CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216023Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 22, 2023
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216023
Product Name, Dosage Form, and Strength:	Posluma (flotufolastat F 18) Injection, 296 MBq/mL to 5,846 MBq/mL (8 mCi/mL to 150 mCi/mL) at end of synthesis
Applicant/Sponsor Name:	Blue Earth Diagnostics Ltd. (Blue Earth)
TTT ID #:	2022-1343-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader (Acting):	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Blue Earth Diagnostics Ltd. (Blue Earth) submitted revised vial container label and shield carton labeling for Posluma (flotufolastat F 18) injection received on May 22, 2023 under NDA 216023. We reviewed the revised vial container label and shield carton labeling for Posluma (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and via email on May 17, 2023.[a]

2 CONCLUSION

Blue Earth implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kane, D. Label and Labeling Review for Posluma (NDA 216023). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 APR 28. TTT ID No.: 2022-1343.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 22, 2023

- Vial Container Label and Shield Carton Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DEVIN R KANE
05/22/2023 02:49:08 PM

STEPHANIE L DEGRAW
05/22/2023 03:00:22 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 2, 2023

To: Thuy Nguyen, Regulatory Project Manager, Division of Imaging and Radiation Medicine (DIRM)

Alice Cheuk, Clinical Reviewer, DIRM

Younsook Kim, Associate Director for Labeling, DIRM

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for POSLUMA (flotufolastat F 18 gallium) injection, for intravenous use

NDA: 216023

Background:

In response to DIRM's consult request dated May 2, 2023, OPDP has reviewed the proposed Prescribing Information and carton and container labeling for the original NDA submission for Posluma.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on May 1, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

13 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DAVID F FOSS
05/02/2023 03:24:13 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 28, 2023
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 216023
Product Name, Dosage Form, and Strength:	Posluma (flotufolastat F 18) Injection, 296 MBq/mL to 5,846 MBq/mL (8 mCi/mL to 158 mCi/mL) (b) (4) (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Blue Earth Diagnostics Ltd. (Blue Earth)
FDA Received Date:	December 22, 2021, May 25, 2022 and August 17, 2022
TTT ID #:	2022-1343
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

Blue Earth Diagnostics Ltd. (Blue Earth) submitted a resubmission for NDA 216023 for Posluma (flotufolastat F 18) Injection on May 25, 2022. Posluma is a radioactive diagnostic agent proposed for positron emission tomography (PET) (b) (4) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer (b) (4) We evaluated the proposed Posluma prescribing information (PI), vial container label, and shield carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On December 22, 2021, Blue Earth Diagnostics Ltd. (Blue Earth) originally submitted their marketing application for NDA 216023 Posluma (flotufolastat F 18) Injection. On February 17, 2022, Blue Earth withdrew the marketing application for NDA 216023 following a teleconference with the Agency on February 15, 2022. On May 25, 2022, Blue Earth resubmitted the marketing application for NDA 216023 with full study datasets, final clinical study report, and updated studies to support the proposed indication.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Blue Earth Diagnostics Ltd. (Blue Earth) resubmitted a 505(b)(1) application to obtain marketing approval of Posluma (flotufolastat F 18) injection. We performed a risk assessment of the

proposed prescribing information (PI), vial container label, and shield carton labeling for Posluma to determine whether there are deficiencies that may lead to medication errors and other areas of improvement.

Our evaluation of the proposed PI, vial container label, and shield carton labeling for Posluma identified areas of vulnerability that may lead to medication errors. For example, for the PI, we recommend revising [redacted] (b) (4) to read "end of synthesis", including a comma in all numeric values greater than 1,000, removing the use of trailing zeros, and including the appropriate units after all numeric values. For the vial container label and shield carton labeling, we recommend including a comma for all numeric values greater than 1,000 and presenting the strength in terms of megabecquerels (MBq) and millicuries (mCi) to align with the presentation used in the PI. We provide our complete recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Posluma prescribing information (PI), vial container label and shield carton labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Blue Earth Diagnostics Ltd. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We note the first bullet under Highlights of Dosage and Administration states [redacted] (b) (4) We recommend removing this bullet as it is not needed in Highlights and this information will be covered in a new statement we propose in a recommendation below (see A1d).

