the R01 study events.



- **Dietary restrictions/instructions:** Enrolled subjects fasted for 4 to 6 hours before the Fluciclovine PET/CT scan was performed. Prior to the ¹¹¹In-capromab pendetide scans, subjects followed a standard clinical protocol
- **Concurrent medications:** Not applicable for this diagnostic imaging study
- **Treatment compliance:** Not applicable.
- **Subject completion, discontinuation, or withdrawal:** Subjects who had both scans and follow up data to allow a reference standard determination were considered to have completed the trial with sufficient data for endpoint analysis. Study dropout is not a concern of the reviewer given 91 of 93 enrolled subjects had sufficient data for truth determination to be made for the prostate bed.

Study Endpoints

- **Primary Endpoints:** The sponsor and investigators described study endpoints in terms of sensitivity, specificity, accuracy, positive predictive value and negative predictive value. However, the reviewer notes this is an inaccurate way to describe the study analyses and results because the investigational imaging agent directed biopsies of the prostate bed and lesions outside the prostate bed, thus this type analysis is not a true measure of diagnostic performance in terms of sensitivity and specificity. The endpoints would be better described as localization or detection rates in patients with known disease recurrence and will be referred to as such in this review. The reviewer believes although the endpoints are mischaracterized in the original paper, the study results (localization rates) are clinically valuable in this population of patients given that it is paramount to identify sites of disease in patients with rising PSA (following guidelines) after definitive therapy for primary prostate cancer. In addition, it is known that current imaging (CT, MRI, SPECT) procedures in this population are imperfect.

Reviewer Comments:

Similar endpoint data allowed for the approval ¹¹C-Choline, where the investigational agent identified an acceptable number of positive lesions (histology truth standard) in patients suspected of having disease recurrence based on PSA values and with non-informative conventional imaging. Thus, there is regulatory precedent for approval of imaging agents in this type population with performance measures other than the preferred measure of sensitivity and specificity.

- **Exploratory and Secondary endpoints:** None.

Statistical Analysis Plan: There was no review or agreement upon the sponsor's statistical analysis plan and no apparent hypothesis testing for the original Emory study.

- The paper does not describe a null hypothesis. The sponsor calculated the 95% CI of each endpoint as a binomial proportion (shown as 95% CI x, y after each estimate. Inter-reader agreement was assessed and the k statistic was calculated.

Using the McNemar chi-square test, the sponsor analyzed what was described as "sensitivity", "specificity" and "overall accuracy" between ¹⁸F-Fluciclovine and ¹²³I-Prostascint scan image read results. Differences in positive predictive value and negative predictive value "were assessed using approximate tests based on the difference between 2 proportions". A logistic regression model was constructed to determine the probability of positive scan interpretations at various PSA cutoffs. Statistical significance was determined using a type I error rate of alpha = 0.05. Statistical analysis was done using MatLab (R2013a) version 8.1.0.604 and R.

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- There were no pre-specified methods of handling missing data. However, this does not appear to be significant issue with the study.
- There were no interim analyses conducted.
- Subgroup analyses included diagnostic performance for the prostate bed and extra-prostatic sites.

Reviewer Comment: Please refer to the statistical review by Anthony Mucci for a detailed evaluation of the statistical analysis.

Protocol Amendments: There were no protocol amendments identified for this study conducted under IND (b) (4).

6.1.2. Study Results

Compliance with Good Clinical Practices

Review of the original paper reveals that Emory IRB approval was obtained and this study was conducted under Investigational New Drug Application (b) (4).

Financial Disclosure

One investigator (out of 13 total study authors), (b) (6), stated a financial interest/relationship with (b) (6) and royalties related to Fluciclovine F18 Injection. Given he was not the lead investigator and the number of investigators involved, this does not raise a serious concern in my mind.

Patient Disposition

115 patients were eligible for the published analysis, of which 5 did not have ¹¹¹In-capromab pentetide studies available. Of the 110 remaining patients, 93 met study criteria of ¹¹¹In-capromab pentetide as well as Fluciclovine imaging acquired within 90 days of each other.

Protocol Violations/Deviations

None reported.

Table of Demographic Characteristics

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Table 3: Demographic characteristics of R01 subjects.

Demographic Parameters	Total (N=93)
Sex	
Male	93
Age	
Mean years (SD)	68 (7.6)
Median (years)	68
Min, max (years)	49,90
Original Therapy	
Prostatectomy	24 (26%)
Non-Prostatectomy	69 (74%)
PSA (ng/ml)	
Mean (SD)	9.8 (31.5)
Median	4
Min, max	0.11, 301.7
Original Gleason Score	
Mean (SD)	6.9 (0.8)
Median	7
Min, max	5, 10

Reviewer Comments: *The reviewer notes data on race and ethnicity were not published in the original Emory R01 manuscript. Non-prostatectomy therapy included radiation therapy, brachytherapy, cryotherapy and/or androgen deprivation therapy. The PSA values were obtained within a mean of 12.7 (\pm 33.9) days from scanning.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Not applicable to the studies conducted to support the proposed indication for this single micro-dose radio-diagnostic agent.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

- Treatment Compliance: Not applicable.

Efficacy Results – Primary Endpoint

Table 4: Emory R01 study original published results with histology truth standard.

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

Reviewer Comments: *The reviewer notes in the original R01 study published manuscript there were 77 total true positive findings by ¹⁸F-Fluciclovine PET scanning and 56 true positives using ¹¹¹In-Prostascint SPECT imaging. The number of false negative ¹⁸F-Fluciclovine scans totaled 24 as compared to 56 false negative scans with ¹¹¹In-Prostascint. This is an important finding given that every patient scanned was known to have prostate cancer recurrence based on elevated serum PSA (repeated measurements based on current guidelines). Thus, with a 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 ¹⁸F-Fluciclovine in this population.*

Data Quality and Integrity – Reviewers’ Assessment

The reviewer has not discovered any reason to question the integrity of the data presented in the original Emory R01 study.

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Efficacy Results – Secondary and other relevant endpoints

Not applicable, efficacy endpoints reported above for this study.

Additional Analyses Conducted on the Individual Trial

See section 6.3.2 for the FDA analyses conducted as part of the sponsor's BED001 study (re-analysis of Emory data).

6.2. Study BED001 (Emory Data)

6.2.1. Study Design

Overview and Objective

Study BED001 was the sponsor's re-analysis of imaging data from the previously conducted R01 study at Emory University. The sponsor obtained ownership of the data, developed a statistical analysis plan and re-analyzed the diagnostic performance of ¹⁸F-Fluciclovine as compared to histology standard of truth. 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 made with ¹¹¹In-Capromab Pendetide).

Trial Design

- **Basic Design:** See description for R01 study above, as the study procedures were identical to those described above for the original Emory study. The only differences in study BED001 compared to R01 are related to the primary endpoints and statistical analysis plan. The reviewer notes that ¹⁸F-Fluciclovine was not compared to ¹¹¹In-Capromab Pendetide and histology was the only allowed reference standard.
- **Primary Endpoints:** Positive Predictive Value (PPV) on a subject, lesion and region level for the prostate bed, pelvic lymph nodes and extra prostatic sites. $PPV = a/(a+b)$. The reviewer notes that for purposes of establishing the accuracy and clinical usefulness of Axumin in the proposed patient population, we focused on the regional analysis data. These data provide an estimate of the value of a positive Axumin PET scan in the prostate bed, pelvic lymph nodes and extra prostatic sites. Since pathological analysis of tissues outside the prostate was not performed unless imaging detected positive sites, the "true negative" and "false negative" data is not as valuable in the pelvic lymph node and extra prostatic sites. True negative and false negative data is valuable data in the prostate bed as all subjects underwent prostate biopsy given the suspicion of disease recurrence.

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- **Reference Standards:** On site pathological evaluations of the prostate bed and tumor deposits outside the prostate bed were used to establish truth.

Safety Assessments: Safety evaluations were performed for all subjects who were included in the database, and received at least one dose of Fluciclovine. For laboratory parameters, vital signs and ECG, baseline was defined as the last measure prior to fluciclovine administration. In general, laboratory parameters (hematology, biochemistry and coagulation), vital signs and ECG were summarized as per the following time windows:

- Within 24 hours of injection
- From 24 hours to 7 days of injection
- From 7 days to 35 days of injection

All laboratory parameters (including urinalysis) measured and recorded in the subject's medical notes before (closest but prior to) administration of Fluciclovine and up to 35 days after the administration of fluciclovine were recorded. Blood samples for determination of parameters were taken at the times given in the Study Schedule. Analyses were done at the Emory University hospital laboratory using routine methods.

In the original R01 study (relevant to BED001 results), temperature, pulse, respiration rate and blood pressure were assessed prior to fluciclovine infusion and every 15 minutes during the infusion, and during the follow up period, according to standard practice. In BED-001 the results of any physical examination, performed by either the investigator, a sub-investigator or by qualified staff and reported in the subject's medical notes, at any visit before and after fluciclovine were recorded.

Electrocardiograms

In BED-001 the results of any electrocardiogram (ECG) reported in the subject's medical notes were recorded (including machine calculated heart rate, PR, QT and QTc intervals).

Laboratory Evaluations

The following laboratory parameters (figure 2) were assessed (submission snapshot).

Figure 2: Laboratory parameters assessed in study BED001.

Biochemistry	Haematology
Aspartate aminotransferase (AST)	Haemoglobin (Hb)
Alanine aminotransferase (ALT)	Haematocrit
γ glutamyl transpeptidase (GGT)	Red blood cell count (RBC)
Alkaline phosphatase (ALP)	Red blood cell distribution width (RDW)
Total and direct bilirubin	Mean cell haemoglobin (MCH)
Total and LDL-cholesterol	Mean corpuscular haemoglobin concentration (MCHC)
Triglycerides	Mean corpuscular volume (MCV)
Creatinine	White blood cell count (WBC)
Creatine kinase (CK)	Differential blood count, platelets
Lactate dehydrogenase (LDH)	Coagulation
Urea	Prothrombin time
Blood urea nitrogen (BUN)	International normalised ratio (INR)
Albumin	Activated partial thromboplastin time (APTT)
Globulin	Urinalysis
Potassium	pH
Sodium	Glucose
Calcium	Proteins
Chloride	Ketones
Bicarbonate	Bilirubin
Glucose (random or fasting)	Urobilinogen
Phosphate	Nitrite
Urine microscopy	Blood
White blood cells	Leukocytes
Red blood cells	Specific gravity
Epithelial cells	Colour
Organisms	
Casts	
Crystals	

Statistical Analysis Plan

- The division provided guidance to the sponsor related to the statistical analysis plan for study BED001 during the August, 2015 teleconference and the preceding written response to the sponsor’s meeting package. [Please see section 3.2 for details.](#)
- **Null Hypothesis:** H0: PPV0 = 0.50 versus H1: PPV1 ≥ 0.50. The assumed PPV to be observed in the study was 0.65. The one-sided type I error was controlled at 0.025 and the power was to be >0.80. Based on these assumptions, 85 patients with complete data were required to demonstrate statistical significance in the effectiveness endpoint of PPV.

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- Missing data: Not an issue.
- Interim analyses: Not conducted.
- Subgroup analyses included Fluciclovine PET scan performance compared to biopsy standard of truth for age, weight, race, cancer therapy, original Gleason Score, and PSA (value at time of scan, doubling time and velocity).
- Please refer to the statistical review by Anthony Mucci for a detailed evaluation of the statistical analysis.

6.2.2. Study Results

Patient Disposition

137 patients with recurrent prostate cancer were enrolled in the BED001 study at Emory University; 115 of these subjects were eligible and enrolled in the R01 study, 22 were enrolled in other studies at the Emory site. Ninety nine (99) out of the 115 subjects had histology standard of truth available for the efficacy analysis. There are a total of 105 data points (scan results) from these 99 patients as six of these patients had imaging and truth standard data available from two time points.

Demographic Characteristics

Table 5: Demographic characteristics of the BED001 study subjects.

Demographic Parameters	Emory BED 001	Emory BED R01 Analysis
	N=137	N=115
Sex		
Male	137	115
Age	137	115
Mean years (SD)	68 (7.6)	NC
Median (years)	68	NC
Min, max (years)	49,90	NC
Race		
Black or African American	26 (19%)	21 (18%)
Asian	1 (<1%)	1 (1%)
White	98 (1.5%)	83 (72%)
Other	1 (<1%)	0
Missing	11 (8%)	10 (9%)
Recurrent Prostate CA Therapy	131	115
Radical Prostatectomy Only	19	15
Radical Prostatectomy + Others	5	4
Radiation Therapy Only	40	16
Radiation Therapy + Others	52	42
Others	15	38
PSA (ng/ml)	125	NC
Mean (SD)	6 (7.5)	
Median	2.9	
Min, max	0,05, 44.8	
Gleason Score	92 (67%)	84 (73%)
≤ 6	38 (41.3%)	36 (43%)
7	29 (42.4%)	35 (42%)
8-10	15 (16.3%)	13 (15%)
Subjects having a Fluciclovine PET/CT scan	137	115
Total number of Fluciclovine scans	149	128

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Reviewer Comment: *The 137 subjects described above for the Emory BED001 study include the 115 R01 study patients plus and additional 22 patients that were enrolled in non-R01 studies; safety data is available for all 137 subjects, the efficacy analyses were conducted on the R01 subject population.*

Table 6: BED001 Primary Efficacy Results as reported by the sponsor.

	Overall (Subject Level)	Prostate Region	Extra-Prostatic Region (pelvic nodes, soft tissue, bone)
N	105	98	29
True Positive	73	57	27
False Positive	19	27	2
True Negative	12	12	-
False Negative	1	1	-
PPV	79% (73/92)	68% (57/84)	93% (27/29)
NPV	92% (12/13)	92% (12/13)	
“Sensitivity”		98% (57/58)	
“Specificity”		31% (12/39)	

Reviewer’s Comments:

Due to the fact that imaging procedures (Fluciclovine plus conventional imaging results) guiding the truth standard biopsies which prevents true sensitivity and specificity calculations, I believe that the true positives and false positives (and PPV) are the most valuable data presented in the sponsor’s results. When considering the proposed clinical use, it is important to note that all patients were considered to have disease recurrence. The key to determining the best individual treatment plan for a patient known to have residual disease is to determine where the residual disease is located in the body. Thus, an imaging test that is able to accurately and reliably

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localize the known disease recurrence will be clinically useful in this population. Given the reasonable number of true positives and PPV seen above using an appropriate truth standard, coupled with the knowledge from the original Emory R01 study results that Fluciclovine PET imaging identified more sites of disease recurrence than the approved imaging test (¹¹¹Indium tracer), the reviewer believes these data help validate the sponsor’s claim that Fluciclovine is clinically useful in prostate cancer recurrence.

The reviewer notes that for the extra-prostatic region, 24/29 (83%) of the subject level data came from patients with positive lesions in the pelvic lymph nodes. Thus, we have limited information on the performance characteristics in lesions outside the pelvis. Based on the data tables the reviewer calculates the PPV for lesions outside the pelvis was 80% (4/5), as there were four true positives and one false positive the “other nodal, bone or soft tissue” region. Thus there were twenty three true positives in the pelvic region and one false positive, equaling a positive predictive value there of 96%. These are all acceptable positive predictive value estimates.

Subgroup Analyses.

There were no significant differences in efficacy observed in subpopulation analyses including age, sex, and race and ethnicity. Differences were seen for PSA quartiles, as shown in the below table.

Table 7: Results by PSA Quartile on a subject level for study BED001.

N = 99				
PSA Value (ng/mL)	≤ 1.05	> 1.05 to ≤ 3.98	> 3.98 to ≤ 8.9	> 8.9
No. Subjects	16	31	25	27
True Positive	3	23	20	23
True Negative	4	5	4	4
False Positive	8	3	1	
False Negative	1	0	0	
PPV	27%	88%	95%	100%
NPV	80%	100%	100%	100%

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Reviewer Comments: *There is a numerical difference between the reported diagnostic performances of Fluciclovine when looking at different PSA levels. In the group of patients (N=16) with a PSA level less than 1.06, there are actually more false test results than true test results and the PPV is obviously lower than seen in the other PSA value subgroups. Although the numbers are small in these subgroups, I believe these are important data with clinical implications and should be mentioned in the product labeling. Please note these data points are not included in the statistical reviewer's tables and were not confirmed by the statistical team, but the results are consistent with the performance expectations of tracers in patients with varying PSA values.*

6.3 Study BED002 (Emory Data)

6.3.1 Study Design

Overview and Objective

Study BED002 was the sponsor's re-read study of images obtained previously from the R01 study at Emory University. The sponsor obtained ownership of the data, developed a reader training program, statistical analysis plan and then compared the performance of ¹⁸F-Fluciclovine as compared to histology standard of truth following independent, blinded, centralized reads (American College of Radiology laboratory) 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 made with ¹¹¹Indium imaging).

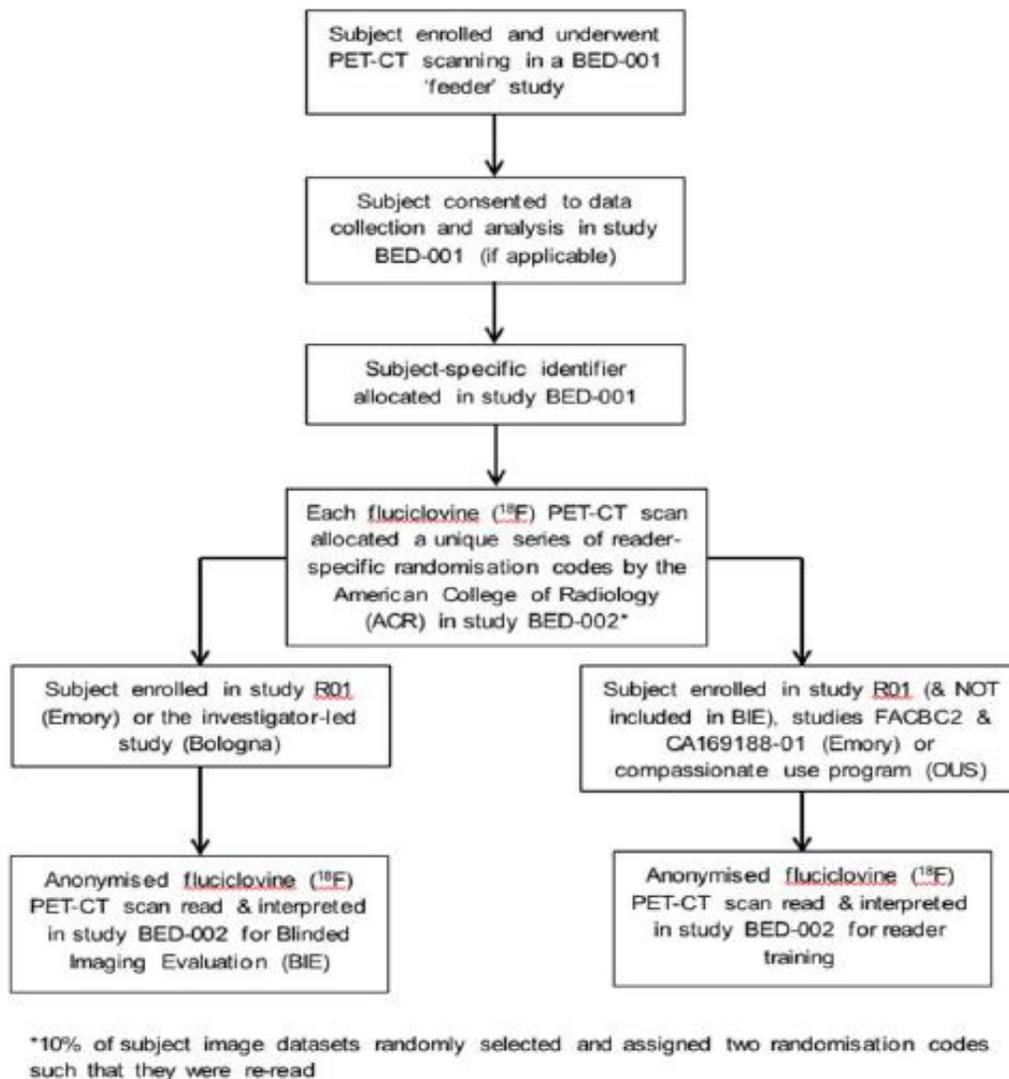
Trial Design

- **Basic Design:** See description for R01 study above, as the study procedures were identical to those described for the original Emory study. The only differences in study BED002 compared to R01 (and BED001) are related to the independent, blinded image re-reads, and statistical analyses. ¹⁸F-Fluciclovine was not compared to ¹¹¹In-Capromab Pendetide and histology was the reference standard for primary efficacy analyses.
- **Primary Endpoints:** There was not one designated primary endpoint. The sponsor calculated PPV, NPV, "Sensitivity", "Specificity", and "Detection Rate". This review will focus on the PPV on a subject, lesion and region level for the prostate bed, pelvic lymph nodes and extra prostatic sites. $PPV = a/(a+b)$. Since pathological analysis of tissues outside the prostate was not performed unless imaging detected positive sites, the "true negative" and "false negative" data is not as valuable in the pelvic lymph node and extra prostatic sites. True negative

and false negative data is useful data in the prostate bed as all subjects?? were to receive prostate biopsy given the suspicion of disease recurrence.