b. As currently presented, we note the recommended dose bullet reads [redacted] (b) (4) We recommend revising this bullet to read "Recommended dose is 296 MBq (8 mCi) administered as an intravenous bolus injection".

c. We note the proposed fourth bullet under Highlights of Dosage and Administration provides [redacted] (b) (4) We recommend removing this bullet as this information is not required in Highlights.

d. As currently presented, there is not a bullet referring the end user to the full prescribing information for more detailed preparation, administration, and dosing information. We recommend including a bullet at the end of Highlights of Dosage and Administration that reads

"See full prescribing information for additional preparation, handling, administration, imaging, and radiation dosimetry information. (2)".

2. Dosage Forms and Strengths

   a. We note there is a numeric value greater than 1,000 that is presented without a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid confusion. Revise "5846 MBq/mL" to read "5,846 MBq/mL".

   b. As currently presented, the strength is based on (b) (4) (b) (4) We recommend revising this language to read "end of synthesis".

B. Prescribing Information

1. Section 2: Dosage and Administration

   a. As currently presented, (b) (4) We recommend including subheadings in Section 2.2 in order to separate out the important information. We recommend including one subheading for "Recommended Dose" and a second subheading for "Preparation and Administration Instructions".

   b. We note there are numeric values presented in Section 2 Dosage and Administration that contain trailing zeros. We recommend removing trailing zeros in order to avoid potential for misinterpretation of the numeric value. For example, in Table 1, revise "0.0040" to read "0.004".

2. Section 3: Dosage Forms and Strengths

   a. We note there is a numeric value greater than 1,000 that is presented without a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid confusion. Revise "5846 MBq/mL" to read "5,846 MBq/mL".

   b. As currently presented, the strength is based on (b) (4) (b) (4) We recommend revising this language to read "end of synthesis".

3. Section 16: How Supplied/Storage and Handling

   a. As currently presented, there is a numeric value greater than 1,000 presented in Section 16.1 How Supplied without a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid confusion. Revise "5846 MBq/mL" to read "5,846 MBq/mL".

   b. We note there are numeric values presented in Section 16 How Supplied that are not followed by the appropriate units. We recommend including the appropriate units after all numeric values in order to avoid confusion.

Revise “296 to 5846 MBq/mL (8 to 158 mCi/mL)” to read “296 MBq/mL to 5,846 MBq/mL (8 mCi/mL to 158 mCi/mL)”.

c. To improve clarity, we recommend revising Section 16 How Supplied to read “Posluma is supplied in a 50 mL multiple-dose vial containing approximately 25 mL of a clear, colorless injection at a strength of 296 MBq/mL to 5,846 MBq/mL (8 mCi/mL to 158 mCi/mL) of flotufolastat F 18 at end of synthesis”.

d. We note Section 16.2 Storage and Handling does not provide information regarding the expiration of Posluma. We recommend including the statements “The expiration date and time are provided on the container label. Use Posluma within 10 hours from end of synthesis.” at the end of the storage information in Section 16 Storage and Handling.

4.2 RECOMMENDATIONS FOR BLUE EARTH DIAGNOSTICS LTD.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Vial Container Label & Shield Carton Labeling)

1. We note there are blanks present on the proposed vial container label and shield carton labeling for the activity in terms of “mCi”. However, there are no blanks for presenting the radioactivity in terms of “MBq”. We recommend including blanks for the radioactivity in terms of “MBq” and in “mCi” to align with the Posluma PI.

2. We note there are numeric values greater than 1,000 presented on the proposed vial container label and shield carton labeling without a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid confusion. In the statement “Each mL contains…” revise “5846 MBq” to read “5,846 MBq”.

3. As currently presented, the proposed vial container label and shield carton labeling states [redacted] (b) (4). We recommend revising this statement to read “calculate correct dosage from end of synthesis”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Posluma received on May 25, 2022 from Blue Earth Diagnostics Ltd..