- **Reference Standards:** The same as R01 and BED001, on-site pathological evaluations of the prostate bed and tumor deposits outside the prostate bed were used to establish truth.
- **Blinded, Independent Image Reads**
Subjects were assigned a unique code number for data entry purposes in study BED-001 which was used to identify the subject's images in study BED-002; no personal identifiers were collected. Copies of anonymized Fluciclovine PET-CT images were transferred to the American College of Radiology (ACR) central core laboratory for evaluation by readers blinded to any subject specific information (i.e. medical history, results of on-site reads of the fluciclovine (18F) PET images, results of conventional imaging, histopathology results, the final diagnosis and outcome). Prior to conducting the BIE read, all readers underwent initial training using a standardized training protocol and example cases from a separate set of training images.

Figure 3: Study Schema BED001 (snapshot from submission).



Statistical Analysis Plan

- **Null Hypothesis:** H0: PPV0 = 0.50 versus H1: PPV1 ≥ 0.50. The assumed PPV to be observed in the study was 0.65. The one-sided type I error was controlled at 0.025 and the power was to be >0.80. Based on these assumptions, 85 patients with complete data were required to demonstrate statistical significance in the effectiveness endpoint of PPV.
- **Missing data:** This was not an issue, as all subjects meeting enrollment criteria were included in the efficacy analyses.

6.3.2 Study Results

Table 8: BED002 Study results as reported (Prostate Bed Region).

	Reader 1	Reader 2	Reader 3
N	98	97	96
True Positive	58	56	47
False Positive	29	26	15
True Negative	10	12	24
False Negative	1	3	10
PPV	67% (58/87)	68% (56/82)	76% (47/62)
NPV	91% (10/11)	80% (12/15)	71% (24/34)
Sensitivity	98% (58/59)	95% (56/59)	83% (47/57)
Specificity	26% (10/39)	32% (12/38)	62% (24/39)

Reviewer Comments: *The reviewer notes the above reported imaging results for the prostate bed are acceptable from a clinical perspective and compare favorably with the results in BED001. In the proposed population, I believe the imaging test should have a low number of false negatives and high number of true positives (sensitivity= TP/TP+FN) to accurately identify sites of disease recurrence. When examining the above table, the relatively low number of false negatives and sensitivity of the test in this region speaks favorably for Fluciclovine. While the number of false positives and lower specificity is an issue, the reviewer believes the added value of potentially detecting more sites of disease recurrence compared to current imaging modalities outweighs the risks associated with false positive image findings. Additionally, the false positives in the prostate bed may be falsely elevated due to known difficulties/problems with prostate bed biopsy samples. At worst, a false positive image finding will likely result in additional testing plus potential biopsy of a site to confirm disease presence. In most cases no*

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harm will be done to patients with the exception of additional expense/time expenditure for confirmatory tests to be conducted. I believe the benefit of locating disease recurrence in more patients outweighs the risk of potential false positive image findings.

Reader three had a lower number of true positives and false positives for the prostate bed region, and a higher number of true negatives and false negatives, resulting in lower “sensitivity” and higher “specificity”. I believe this is due to the reader’s inherent higher threshold to call scans positive, which would explain all the numerical differences with reader one and reader two. Readers one and two had very similar image interpretations, resulting in higher “sensitivity” and lower “specificity” with regards to reader three. The consistency of results from readers one and two with results reported in the BED001 analysis provide further validation of the above results in my mind. However, the different results seen for reader three should spark a discussion on the need for language regarding reader training in the product labeling.

Table 9: BED002 Study Results as reported. (Extra-Prostatic: pelvis, soft tissue, bone)

	Reader 1	Reader 2	Reader 3
N	30	30	27
True Positive	26	27	23
False Positive	2	2	2
True Negative	0	0	0
False Negative	2	1	2
PPV	93% (26/28)	93% (27/29)	92% (23/25)
NPV	0% (0/2)	0% (0/1)	0% (0/2)

Reviewer Comments: *The above data support that lesions identified on Fluciclovine PET scans are likely to represent cancer positive lesions in sites outside the prostate bed. Although the numbers are relatively small and we do not have an estimate of the sensitivity of the test (TP/TP+FN) for detecting lesions in this region given biopsies would not have been performed with negative Fluciclovine imaging (negative scans have no truth standard determination unless other imaging was positive or clinician suspicion was high for a given site), we do have reasonable assurance that when the test identifies a lesion in this population/region it is likely*

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positive for cancer. These data may be the most important in the application given that identifying sites of recurrence in the pelvic lymph nodes (and/or distant sites) would likely result in a change of treatment plans for these subjects assuming other imaging tests were negative. Additionally, these data are very similar to study BED001 results in this region and further add to the reviewer’s confidence that these results accurately describe the ability of Axumin to identify prostate cancer lesions outside the prostate bed.

Efficacy Results – Secondary and other relevant endpoints

The next two tables are snapshots from the submission for inter-reader and intra-reader agreement results. The reviewer notes these data were not verified by the statistical team.

Figure 4: Fluciclovine F18 Injection Inter-Reader Agreement for Lesion, Region and Subject Level.

	Reader 1 vs. Reader 2				Reader 1 vs. Reader 3				Reader 2 vs. Reader 3				Agreement Among 3 Readers			
	Lesion	Region		Subj	Lesion	Region		Subj	Lesion	Region		Subj	Lesion	Region		Subj
		P	E-P			P	E-P			P	E-P			P	E-P	
N	6544	121	121	121	6586	121	121	121	6871	121	121	121	6496	121	121	121
Agreement (%)	96.4	91.7	81.8	93.4	95.9	77.7	76.0	77.7	96.8	79.3	74.4	79.3	94.7	74.4	70.3	76.0
Disagreement (%)	3.6	8.3	18.2	6.6	4.1	22.3	24.0	22.3	3.2	20.7	25.6	20.7	5.3	25.6	28.7	23.0
Cohen’s Kappa [95% CI]	0.59* [0.55, 0.64]	0.67* [0.48, 0.85]	0.64* [0.50, 0.77]	0.57 [0.33, 0.81]	0.5 [0.45, 0.55]	0.43* [0.27, 0.58]	0.56 [0.45, 0.68]	0.28 [0.12, 0.44]	0.55* [0.50, 0.60]	0.49 [0.33, 0.64]	0.53 [0.41, 0.65]	0.37 [0.20, 0.54]	0.54* [0.53, 0.56]	0.50 ^o [0.40, 0.59]	0.57 [^] [0.48, 0.66]	0.36 [^] [0.27, 0.44]

Reviewer Comments: *The above inter-reader agreement results show favorable agreement between readers one and two, but lower agreement for both readers one and two when they are compared to reader three. When reviewing the performance of all readers for identifying lesions in the prostate bed, it is clear that reader three called fewer lesions positive and therefore had lower “sensitivity” for detecting lesions in that region. This more conservative reads by reader three explain the lower agreement with both reader one and two. Overall, the inter-reader agreement may be acceptable, but these data prompt the reviewer to consider the inclusion of recommending reader training text in the product labeling.*

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Figure 5: Fluciclovine F18 Injection Intra-Reader Agreement for Lesion, Region and Subject Level

	Reader 1				Reader 2				Reader 3			
	Lesion	Region		Subject	Lesion	Region		Subject	Lesion	Region		Subject
		P	E-P			P	E-P			P	E-P	
N	641	12	12	12	682	12	12	12	739	12	12	12
Agreement (%)	97.8	100	83.3	100	96.9	100	75.0	100	99.1	91.7	83.3	83.3
Disagreement (%)	2.2	0.0	16.7	0.0	3.1	0.0	25.0	0.0	0.9	8.3	16.7	16.7
Cohen's Kappa [95% CI]	0.75* [0.62, 0.87]	1.00 [1.00, 1.00]	0.67 [0.27, 1.00]	N/A	0.58 [0.42, 0.74]	1.00 [1.00, 1.00]	0.54 [0.14, 0.94]	1.00 [1.00, 1.00]	0.75* [0.57, 0.92]	0.84* [0.57, 1.00]	0.64 [0.27, 1.00]	0.68 [0.35, 1.00]

Reviewer Comments: The above sponsor provided data (snapshot from submission) on intra-reader agreement results from the blinded, independent, central re-reads reveal acceptable performance within readers when each reader performed repeat reads of the 12 image sets. The reviewer notes higher between read variability within readers for lesions located outside the prostate bed (E-P results).

FDA Statistical Team Analyses

The FDA primary statistical reviewer conducted the following analyses of the sponsor's data for both the BED001 (on site reads) and BED002 (centralized expert re-reads) clinical studies. These data played a valuable role in validating the sponsor's analyses and the original Emory published manuscript results.

Table 10: Efficacy Analyses for Prostate Bed Region by FDA Statistical Reviewer.

	On –Site (BED001)	RDR1 (BED002)	RDR2 (BED002)	RDR3 (BED002)
N (Regions)	97	98	97	96
TP	57	58	56	47
FP	27	29	26	15
TN	12	10	12	24
FN	1	1	3	10
SE	98% (94%)	98% (95%)	95% (91%)	83% (73%)
SP	31% (16%)	26% (12%)	32% (17%)	62% (51%)
PPV	68%	67%	68%	76%

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	(58%)	(57%)	(58%)	(65%)
NPV	92% (77%)	91% (73%)	80% (60%)	71% (55%)

Reviewer Comments: As seen in the above table, the reviewer notes the FDA statistical reviewer has verified the sponsor's results for both the BED001 re-analysis data and the BED002 re-read data. These 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 sponsor interpretations.

Table 11: Efficacy Analyses for Extra-Prostatic Regions by FDA Statistical Reviewer.

	On -Site	RDR1	RDR2	RDR3
N (Subjects)	29	28	28	25
TP	27	25	26	22
FP	2	2	2	2
TN	0	0	0	0
FN	0	1	0	1
SE	27/27 (100%)	25/26 (96%)	26/26 (100%)	22/23 (96%)
SP	0/2	0/2	0/2	0/2
PPV	27/29 (93%)	25/27 (93%)	26/28 (93%)	22/24 (92%)
NPV	0/0	0/1	0/2	0/1

Reviewer Comments: The FDA statistical reviewer also verified the sponsor's results for the BED001 re-analysis data and the BED002 re-read data for the extra-prostatic sites. These data also compare favorably with each other and further support to the integrity and accuracy of data from the original published Emory study (R01).

6.4 Supportive Studies

6.4.1 Overview of Studies

The below table summarizes additional supportive studies that were submitted in support of the proposed indication. The bulk of these data originate from the Bologna study originally published in 2015, which the sponsor re-analyzed in study BED001 and performed an independent, blinded re-read of the images in studies BED002 and BED007.

Table 12: Supportive Studies.

Study	Population	Design	Endpoints	Comparator/Reference Standards	Image Reads	Comments
Bologna Paper	Recurrent Prostate CA	Prospective, single center, open label study comparing Fluciclovine to ¹¹ C-Choline; N=50	Detection Rates	Comparator study: ¹¹ C-Choline	On site readers	Higher number of positive Fluciclovine scans reported compared to FDA approved imaging agent. No FDA verification of results.
BED001 Bologna	Recurrent Prostate CA	Re-analysis of Bologna data; N=88 (96 scans)	Agreement	¹¹ C-Choline comparator	On site reads	Acceptable agreement results reported.
BED002 Bologna	Recurrent Prostate CA	Re-read of Bologna Fluciclovine scans; N=88 (96 scans)	Agreement	¹¹ C-Choline comparator	Blinded, Independent reads of Bologna Fluciclovine images.	Acceptable agreement results reported, although wide variability between 3 readers for prostate bed region.

Reviewer Comments: *The reviewer notes that additional subjects were added to the sponsor's analyses (BED001 and BED002) of the Bologna data as the study was ongoing at the time of the original published manuscript. Sensitivity and specificity could not be calculated because a truth standard was not employed; all patients were assumed to be positive based on rising PSA levels.*

6.4.2 Study Results

Table 13: Patient demographics of original published Bologna manuscript; N=50 subjects.

Demographic Parameter	Result
Age, years	

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Mean (SD)	50 (6)
Range	55-78
PSA Level (ng/mL)	
Mean	3.2 (3.9)
Range	0.24-15.6
Months from surgery	
Mean (SD)	65 (46)
Range	5-156
Gleason Score	
≤6	4 (8%)
7	31 (62%)
8-10	15 (30%)

Table 14: Bologna Study: Original Published Results.

N=50 subjects	¹¹ C-Choline (-)	¹¹ C-Choline (+)
¹⁸ F-Fluciclovine (-)	33	0
¹⁸ F-Fluciclovine (+)	6	11

Reviewer Comments: A numerically higher number of subjects (17 vs 11) were reported positive with Fluciclovine compared to the FDA approved comparator, thirty three (33) patients were negative with both tracers, there were six (6) patients positive by Fluciclovine, but negative by the comparator, and none were positive with the comparator and negative by Fluciclovine. Sensitivity and specificity could not be calculated because patient follow up was ongoing at the time this paper was published. These published results speak positively in favor of Fluciclovine given the patient population was assumed to have prostate cancer recurrence by standard of care laboratory evaluations (PSA levels; these results were not verified by statistical reviewers.

Table 15: Bologna Study: Fluciclovine positive patients.

N= 17		
Fluciclovine Positive Patients	¹⁸ F-Fluciclovine	¹¹ C-Choline
6	1	1
1	3	3
1	9	9
2	2	1
1	4	3
3	1	0
2	2	0
1	4	0

Reviewer Comments: *The above table displays results from the patients that were positive by Fluciclovine PET imaging. As shown, there were six patients with lesions found by Fluciclovine that were negative by the FDA approved comparator and multiple lesions were found by Fluciclovine in three of these subjects. No patients in this analysis were positive by the comparator and negative by Fluciclovine imaging. These results lend secondary support to Fluciclovine use in this population when compared to an FDA approved PET imaging agent; again, these results have not been verified by the statistical reviewers.*

Patient demographics of BED001 and BED002 Bologna study subjects.

Ninety one (91) subjects were enrolled into the study; three (3) of these were excluded for refusal of consent (2) and lack of contact from site to request data access (1). Thus, the data analyses include 88 of the original 91 enrolled subjects.

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Table 16: Demographic characteristics of the BED001 and BED002 Bologna study subjects.

Demographic Characteristics	N=88
Age	88
Mean years (SD)	69 (6.8)
Median (years)	69
Min, max (years)	55, 87
Race & Ethnicity	88
White	88 (100%)
Not Hispanic or Latino	88 (100%)
PSA (ng/ml) at baseline	88
Mean (SD)	2.9 (4)
Median	1.5
Min, max	0.1, 21
Gleason Score	73 (83%)
≤ 6	8 (9%)
7	36 (41%)
8-10	29 (33%)
Subjects having a Fluciclovine PET/CT scan	88
Total number of Fluciclovine scans	96

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Table 17: BED001 Bologna data agreement estimates (Fluciclovine vs. ¹¹C-Choline).

N=88 subjects, 96 scans.	
Region	Agreement
Prostate/Prostate Bed	97%
Pelvic Lymph Nodes	89%
Other Nodal, Bone or Soft Tissue	77%
Subject Level	78%

Table 18: BED002 Bologna data agreement estimates (expert Fluciclovine vs. ¹¹C-Choline).

N=88 subjects, 95 scans.			
Region	Reader 1 Agreement	Reader 2 Agreement	Reader 3 Agreement
Prostate/Prostate Bed	64%	72%	92%
Extra-Prostatic	72%	74%	77%
Subject Level N-95	61%	67%	77%

Reviewer Comments: *The above two tables demonstrate agreement (Fluciclovine versus ¹¹C-Choline) estimates ranging from 64% to 97% (depending on region) for the onsite reads (BED001) and the blinded, independent reads conducted by the sponsor (BED002). Although the variability seems higher in the BED002 study, these results combined provide some added confidence to the primary data (sections 6.2 and 6.3) that supports test tracer's ability to detect lesions in the population of proposed clinical use. No standard of truth was employed, so we do not know the true sensitivity and specificity of the test and comparator imaging agents in this study population. The secondary statistical reviewer has included, but not verified, the above agreement estimates for the subject level analyses in her review.*

Note there were a high number of negative scans in these studies which is consistent with the original Bologna published manuscript: BED001-51 negative scans by Fluciclovine, 49 negative scans by ¹¹C-Choline for the subject level analysis. BED002 Subject Level Analysis- Reader 1 and Reader 2 showed 38 and 45 negative Fluciclovine scans, Reader 3 categorized 65 Fluciclovine scans as negative. The on-site read had previously categorized 49 ¹¹C-Choline scans as negative. Reader 3 appears to have had a higher threshold for calling Fluciclovine scans positive, as also

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seen in the Emory data results.

7 Integrated Review of Effectiveness

7.1.1. Primary Endpoints

Primary endpoints were different among the sponsor's efficacy studies and for the original Emory and Bologna investigations.

7.1.2. Secondary and Other Endpoints

Not applicable.

7.1.3. Subpopulations

There were no significant differences in efficacy observed in subpopulation analyses including age, sex, and race and ethnicity. Lower performance estimates were seen for PSA levels below 1.05 ng/mL, which should be described in the product labeling.

7.1.4. Dose and Dose-Response

The following is taken from the clinical pharmacology review: Clinical trials from various institutions (Oslo University, Bologna University, Emory University and Aleris, Norway) studied doses of ¹⁸F-Fluciclovine varying from 162 - 485 MBq (4.4 to 13.1 mCi). The investigators from Oslo University used a dose of 200 MBq and concluded that ineffective images were obtained. The basis for selecting doses does not appear in the submission or in the literature. No dose finding studies were identified in the literature or were conducted by the applicant. The proposed package insert recommends a dose of 370 MBq or 10mCi by intravenous injection in a total volume not exceeding 5 mL. The mass dose of ¹⁸FFluciclovine is 2 ug/mL (max of 10 ug).

In the Emory study (primary efficacy data) the mean and median dose administered in patients with a positive scan finding (n=90) was 357.7MBq (9.7mCi) and 370MBq (10mCi) while in those with negative findings on the fluciclovine PET-CT scan (n=14) the mean and median dose administered was 361.8MBq (9.8Ci) and 362.6 MBq (9.8mCi), respectively.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2. Additional Efficacy Considerations

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7.2.1. Considerations on Benefit in the Post market Setting

The two important considerations for the post-market setting include:

- PSA levels in patients undergoing Axumin PET imaging. In the BED001 study results, we see that in patients with PSA values around 1 and below, the estimated diagnostic performance of Axumin is lower than for higher PSA values.
Reviewer's Comment: *I believe this information should be mentioned in the product labeling for clinicians to consider when considering Fluciclovine PET/CT.*
- Use of Axumin in primary prostate cancer.