Table 2. Relevant Product Information for Posluma	
Initial Approval Date	N/A
Active Ingredient	flotufolastat F 18
Indication	POSLUMA injection is a radioactive diagnostic agent indicated for positron emission tomography (PET) (b) (4) of prostate-specific membrane antigen (PSMA) positive lesions in men (b) (4) (b) (4)
Route of Administration	Intravenous
Dosage Form	Injection
Strength	296 MBq/mL to 5,846 MBq/mL (8 mCi/mL to 158 mCi/mL) (b) (4) (b) (4)
Dose and Frequency	(b) (4)
How Supplied	
Storage	

APPENDIX G.LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Posluma labels and labeling submitted by Blue Earth Diagnostics Ltd..

- Vial Container Label and Shield Carton Labeling received on August 17, 2022
- Prescribing Information (Image not shown) received on August 17, 2022, available from \\CDSESUB1\EVSPROD\nda216023\0014\m1\us\draft-labeling-text.pdf

G.2 Label and Labeling Images

- Vial Container Label and Shield Carton Labeling

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

DEVIN R KANE
04/28/2023 08:27:30 AM

STEPHANIE L DEGRAW
04/28/2023 04:15:47 PM

Clinical Inspection Summary

Date	1/13/2023
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D., Acting Branch Chief Good Clinical Practice Assessment Branch Office of Scientific Investigations (OSI)
To	Thuy Nguyen, Regulatory Project Manager Alice Cheuk, M.D., Medical Officer Anthony Fotenos, M.D., Team Leader Libero Marzella, M.D., Ph.D., Division Director Division of Imaging and Radiation Medicine (DIRM)
NDA	216023
Applicant	Blue Earth Diagnostics, Inc.
Drug	Flotufolastat F-18 (proposed trade name Posluma®)
NME/Original BLA	Yes
Proposed Indication	PET imaging agent in evaluating prostate cancer
Consult Request	8/22/2022
CIS Goal Date	1/25/2023
Action Goal Date	3/24/2023
PDUFA Date	5/25/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In this original New Drug Application (NDA), Blue Earth Diagnostics, Inc. (BED) seeks the approval of flotufolastat F-18 (proposed trade name Posluma®) as an imaging agent for positron emission tomography (PET) in evaluating prostate cancer.

The two major studies supporting this NDA (BED-PSMA-301, BED-PSMA-302) were audited at good clinical practice (GCP) inspections of four study sites, three clinical investigators (CI) and a contract research organization (CRO). Drs. Chapin, Josephson, and Schuster were selected as they had large subject enrollment and no recent inspection history. (b) (4) was selected as the CRO that centrally evaluated PET imaging results.

No significant GCP violations were observed; the two audited studies appear to have been conducted in compliance with GCP principles and regulations. The data for the two studies audited at the four GCP inspections appear acceptable in support of using flotufolastat F-18 as proposed in the NDA.

II. BACKGROUND

Prostate cancer (PC) is the second most frequent cancer in men, typically diagnosed in asymptomatic older men (age ≥ 65 years) by physical (rectal) exam, rising prostate-specific antigen (PSA), and transrectal needle biopsy confirmation (typically sequentially). The overall prognosis is excellent (nearly 100% five-year survival) when organ-limited disease is detected early and readily followed by curative surgery, often radical prostatectomy (RP) with or without regional pelvic lymph node dissection (PLND).

The prostate-specific membrane antigen (PSMA) is a normal glycoprotein component of the prostate cell membrane, abnormally overexpressed in PC and different from PSA. Both PSMA and PSA are enzymes that are not limited to the prostate gland but nonetheless usefully targeted for evaluating the prostate. PSA is an important marker of prostate disease (not specific for PC) assayed in blood typically for PC surveillance. PSMA is tissue-bound and is currently emerging as a useful target for PC localization.

PET imaging agents directed against PSMA appear useful in defining disease extent (staging), more useful than are the currently widely used imaging methods, including magnetic resonance imaging (MRI), computed tomography (CT), and bone scan. The clinical experience to date indicates that PSMA-PET may be clinically most useful in detecting metastatic disease to support the choice of more appropriate systemic therapies in lieu of RP-PLND, including androgen deprivation therapy (ADT) and radiation.