It is likely that once approved, clinicians will use Axumin in certain patients with primary prostate cancer to boost the confidence in already performed, conventional staging tests and/or to assist with treatment planning. In the BED001 study, the sponsor reports data from the Aleris and OUS sites for 61 patients which show 56 true positives and 4 false negatives for the prostate bed region (92% Sensitivity) and the PPV for extra-prostatic sites was 59%.

Figure 6: Primary prostate cancer reported results (BED001 study).

	Region		Patient
	Prostate and Prostate Bed	Extraprostatic	
N	61	59	61
True Pos	56	15	57
False Pos	0	9	
True Neg	0	26	
False Neg	5	11	4
PPV	56/56 (100%)	13/22 (59.1%)	57/57 (100%)
[95 CI]	[93.6, 100]	[36.4, 79.3]	[36.4, 79.3]
NPV	0/5 (0%)	26/37 (70.3%)	0/4 (0%)
[95 CI]		[53.0, 84.1]	
Sensitivity	56/61 (91.8%)	13/24 (54.2%)	57/61 (93.4%)
[95 CI]	[81.9, 97.3]	[32.8, 74.4]	[84.1, 98.2]
Specificity	0/0	26/35 (74.3%)	0/0
[95 CI]		[56.7, 87.5]	

Source: BED 001 Table 14.2.2.2; 14.2.3.2

Reviewer's Comments: *The reviewer recommends caution in the interpretation of these results as they were not verified by the statistical review team.*

Early Exploratory Studies in Primary Prostate Cancer

The following text is taken from the submission.

Study NMK36-PC-P201 was a small pilot safety study assessing the efficacy and safety of 185MBq (5 mCi) doses of Fluciclovine in 10 patients with biopsy confirmed primary prostate

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cancer. Patients were eligible for the study if two or more biopsy cores from a prostate needle biopsy (performed less than three months (90 days) before the date of consent) were positive for prostate cancer and lymph node and/or bone metastases were identified using CT scan, MRI (Magnetic Resonance Imaging) or bone scintigraphy (carried out less than three months (90 days) before the date of consent). Patients were excluded from the study if they had received any prior treatment for their prostate cancer.

Patients were elderly males (mean 69.9 ± 7.9 years), mean height was 162.56 ± 6.89 cm and mean body weight was 64.55 ± 9.37 kg. Mean PSA level was 386.94 ± 662.06 ng/mL, mean Gleason scores (total) were 8.5 ± 1.0 . Four of the ten patients had undergone CT scan, and metastases had been identified in three; eight of the ten had undergone MRI scan, and metastases had been identified in seven. Eight of the ten had had undergone bone scintigraphy and metastases had been identified in five. Results reported were "Fluciclovine PET-CT identified areas of malignancy in the prostate and in extraprostatic sites in all cases pre-identified. In addition, Fluciclovine PET-CT identified additional lymph node metastases in several patients which were not detected with other imaging techniques."

Study NMK36-PC-202 was an open label study of the diagnostic accuracy of Fluciclovine PET-CT in staging of primary prostate cancer in patients with biopsy confirmed disease. Two groups of patients were investigated: patients who were scheduled to undergo radical prostatectomy and patients with CT evidence of lymph node enlargement who were to receive hormone treatment. The performance of fluciclovine PET-CT was compared to contrast enhanced CT and, in patients undergoing radical prostatectomy, to histopathology.

A total of 68 patients received Fluciclovine at either low dose 122 MBq (3.3 mCi; 35 patients) or high dose 244 MBq (6.6 mCi; 34 patients); 66 patients completed the study (44 radical prostatectomy and 22 hormone therapy). Patient age (mean \pm SD) was 67.3 ± 6.0 , PSA level 88.61 ± 168.42 ng/mL (radical prostatectomy: 21.44 ± 19.27 ng/mL, hormone therapy: 211.76 ± 239.76 ng/mL). Gleason scores in the radical prostatectomy group were, in order of frequency, 7 (40.9%, 18/44), 9 (25.0%, 11/44) and 8 (22.7%, 10/44). A score of 9 (50.0%, 12/24) was the most common in the hormone therapy group. All patients were classified histologically frequency, T3a (31.8%, 14/44 cases) and T2a (22.7%, 10/44). The most common stage in the hormone therapy group was T3b (45.8%, 11/24). Regional lymph node and bone marrow metastasis investigations carried out at the study sites before Fluciclovine PET-CT had indicated metastases in respectively 100.0% (24/24) and 58.3% (14/24) of patients in the hormone therapy group, but no metastases were found on pre study imaging in the radical prostatectomy group.

Results of Fluciclovine PET-CT vs standard of truth (results of pathological examination in the radical prostatectomy group and percentage short-diameter shrinkage in the regional lymph nodes on a pelvic contrast CT scan taken after treatment in the hormone therapy group) were

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reported as: PPV, NPV, sensitivity and specificity of Fluciclovine PET-CT (95% CI) for the detection of lymph node metastases in patients with primary prostate cancer in this study is 92.9% (66.1, 99.8) , 82.9% (67.9, 92.8), 65% (40.8, 84.6) and 97.1% (85.1, 99.9) respectively.

Reviewer's Comments

This limited sponsor reported data suggest the diagnostic performance of Fluciclovine PET/CT in primary prostate cancer may be similar to that seen in the confirmatory studies submitted for approval. I support not limiting the indication for Fluciclovine to recurrent prostate cancer patients, as we have no reason to believe the diagnostic performance would be lower in primary prostate cancer with similar characteristics as the studied populations. However, I acknowledge these data may not accurately describe how the agent performs in patients with low risk disease. The decision to limit use of the drug in recurrent prostate cancer will be a decision to be made by the team during labeling meetings.

7.2.2. Other Relevant Benefits

There are no other identified clinical benefits of Axumin that have not been discussed.

7.3. Integrated Assessment of Effectiveness

In my opinion, the sponsor'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 (see section 6.2) and BED002 Emory (see section 6.3) allow a reasonable conclusion to be made that Fluciclovine F18 Injection has sufficient accuracy in identifying prostate cancer in the proposed patient population. These studies compared Fluciclovine F18 Injection PET imaging results to a truth standard (histology) which allowed verification of imaging findings. The 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; negative predictive value, sensitivity and specificity estimates were performed for the in the prostate bed. The consistency of favorable results among the initial study publication, the BED001 re-analysis study and the BED002 re-read study provide confidence to my belief this drug will perform as well or better than the two approved radio-diagnostic agents indicated for use in prostate cancer patients. Additionally, the original published manuscript of the Emory data (2014, fewer subjects than BED studies) showed Fluciclovine detected more lesions than an FDA approved comparator, thus furthering my confidence in the clinical usefulness and reliability of Fluciclovine in this patient population.

In addition, the supportive studies (see section 6.4) BED001 Bologna and BED002 Bologna compared the investigational agent to another FDA approved imaging agent and estimated agreement of Fluciclovine F18 Injection to this approved agent for detecting prostate cancer recurrence in subjects presumed positive for disease (no truth standard). These results show

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acceptable agreement rates with the comparator. And similar to the original Emory published paper, the original manuscript of the Bologna data (2015, fewer subjects than BED studies) showed that Fluciclovine was positive in more patients than the FDA approved imaging agent.

The totality of all these data supports the sponsor’s claim for Fluciclovine F18 Injection PET imaging in prostate cancer patients.

It is important to highlight that we do not have true performance measures in terms of sensitivity and specificity for regions outside the prostate bed due to the nature of how imaging informed truth standard determinations in these regions. I believe the clinical value of Fluciclovine will likely be greatest in subjects who have presumed disease recurrence and are at a moderate to high likelihood of having disease deposits outside the prostate bed including pelvic region and distant sites (bone, liver, etc.). In these subjects, it is my opinion (based on clinical experience, literature reports, and this submission) that Fluciclovine will perform as well or better than the current FDA approved imaging agents for identifying sites of prostate cancer; the submitted data support that positive Fluciclovine F18 Injection PET/CT image findings are likely to represent prostate cancer

Regarding the product labeling, I recommend the following edits:

- Section 1 Indications and Usage**
 Add: “Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, is recommended.”
- Clinical Studies Section**
 I recommend deleting the sponsor’s tables and using only the statistical team’s tables that represent verified results, along with the sponsor’s reported results based on PSA quartile using the table I created which corrects mistakes in the sponsor’s calculations for PPV and NPV. I do not recommend including tables for the Bologna data, these data could be omitted are simply described in paragraph form.

Table 19: Efficacy Analyses for Prostate Bed Region by FDA Statistical Reviewer.

	On –Site (BED001)	RDR1 (BED002)	RDR2 (BED002)	RDR3 (BED002)
N (Regions)	97	98	97	96
TP	57	58	56	47
FP	27	29	26	15
TN	12	10	12	24
FN	1	1	3	10
SE	98%	98%	95%	83%

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	(94%)	(95%)	(91%)	(73%)
SP	31% (16%)	26% (12%)	32% (17%)	62% (51%)
PPV	68% (58%)	67% (57%)	68% (58%)	76% (65%)
NPV	92% (77%)	91% (73%)	80% (60%)	71% (55%)

Table 20: Efficacy Analyses for Extra-Prostatic Regions by FDA Statistical Reviewer.

	On -Site	RDR1	RDR2	RDR3
N (Subjects)	29	28	28	25
TP	27	25	26	22
FP	2	2	2	2
TN	0	0	0	0
FN	0	1	0	1
SE	27/27 (100%)	25/26 (96%)	26/26 (100%)	22/23 (96%)
SP	0/2	0/2	0/2	0/2
PPV	27/29 (93%)	25/27 (93%)	26/28 (93%)	22/24 (92%)
NPV	0/0	0/1	0/2	0/1

Table 21: Results by PSA Quartile on a subject level for study BED001.

N = 99				
PSA Value (ng/mL)	≤ 1.05	> 1.05 to ≤ 3.98	> 3.98 to ≤ 8.9	> 8.9
No. Subjects	16	31	25	27
True Positive	3	23	20	23
True Negative	4	5	4	4
False Positive	8	3	1	
False Negative	1	0	0	
PPV	27%	88%	95%	100%

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NPV	80%	100%	100%	100%
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Reviewer's Comments: *We will make additional minor edits at our ongoing labeling meetings; the final format of the approved drug label is not yet determined.*

8 Review of Safety

8.1. Safety Review Approach

For the safety review, we looked at all reported data comprising 7 clinical studies and including a total of 837 subjects. My detailed review does focus more on the BED001 safety data which constitutes 714 of the 837 subjects available in the database.

8.1.1. Overall Exposure

Table 22: Studies and patients included in the review of safety.

Study	Design	Population	Number of subjects enrolled/evaluable	Study and Comparator Drugs	Endpoints
Phase 1					
GE148-001	Open label single dose	Healthy Volunteers	6/6	Fluciclovine F18	Safety, Bio-distribution
		Primary Prostate CA	6/6		
NMK36-P1	Open label, single dose	Healthy Volunteers	6/6	Fluciclovine F18	Safety, Bio-distribution, Dosimetry
Phase 2					
GE148-002	Open label, single dose	Primary Prostate Ca	25/22	Fluciclovine F18	Safety, Exploratory Efficacy
NMK36-PC-201	Open label, single dose	Primary Prostate CA	11/10	Fluciclovine F18	Safety, Dose ranging, Early Efficacy

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NMK36-PC-202	Open label, 2 dose	Primary Prostate CA	72/68	Fluciclovine F18	Efficacy and Safety
NMK36-BT-201	Open label, single dose	Glioma	5/5	Fluciclovine F18	Safety, Early Efficacy
Phase 3					
BED001	Retrospective, Observational	Recurrent prostate and breast cancers	714/714	Fluciclovine F18	Safety and Positive Predictive Value for identifying recurrent dz

Reviewer Comments: *The reviewer notes the overall safety database for this application includes 837 subjects from the above studies. The vast majority of these patients had a history of recurrent prostate cancer which is the intended patient population.*

8.1.2. Relevant characteristics of the safety population

Table 23: Safety Population Demographics.

	GE148-001	GE148-001	Ge148-002	NMK36-P1	NMK36-201	NMK36-PC202	NMK36-BT-201	BED-001
N	6	6	22	6	10	68 (multi-center)	5	714 (multi-center)
Pop	Healthy Volunteers	Prostate Cancer	Prostate Cancer	Healthy Volunteers	Prostate Cancer	Prostate Cancer	Glioma	Prostate CA Recurrence
Age Mean (Range)	23 (21,24)	67 (60,75)	61 (42,71)	24 (21,29)	70 (54,81)	67 (51,82)	54 ()	67 (42,90)
Male	50%	100%	100%	100%	100%	100%	40%	100%
Female	50%						60%	
Ethnic Origin								74.2% missing
Hispanic/Latino			4.5%					1 subject

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Not H/L	1005	100%	95.5%	100%	100%	100%	100%	
<i>Race</i>								
White	100%	100%	82%					31.2%
Black/Af. American			18%					3.6%
Oriental				100%	100%	100%	100%	

Reviewer Comments: *The above demographic data show the drug has been tested in the proposed population of use with regards to gender and age groups. However, only 30 subjects (3.5% of 837 subjects) of African Americans descent are represented in the above table. This may have implications for post marketing study discussions. Also note that 74.2% of ethnic origin data is missing from the BED001 study.*

8.1.3. Adequacy of the safety database:

Given the intended population and clinical use, the reviewer believes the safety database of 837 subjects is more than adequate to allow an informed judgment as to the safety of the single, micro-dose radio-diagnostic agent Fluciclovine F18 injection. Safety evaluations included treatment emergent adverse events (TEAEs), pre and post treatment changes in laboratory haematology, biochemistry and urinalysis safety evaluations, pre and post treatment 12 lead ECGs, as well as vital signs pre and post dose during imaging sessions.

8.2. Adequacy of Applicant’s Clinical Safety Assessments

8.2.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns identified regarding the data integrity; safety findings across studies are reasonably consistent and are as expected for a single micro-dose PET tracer like Axumin.

8.2.2. Categorization of Adverse Events

The procedure for recording and reporting AEs was defined in the data safety monitoring plans and fulfilled local IRB requirements and FDA regulations; standard terminology and severity categorization was applied. The sponsor considered “treatment emergent” as adverse events that occurred after administration of Fluciclovine regardless of whether or not the AE was considered drug related. The TEAEs reported for BED001 were presented by MedDRA System Organ Class and preferred term in the final study report.

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I believe the sponsor's AE assessment procedures were acceptable and consistent with IRB and regulatory requirements.

8.2.3. Routine Clinical Tests

In my opinion, the sponsor's assessments of clinical laboratory parameters, vital signs, and EKG tracings are acceptable given the proposed use of this micro-dose tracer is a single intravenous administration. *See section 6.2.1 for details on how/when safety data was collected & assessed.*

8.3. Safety Results

8.3.1. Deaths

No deaths were reported in any of the studies. This included a reporting period of within 35 days of Fluciclovine F18 injection for the BED001 study.

8.3.2. Serious Adverse Events

Two serious adverse events were reported for the BED001 study; one subject was from the Norway site and one was from the Bologna site.

Subject 3901 – 0038: 72 year old male, experienced a single episode of grade 3 severe hypertension 33 days after receipt of fluciclovine (18F) for which he was treated and hospitalized. The subject had the ongoing medical conditions recorded in his medical history: hypertension, an enlarged right adrenal gland, left inferior leg edema and high glycosylated hemoglobin. He also had a history of (resolved) cerebral ictus. At the time of the adverse event, he was taking Simvacor, amlodipine and Cotareg and also bicalutamide daily. The event deemed unrelated to fluciclovine (18F), resolved within 3 days.

Reviewer's Comments: *I agree this episode of severe hypertension 3 days post Fluciclovine was likely unrelated to the administration of this micro-dose imaging agent.*

Subject 4702 – 0175: 68 year old male, experienced an abdominal bleed (losing 2.8 litres after prostate surgery resulting in a drop in hemoglobin and a fall in blood pressure and a pulmonary embolism) 4 days after receipt of fluciclovine (18F). The PET scan with 300 MBq fluciclovine (18F) was performed without complications. Three days after the PET examination the patient underwent a robot assisted laparoscopic prostatectomy. The procedure was described as uneventful. On the same evening the patient became pale and semi-conscious and underwent an emergency laparotomy; 2.5 liters of blood was found in the abdomen. The vascular pedicle from the left side of the prostate was bleeding and was ligated; the right side was normal. There was also some slight bleeding from the left port of access, but nothing from the abdominal incision. The patient was given 5 units of red blood cells and four units of Octaplas.

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The immediate post-operative period was uneventful, but 7 days after the PET, 4 days after the procedure he fainted and a bilateral pulmonary embolism was found which affected both upper lobes. The patient was anticoagulated with dalteparin, and recovered uneventfully. These events were life-threatening causing a prolonged hospital stay. At the time of the adverse event, he was not recorded to be taking any medications. The pulmonary embolism was considered secondary to the procedure and possibly the use of Octaplas. All serious events were deemed unrelated to fluciclovine (18F), and resolved within 16 days.

Reviewer's Comments: *I agree this adverse event of abdominal bleeding post-surgery was not related to the administration of Fluciclovine.*

8.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no reported dropouts or discontinuations for any of the studies due to adverse drug effects.

8.3.4. Significant Adverse Events

No significant AEs were identified.

8.3.5. Treatment Emergent Adverse Events and Adverse Reactions

In healthy volunteers (N=12), there were a total of 12 adverse events as seen in the below snapshot from the submission.

	Study	
	GE-148-001 N = 6	NMK36-P1 N = 6
MedDRA SOC MedDRA Preferred Term	Subjects (n (%))	Subjects (n (%))
Any AE	2 (33.3)	2 (33.3)
General disorders and administration site conditions	0	1 (16.7)
Injection site erythema	0	1 (16.7)
Investigations	2 (33.3)	1 (16.7)
Decreased blood fibrinogen	0	1 (16.7)
Blood calcium decreased	1 (16.7)	0
INR increased	1 (16.7)	0

Reviewer's Comments: *Although a relationship cannot be ruled out between decreased blood fibrinogen, my opinion is this case is not directly related to Axumin administration.*

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BED001 Patients

In prostate cancer patients enrolled in study BED001, the following safety results were seen: Of the 714 subjects with all cancer types in the BED001 study, 42 subjects (5.9%) had a TEAE. TEAEs were reported in 15 subjects (8.9%) at Emory, 14 (15.9%) at Bologna, 3 (1.5%) at Aleris and 10 (3.8%) at OUS. In these 714 subjects with all cancer types in the BED001 study, there were 82 TEAEs reported at the 4 sites; 47 at Emory, 15 at Bologna, 5 at Aleris and 15 at OUS. Of the 95 subjects with primary prostate cancer, there were 5 TEAEs reported.

In the recurrent prostate cancer safety dataset, 32 of the 596 subjects (5.4%) had a TEAE. TEAEs in this group were reported in 7 subjects (5.1%) at Emory, 14 (15.9%) at Bologna, 3 (2.1%) at Aleris and 8 (3.6%) at OUS. The only AE that occurred in $\geq 1\%$ of enrolled subjects with recurrent prostate cancer was [Injection Site Extravasation](#), which was reported in 9 of 596 of these subjects by the image readers only.