In this original NDA (resubmission), the sponsor seeks the approval of flotufolastat F-18 (proposed trade name Posluma®) as the first-in-class PSMA-directed PET imaging agent for use in: (1) staging prostate cancer prior to initial therapy, evaluated in BED-PSMA-301; and (2) the localization of recurrent disease in previously treated prostate cancer with rising PSA level, evaluated in BED-PSMA-302. The two pivotal studies supporting this NDA were audited at GCP inspections of four study sites, identified for inspection as follows:

- Three CIs with the largest subject enrollment, to include the two that each served as the principal CI for the two studies to be audited
- The CRO where all PSMA-PET scans were centrally managed and interpreted for diagnostic utility, relative to either histopathology (obtained at CI sites) or consensus reading of conventional imaging (metastases without histopathology)

The following protocol summaries were used as a guide to the actual study protocols submitted in the NDA in auditing the studies as conducted at the four study sites. The major study features to be audited in detail were summarized with the intent to facilitate the audit of NDA data reliability.

BED-PSMA-301: LIGHTHOUSE (Principal CI: Brian Chapin, M.D.)

A prospective, Phase 3, multi-center, single-arm, imaging study investigating the safety and diagnostic performance of rhPSMA-7.3 (18F) PET ligand in men with newly diagnosed prostate cancer

This single-arm open-label study was conducted over two years (2020-22) in 372 subjects at 31 CI sites, 27 in the United States (US) and 4 in Europe. The primary study objective was to assess the diagnostic performance of radioactively labeled flotufolastat F-18 (FF-

18) used as the PET imaging agent in detecting (sensitivity) or excluding (specificity) distant metastases in newly diagnosed PC for which RP-PLND appears to be indicated based on unfavorable clinical history, conventional imaging, and biopsy histopathology.

Subject Inclusion

- Men (age > 18 years) with recently diagnosed PC, histopathologic confirmation of adenocarcinoma of prostate
- Unfavorable prognosis (intermediate, high, or very high risk) based on histopathology (Gleason score) and clinical presentation (including PSA level)
- Treatment-naive for PC, including no prior ADT or other hormonal therapy for PC, AND scheduled for standard-of-care surgery, including RP-PLND

Subject Exclusion

- Anticipated need for radiocontrast or PET radiotracer agent (other than FF-18) within 24 hours prior to FF-18 PET
- Participation in an interventional clinical study within 30 days AND receipt of an investigational medication within its five half-lives timeframe
- Any condition that may confound study interpretation or impede study completion, including hypersensitivity to FF-18 (CI judgment)

Study Procedures

Baseline routine conventional imaging was performed within 60 days of screening through one day after screening (within 24 hours of FF-18 PET). Subjects received a single intravenous (IV) bolus injection of FF-18 (8 mCi) followed by PET on Day 1.

- The PET scan was first interpreted locally (single reader, unblinded), then sent (electronically) to be interpreted centrally at an imaging CRO site ((b) (4) by three independent blinded readers).
- To help assure unbiased *blinded* PET interpretation by the central readers: (1) all clinical information relevant to PET interpretation (e.g., conventional imaging results) were withheld; and (2) the order in which the PET scans were presented to the central readers was *randomized*.

Subjects returned to the clinic once between Days 2-6 for safety follow-up and for a discussion of local unblinded PET results. Standard of care surgery (including RP-PLND) was performed within 60 days of FF-18 PET.

Major study endpoints

The co-primary endpoint data verified at inspection consisted of the study variables observed and recorded as either the presence or absence of metastatic PC on three evaluation methods: FF-18 PET, histopathology, and conventional imaging.

- PET lesion anywhere (imaging signal from radiolabeled FF-18)
- Cancer near prostate, confirmed by PLN histopathology
- Cancer distant from prostate, presumed by conventional imaging

The standard of truth (SoT) against which the diagnostic accuracy of FF-18 PET in detecting metastatic PC consisted of histopathology and consensus central interpretation of all available conventional imaging, as follows:

- *For pelvic PET lesions (PLN):* SoT-1 = confirmatory histopathology of PLN removed at RP-PLND, with no consideration given to any available conventional imaging results
- *For distant PET lesions WITH corresponding surgical tissue or biopsy:* SoT-2 = confirmatory histopathology of the lesion in surgical tissue or biopsy corresponding to the PET lesion
- *For distant PET lesions WITHOUT corresponding tissue histopathology:* SoT-3 = consensus central reading of all available conventional imaging (and clinical history), to categorize the distant PET lesion either as true positive FF-18 PET indicating metastatic PC, or as false positive where metastatic PC is not present (true signal but no cancer)

The major study analyses consisted of determining the utility of FF-18 PET as a diagnostic modality in detecting metastatic PC in various clinical contexts (relative to SoT-1, SoT-2, or SoT-3, as applicable) as evidenced by sensitivity, specificity, detection rate, and positive predictive value (not subject to audit at GCP inspection).