For the recurrent prostate cancer subjects, the descending order of TEAEs by system organ class (SOC) in the overall population of 596 subjects was general disorders and administration site conditions (1.7%), neoplasms benign malignant and unspecified (incl. cysts and polyps) (1.3%), gastrointestinal disorders (0.7%), investigations (0.7%), nervous system disorders (0.3%), renal and urinary disorders (0.3%), blood and lymphatic system disorders (0.2%), eye disorders (0.2%), hepatobiliary disorders (0.2%), infections and infestations (0.2%), injury, poisoning and procedural complications (0.2%), musculoskeletal and connective tissue disorders (0.2%), reproductive system and breast disorders (0.2%), skin and subcutaneous disorders (0.2%) and vascular disorders (0.2%).

At any individual site the treatment emergent events occurring with a frequency of $\geq 1\%$ in descending order of frequency were injection site extravasation (9 cases, 10.2%), gastrointestinal disorder (2 cases, 1.5%), rectal polyp (1 case, 1.1%), gallbladder cholesterolosis (1 case, 1.1%), and hypertension (1 case, 1.1%).

The greatest intensity for a reported TEAE was one case of [Grade 3 hypertension](#) at the Bologna site; there were no other TEAEs of Grade 3 severity reported. One subject report [Grade 2 Malaise and Pain](#) at the Aleris site. All other TEAEs reported were of Grade 1 intensity.

Generally, reported AEs were not considered to be related to Fluciclovine administration. Of note, the 9 cases of extravasation (all at the Bologna site) were not reported in association with injection site reactions and were noted only on scan images.

Of the 95 subjects with primary prostate cancer, 2 (2.1%) subjects reported a TEAE; both of these subjects received fluciclovine (¹⁸F) at OUS. There were 5 TEAEs occurring in 2 subjects of the 34 primary prostate cancer subjects from OUS: these were ventricular extrasystoles in 1 subject and another subject was reported to have experienced the 4 TEAEs of post-procedural hemorrhage, post procedural pulmonary embolism, blood pressure decreased and hemoglobin decreased. No other sites reported TEAEs for those patients who received Fluciclovine as part of patient diagnostic assessment for primary prostate cancer.

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In the 23 subjects with non-prostate cancer, 8 subjects (34.8%) reported TEAEs; all these subjects were from the Emory site.

Common Adverse Events in study BED001

From the submission:

“At any individual site the treatment emergent events occurring with a frequency of $\geq 1\%$ in descending order of frequency were injection site extravasation (9 cases, 10.2%), gastrointestinal disorder (2 cases, 1.5%), rectal polyp (1 case, 1.1%), gallbladder cholesterosis (1 case, 1.1%), and hypertension (1 case, 1.1%).”

“The worst intensity for a reported TEAE was one case of Grade 3 hypertension at the Bologna site; there were no other TEAEs of Grade 3 severity reported. There was one report of Grade 2 malaise and pain at the Aleris site. All other TEAEs reported were of Grade 1 intensity.”

The sponsor states “There was no clear pattern of adverse events which emerged from any of the clinical data. There was no effect of fluciclovine (¹⁸F) dose on the frequency or nature of TEAEs reported”.

Reviewer’s Comments: I agree with the above comments by the sponsor as there is no clear pattern of AEs in the submitted data; Fluciclovine appears well tolerated at the intended dose in this population.

For all subjects in the BED001 study, the most common individual AEs I observe in the data sets that are in my opinion possibly related to study drug injection include 1) Injection Site Extravasation (1.5%), 2) Gastrointestinal Disorder (0.3%), Hemoglobin Decreased (0.3%), Loss of Consciousness (0.2%), Pain (0.2%), Hypertension (0.2%), Blood Creatinine Increased (0.2%), White Blood Cell Count Increased (0.2%), Muscular Weakness (0.2%).

The most clinically notable in my opinion are Injection Site Extravasation, Pain, LOC, Hypertension, and Muscular Weakness; these could possibly be related to vasovagal and allergic type reactions seen with intravenous injections. These AEs should be included in the drug labeling.

Other AE Data

Most of the below text is from the submission.

GE-148-001: In the GE148-001 study a total of 4 adverse events were reported in 4 subjects, 2 adverse events in two healthy volunteers (described above) and two events in 2 prostate cancer subjects. All 4 AEs were of mild intensity. One TEAE in a prostate cancer subject was considered as at least possibly related to fluciclovine.

There were no SAEs, AEs leading to discontinuation of study radiotracer, or AEs leading to death during the study in the prostate cancer group.

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GE-148-002: In the GE148-002 study, a total of 6 adverse events (of which there were 3 TEAEs, all of mild intensity) were reported in 6 prostate cancer subjects. Two TEAEs were considered as at least possibly related to fluciclovine.

NMK36-PC-P201: In the NMK36-PC-P201 study, a total of 2 adverse events both of mild intensity, were reported in 2 prostate cancer subjects. Neither TEAE was considered to have a causal relationship to fluciclovine.

NMK36-PC-P202: In the NMK36-PC-P202 study, a total of 7 adverse events, were reported in 7 prostate cancer subjects. Two cases of nasopharyngitis were of moderate intensity and the remaining AEs were of mild intensity. The causal relationship to fluciclovine to the AE of Blood fibrinogen increased could not be ruled out; all other AEs were considered not related.

NMK36-BT-201: There were three adverse events, in two of the five patients in the safety analysis set. None of these adverse events were serious, all were mild in severity, and all patients recovered without requiring medical intervention. Adverse events reported were headache (2 events in 1 patient), and malaise (1 event in 1 patient). One of the headache events was considered to be related to receipt of fluciclovine; the patient recovered without requiring medical intervention.

8.3.6. Laboratory Findings

Most of the following text is taken from the submission.

Study NMK36-P1: There were small but non-clinically significant changes in the laboratory test parameters measured from baseline to the follow-up period in the study subjects. The only change of clinical relevance was a single case of decreased blood fibrinogen, which was mild and not serious (low serum fibrinogen of 169.8 mg/dL (relevant normal range was 180-380 mg/dL) on day 7, which recovered to 243.8 mg/dL on day 17).

Study GE148-001: There were no clinically significant changes in the healthy volunteers and prostate cancer subjects in the hematology and biochemistry laboratory test parameters. One subject had decreased serum calcium, reported as an AE, which returned to within the normal range at 24 hours after fluciclovine (¹⁸F) administration. There were no clinically relevant changes in the coagulation parameters assessed except for one cases of (mild) INR increased, reported as an AE, and which resolved without treatment.

Study GE148-002: Only small (and mild) biochemistry changes were seen in any subjects. Ten subjects had slight increases in serum creatinine compared to baseline (with a mean increase of < 6 umol/L) and all measured values remained within the normal range (68-105 umol/L). There were few changes in hematology variables during the study; two subjects had changes in their white cell counts and three subjects had changes in their platelet results between baseline and

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the end of the last PET scan (these changes occurred in subjects with clinically notable baseline values in the same parameter).

Study NMK36-PC-201: Small changes were reported in the following hematology and biochemistry variables which were considered both clinically minor and also not of clinical relevance. There was a mean increase in the neutrophil count of $5.93 \pm 4.27\%$ ($p=0.002$) and a mean decrease in lymphocyte count of $4.84 \pm 3.66\%$ ($p=0.002$). Biochemistry changes were an increase in urea nitrogen of 2.10 ± 1.66 mg/dL ($p=0.003$) and a decrease in LDH of 21.4 ± 26.5 U/L ($p=0.031$).

Study NMK36-PC-202: A small increase from baseline was reported in the hematology variable of basophil count ($0.10 \pm 0.26\%$; $p=0.003$). The following changes were reported for the biochemistry variables; AST (-1.4 ± 4.7 U/L; $p = 0.018$), LDH (-5.7 ± 20.3 U/L; $p = 0.024$), creatine phosphokinase (9.29 ± 36.32 U/L; $p=0.039$), triglycerides (-13.2 ± 41.7 mg/dL; $p=0.011$) and urea nitrogen (0.80 ± 2.43 mg/dL; $p=0.008$).

Study NMK36-BT-201: In the glioma Study NMK36-BT-201 there was a statistically significant but clinically unimportant increase in plasma fibrinogen noted on the post treatment compared to pre-treatment hematological evaluation in all patients in this study. The increase was <14 mg/dL and was not associated with other clotting abnormalities.

Study BED001: The submission states: "In the BED001 study there was limited consistent and prospectively managed laboratory data. Therefore, only listings and not tabulations of the laboratory parameters were produced."

The site with the largest amount of laboratory test result data in the recurrent prostate cancer population available was the Emory site: 115 patients who received 128 administered doses of fluciclovine in the R01 study. During the conduct of the R01 study, the site instigated a protocol amendment and increased the regularity of monitoring of laboratory parameters.

The submission states:

- In the more intensively monitored patients (those recruited later to the study), both the hematology and biochemistry parameters remained stable with little change between the day of fluciclovine administration and the follow-up, a week later. There were no pre- fluciclovine administration laboratory test results.
- There were few effects or trends of fluciclovine administration on individual hematology and biochemistry parameters; changes observed were considered not clinically significant.
- Decreases in hemoglobin between baseline and the follow up blood test were noted; in some of these cases with falls exceeding 1g/dL, were related to operative intervention.

Reviewer's Comments: *Review of the available laboratory data sets reveals no clinically concerning changes in parameters assessed from the day of imaging to the follow up testing.*

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The minor fluctuations observed are likely due to underlying medical conditions and/or dehydration in some patients.

8.3.7. Vital Signs

Much of the below text is taken from the submission.

BED001

The sponsor describes limited vital sign data collection among all the sites thus, only listings of the data were provided. The bulk of vital sign data is from the Emory site, as there were no repeated data available for vital signs from the Bologna, Aleris and OUS site.

In the recurrent prostate cancer dataset, there were 3 subjects whose systolic blood pressure rose at least 10mm Hg within 35 days of the fluciclovine (¹⁸F) scan compared with the result at baseline. These subjects were all taking medication which can affect blood pressure.

There were 6 patients (of whom 4 subjects were taking anti-hypertensive medication) whose systolic blood pressure decreased at least 10mm Hg within 35 days of the fluciclovine scan compared with the result at baseline. In addition, one subject from this site with recurrent prostate cancer (0101-0159, taking anti-hypertensive medication) had a rise in blood pressure recorded (+43 mmHg) 9 days after the fluciclovine scan from a low systolic blood pressure of 98 mmHg at baseline.