BED-PSMA-302: SPOTLIGHT (Principal CI: David Schuster, M.D.)

A prospective, Phase 3, multi-center, single-arm, imaging study investigating the safety and diagnostic performance of rhPSMA-7.3 (18F) PET ligand in men with suspected prostate cancer recurrence based on elevated PSA following prior therapy

This was a single-arm study conducted over one year (2020-21) in 391 subjects enrolled at 28 CI sites, 25 in US and 3 in Europe. The study was conducted in men with suspected biochemical recurrence (BCR) of PC electing to receive repeat curative therapy. The co-primary study objectives were to assess the correct detection rate (CDR) and the PPV of FF-18 PET in detecting BCR, using histopathology or confirmatory conventional imaging as SoT.

Subject Inclusion

- Men (age >18 years) with history of localized adenocarcinoma of prostate, previous treatment with curative intent (PTCI) AND rising PSA suggestive of BCR:

  RP as PTCI: PSA ≥ 0.2 ng/mL
  RT as PTCI: PSA ≥ 2.0 ng/mL over post-RT nadir PSA
  Non-surgical focal ablation (NSFA) as PTCI: PSA ≥ 2.0 ng/mL over post-NSFA nadir PSA

- Eligible for and electing repeat curative therapy with RP, RP+RT, RP+ADT, external beam radiation therapy (EBRT), or NSFA including high-intensity focused ultrasound (HIFU)

Subject Exclusion

- Anticipated need for radiocontrast or PET radiotracer agent (other than FF-18) within 24 hours prior to FF-18 PET
- Participation in an interventional clinical study within 30 days AND receipt of an investigational medication within its five half-lives timeframe

- Previous orchiectomy or any other current ADT/hormonal therapy, or any condition that may confound study interpretation or impede study completion, including hypersensitivity to FF-18 (CI judgment)

Study Procedures

Subjects received a single IV bolus injection of FF-18 (8 mCi) followed by PET on Day 1. The PET scans were interpreted centrally at an imaging CRO site (three blinded readers).

To help assure unbiased *blinded* PET interpretation by the central readers: (1) all clinical information relevant to PET interpretation was withheld, including all conventional and confirmatory imaging results; and (2) the order in which the PET scans were presented to the central readers was *randomized*.

The SoT against which the diagnostic accuracy of FF-18 PET in detecting BCR-PC consisted of histopathology and consensus central interpretation of all available conventional imaging, which included new confirmatory imaging, as follows:

- Within 60 days after FF-18 PET, either a tissue biopsy or confirmatory conventional imaging was obtained for each anatomic region (left/right pelvis or distant), which served as the SoT for any PET lesion identified in each region.
- The SoT evaluation (biopsy or confirmatory imaging) was repeated at 90 days after FF-18 PET if still needed for definitive diagnostic confirmation.

Major study endpoints

The co-primary endpoint data verified at inspection consisted of the study variables observed and recorded as either the presence or the absence of recurrent PC on three evaluation methods: FF-18 PET, histopathology, and conventional imaging.

- PET lesion anywhere (imaging signal from radiolabeled FF-18)
- Cancer consistent with recurrent PC, confirmed by histopathology
- Presumed recurrent PC, as determined by confirmatory conventional imaging

Confirmatory conventional imaging was interpreted by a panel consisting of three independent central readers different from those who interpreted the FF-18 PET images. This SoT panel reviewed all conventional scans (historical, baseline, and confirmatory) to determine the SoT result by consensus, either TP or FP for any PET lesion without histopathology. The SoT panel members were provided with a brief clinical history but otherwise remained blinded.

The major study analyses consisted of determining the utility of FF-18 PET as a diagnostic modality in detecting BCR-PC using histopathology or consensus conventional imaging as SoT, as evidenced by CDR, PPV, and/or impact on clinical management (not subject to audit at GCP inspection).

III. INSPECTION RESULTS

1. Brian Chapin, M.D.

1220 Holcombe Boulevard
Houston, TX 77030

Inspection Dates: November 14 – 17, 2022

BED-PSMA-301, Site 10021 (primary CI): 22 subjects were screened, 22 were enrolled, and 22 completed the study. Subject case records were reviewed in detail for all subjects.

The inspection confirmed compliance with GCP principles and regulations; no significant deficiencies were observed. Study files and subject case records were well maintained. No unreported protocol deviations or adverse events (AEs) were discovered. The observed efficacy data (as noted in protocol summary above, Section II) were audited in detail and were determined to be verifiable against those reported in the NDA, as were the AE data.

2. David Josephson, M.D.

8635 West 3rd Street, Suite 1 West
Los Angeles, CA 90048-6102

Inspection Dates: October 11 – 13, 2022

BED-PSMA-301, Site 10011: 21 subjects were screened, 20 were enrolled, and 12 completed the study (8 withdrew consent, chose non-study care). Subject case records were reviewed in detail for all subjects.

The inspection confirmed compliance with GCP principles and regulations; no significant deficiencies were observed. Study files and subject case records were well maintained. No unreported protocol deviations or AEs were discovered. The observed efficacy data (as noted in protocol summary above, Section II) were audited in detail and were determined to be verifiable against those reported in the NDA, as were the AE data.

3. David Schuster, M.D.

1364 Clifton Road, NE
Atlanta, GA 30322

Inspection Dates: October 31 – November 3, 2022

BED-PSMA-302, Site 10072 (primary CI): 41 subjects were screened, 41 were enrolled, and 39 completed the study (1 excluded, 1 died). Subject 06 died of respiratory failure from pre-existing pulmonary and mediastinal fibrosis unrelated to study interventions. Subject case records were reviewed in detail for all subjects.

The inspection confirmed compliance with GCP principles and regulations; no significant deficiencies were observed. Study files and subject case records were well maintained. No unreported protocol deviations or AEs were discovered. The observed efficacy data (as noted in protocol summary above, Section II) were audited in detail and were determined to be verifiable against those reported in the NDA, as were the AE data.

4. (b) (4)
(b) (4)

Inspection Dates: (b) (4)

BED-PSMA-301 and BED-PSMA-302: The imaging CRO (b) (4) performed the major study tasks related to image interpretation, including reader training, image randomization, reader oversight, and database management. PET images, conventional SoT images, and imaging records were reviewed in detail for 34 subjects (17 per study).

No significant deficiencies were observed; the inspection confirmed good compliance with GCP principles and regulations in the central management and interpretation of the PET images for the two pivotal studies.

- (b) (4) adhered to the contractual agreement with the sponsor and followed the study protocols, PET imaging manuals, and center standard operating procedures.
- The sponsor BED (and not (b) (4)) performed the *analysis* of the central read data. BED performed routine monitoring of the study conduct (b) (4)
- Database interface and system controls appeared robust, including special controls to prevent errors in managing images and imaging data.
- Study files and subject case records were well maintained and were readily available for audit review. No unreported protocol deviations were discovered.
- No significant concerns were observed regarding image interpretation, including image randomization and reader performance (training, independence, and blinding).

Subjects were not managed at this CRO site and AE data audit were not applicable to this inspection. The primary endpoint data were audited in detail to include imaging results for FF-18 PET and SoT. All audited data were verifiable against those reported in the NDA.

{See appended electronic signature page}

John Lee, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
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CONCURRENCE: *{See appended electronic signature page}*

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DIRM/Division Director/Libero Marzella
DIRM/Team Leader/Anthony Fotenos
DIRM/Clinical Reviewer/Alice Cheuk
DIRM/Regulatory Project Manager/Thuy Nguyen

OSI/Office Director/David Burrow
OSI/Deputy Office Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Regulatory Officer/LaKisha Williams
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
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