In the primary prostate cancer dataset, there were 8 subjects whose systolic blood pressure fell or rose at least 10mm Hg within 35 days of the fluciclovine scan compared with the result at baseline, all of whom were taking medication which can affect blood pressure. As can be expected, these changes in blood pressure were frequently accompanied by a change in pulse.

Reviewer's Comments: The described changes in blood pressure do not appear to be related to Axumin when accounting for the context of events and time of occurrence. Any recorded changes in blood pressure during the follow up period were likely due to patients' underlying medical conditions, dehydration, anxiety/stress, and/or medication compliance/use on those specific days.

NMK36-P1: There were small but non-clinically significant changes in some of the vital signs of the subjects during the study. Systolic blood pressure of subjects decreased immediately before, and at 15 and 60 minutes after administration which was a statistically, but not clinically, significant change. There was also a decrease in body temperature at day 7.

GE148-001: There was a decrease in mean systolic blood and mean diastolic blood pressure from baseline over the first few hours in both healthy volunteers and prostate cancer patients but which returned towards the baseline level at the end of the observation period. No significant changes in the vital signs were noted or adverse events reported.

GE148-002: The mean systolic and diastolic blood pressure decreased from baseline at the 10 and 30 minute assessment, and then returned to slightly above the baseline value at the end of the last PET

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scan. Heart rate was decreased at all assessments after baseline and only a small change or no change was observed in the respiratory rate and tympanic temperature, respectively, after baseline.

NMK36-PC-201: The only notable change in vital signs reported was a mean change of -8.1 ± 10.7 mm Hg which was a clinically minor change without clinical importance.

NMK36-PC-202: There were no significant changes in heart rate, or systolic or diastolic blood pressure from baseline.

NMK36-BT-201: Investigation of vital signs revealed no significant changes two days after administration, compared with before administration.

***Reviewer's Comments:** Given the type of drug (micro-dose radio-diagnostic agent) and single injection dosing, the review teams allow for some leniency in the data requirements for vital sign assessments. We have no reason to believe based on available vital sign data and what is known about Axumin that it will significantly affect vital signs in a way that poses danger to patients. That said, we can see allergic type and vasovagal reaction with all injected drugs, and we will monitor for these type events in the post-marketing reports for Axumin.*

8.3.8. Electrocardiograms (ECGs)

BED001 study

The submission states: "ECG tracings were not routinely performed at sites which used fluciclovine (18F) under the aegis of a compassionate use program or investigator-sponsored study. Thus, limited information is available regarding the cardiac effects of fluciclovine (18F)." Of the available data, the only abnormal ECG tracings from the BED001 study are related to QT intervals and discussed in section 8.3.9.

Other Studies

The following text is taken from the submission.

NMK36-P1: No reported abnormal ECG changes in any subject during the study evaluation period.

GE148-001: There were no significant changes in mean values of shifts from baseline and no clinically significant (or non-clinically significant) ECG findings in any health volunteer or subject with prostate cancer during the study evaluation period.

GE148-002: Mean changes between baseline and the end of the PET scan were not clinically significant. There were no ECG related AEs reported and all subjects had normal physical and cardiovascular examinations at the time of the final ECG.

One subject had two separate ECG recordings with a QTcB value > 501 ms but without any clinical abnormality at baseline. Two subjects had QTc changes > 60 ms after fluciclovine (18F) injection.

NMK36-PC-201: Changes in ECG tracings during the evaluation period were minimal; subjects either had normal ECG tracing results at both baseline and at Day 2 or changed from an abnormal result at baseline to a normal result at Day 2.

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NMK36-PC-202: No patients had ECG recordings that were normal before administration and then abnormal after administration of fluciclovine.

NMK36-BT-201: There was no abnormal variation in 12-lead ECG two days after administration, compared with before administration.

Reviewer's Comments: *There is no evidence to suggest a onetime micro-dose injection of Fluciclovine will affect heart conduction patterns; the review teams are in agreement on this opinion.*

8.3.9. QT

The clinical pharmacology team determined the likelihood of QT or QTc prolongation is remote, partially supported by the fact that Axumin is injected once as a micro-dose. There were no clinically significant or non-clinically significant ECG findings or QTc intervals >500 msec at any time point during the studies.

From ECG data collected in the BED001 study, there were 22 reports in 21 subjects (22 exposures to fluciclovine where the QTc interval was > 450 msec. Of these, two cases (both at the Emory site) occurred within 35 days of the administration of the radiotracer. Subject 0101-0065 had a QTC interval of 473 msec and subject 0101-0198 had a QTC interval of 609 msec recorded 20 and 8 days, respectively, after fluciclovine administration. There was no ECG recording performed prior to fluciclovine (¹⁸F) use/scanning for these subjects.

Reviewer's Comments: *I see no reason to believe these QT intervals of 473msec and 450 msec (borderline normal) are in any way related to study drug administration given the timing of events in relation to Fluciclovine injection; there are also no concerns based on non-clinical studies that Fluciclovine could prolong QT intervals.*

GE148-002:

One subject had two separate ECG recordings with a QTcB value > 501 ms but without any clinical abnormality at baseline. Two subjects had QTc changes > 60ms after fluciclovine (¹⁸F) injection.

Reviewer's Comments: *I agree with the clinical pharmacology team that the totality of available data suggest a single injection of Axumin has no significant effect on QT intervals*

8.3.10. Immunogenicity

Not studied and there are no concerns regarding immunogenicity of Axumin.

8.4. Analysis of Submission-Specific Safety Issues

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Radiation Dosimetry Estimates: The effective radiation dose resulting from the administration of 370 MBq for an adult weighing 75 kg, is about 8.2 mSv. If a CT scan is simultaneously performed as part of the PET procedure, exposure to ionising radiation will increase in an amount dependent on the settings used in the CT acquisition and the operator. For an administered activity of 370 MBq the typical radiation doses delivered to the critical organs, pancreas, the cardiac wall and uterine wall are 37.8 mGy, 19.1 mGy and 16.5 mGy, respectively.

Reviewer's Comments: *The estimated radiation dosimetry is comparable to numerous other radio-diagnostic agents and nuclear medicine procedures. This low level of radiation exposure has a favorable benefit/risk favorable in my mind for the proposed population and is acceptable.*

8.5. Specific Safety Studies/Clinical Trials

Not applicable.

8.6. Additional Safety Explorations

8.6.1. Human Carcinogenicity or Tumor Development

Human carcinogenicity has not been studied for this single micro-dose imaging agent.

8.6.2. Human Reproduction and Pregnancy

Not applicable. Fluciclovine F18 is not intended for use in women and there were no exposures in pregnancy and no exposures in lactating women.

8.6.3. Pediatrics and Assessment of Effects on Growth

A full pediatric waiver was granted for Axumin.

8.6.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no known or suspected potential for drug overdose, abuse, withdrawal or rebound associated with the use of Fluciclovine F18 Injection.

8.7. Safety in the Post-market Setting

8.7.1. Safety Concerns Identified Through Post-market Experience

Not applicable.

8.7.2. Expectations on Safety in the Post-market Setting

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There are no identified safety concerns for the post-market setting.

8.8. **Additional Safety Issues From Other Disciplines**

None reported.

8.9. **Integrated Assessment of Safety**

A total of 837 patients were included in the clinical study data submitted to support the safety of a single micro-dose of Axumin for PET imaging in patients with prostate cancer; 714 of these subjects were enrolled in the BED001 study. These data included patients with primary prostate cancer, recurrent prostate cancer, healthy volunteers, glioma patients, and breast cancer patients. There were no deaths, no serious adverse events attributed to study drug administration, and no significant safety issues identified. The observed adverse events and radiation dosimetry estimate of 8.2 mSv per dose are similar to other radio-diagnostic imaging agents including those with FDA approval for use in prostate cancer patients. Review the available laboratory and vital sign assessments do not reveal any clear pattern of change from baseline/day of injection to follow up testing suggestive of drug effect on tested parameters; minor changes note appear to be consistent with background event rates.

Based on review of these data, other discipline opinions and what is known about this compound, I have no uncertainties regarding the clinical safety of a single 10mCi intravenous dose of Axumin in the intended population.

9 Advisory Committee Meeting and Other External Consultations

The review teams determined no advisory meeting was necessary.

10 Labeling Recommendations

10.1. **Prescribing Information**

See the end of section 7.3 for my recommendations.

10.2. **Patient Labeling**

I do not see a need for development of either a medication guide, patient package insert (PPI), or instructions for use.

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10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile Fluciclovine F18 Injection, there are no additional risk management strategies required beyond the recommended labeling. The subsequent subsections are not applicable for this review and have been omitted.

12 Requirements and Commitments

None recommended.

13 Appendices

13.1. References

Up To Date (www.uptodate.com) Reviews:

1. Clinical presentation and diagnosis of prostate cancer.
2. Prostate cancer: Risk stratification and choice of initial treatment.
3. Initial management of regionally localized intermediate, high, and very high-risk prostate cancer.
4. Rising serum PSA following local therapy for prostate cancer: Diagnostic evaluation.
5. Rising or persistently elevated serum PSA following radical prostatectomy for prostate cancer: Management.

Others

5. Schuster, David M. et al. Anti-3-[18F] FACBC positron emission tomography-computerized tomography and ¹¹¹In-capromab pendetide single photon emission computerized tomography-computerized tomography for recurrent prostate carcinoma: results of a prospective clinical trial. *The Journal of Urology*.; Volume 191, 1446-1453, May 2014.
6. Nanni, Cristina et al. 18F-Fluciclovine PET/CT for the detection of prostate cancer relapse, a comparison to ¹¹C-Choline PET/CT. *Clinical Nuclear Medicine*; Volume 40(8):386-9, August 2015.

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13.2. Financial Disclosure

No financial conflicts of interests were identified.

Covered Clinical Study (Name and/or Number): BED001 and BED002

Was a list of clinical investigators provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

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APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHILLIP B DAVIS
03/04/2016

NUSHIN F TODD
03/04/2016