

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212155Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2)
Application Number	NDA 212155
Priority or Standard	Standard
Submit Date	February 27, 2019
Received Date	February 27, 2019
PDUFA Goal Date	May 27, 2020
Division/Office	Division of Imaging and Radiation Medicine (DIRM) / Office of Specialty Medicine (OSM)
Review Completion Date	May 20, 2020
Established/Proper Name	Fluoroestradiol F 18
(Proposed) Trade Name	Cerianna
Pharmacologic Class	Radioactive Diagnostic Agent for Positron Emission Tomography
Applicant	Zionexa
Dosage form	Injection
Applicant Proposed Dosing Regimen	222 MBq with an allowable range from 111 MBq to 222 MBq (3 mCi to 6 mCi)
Applicant Proposed Indication(s)/Population(s)	For use with positron emission tomography (PET imaging) for characterization of estrogen receptor (ER) status (b) (4) breast cancer.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	363678002 Positron emission tomographic imaging - action
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For use with positron emission tomography (PET) imaging for detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer. Limitations of Use: Tissue biopsy should be used to confirm recurrence of breast cancer and to verify ER status by pathology. Cerianna is not useful for imaging other receptors, such as human epidermal growth factor receptor 2 (HER2) and the progesterone receptor (PR).
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	315004001 Metastasis from malignant tumor of breast (disorder)
Recommended Dosing Regimen	222 MBq (6 mCi), with a range of 111 MBq to 222 MBq (3 mCi to 6 mCi), administered as a single intravenous injection of 10 mL or less over 1 to 2 minutes

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Su-Lin Sun/ Sharon Thomas
Nonclinical Reviewer	Jonathan Cohen, PhD
Nonclinical Team Leader	Adebayo Laniyonu, PhD
Office of Clinical Pharmacology Reviewer	Christy John, PhD
Office of Clinical Pharmacology Team Leader	Nam Atiqur Rahman, PhD
Clinical Reviewer	Qi Feng, MD, PhD
Health Physics Reviewer	Stanley, Stern PhD
Clinical Team Leader	Anthony Fotenos MD, PhD
Statistical Reviewer	Jyoti Zalkikar, PhD
Statistical Acting Deputy Director	Sue-Jane Wang, PhD
Cross-Disciplinary Team Leader	Anthony Fotenos MD, PhD
Division Director (DIRM)	Libero Marzella MD, PhD
Acting Deputy Director (OSM)	Alex Gorovets, MD

Additional Reviewers of Application

OPQ /Drug Substance	Soumya Mitra
OPQ/Drug Product	Dhanalakshmi Kasi
Microbiology	Xia Xu
Biopharmaceutics	Hansong Chen
Facility	Krishna Ghosh
OPDP	David Frost
OSE/DEPI	Richard Swain
OSE/DMEPA	Sarah Vee
OSE/DRISK	Till Olickal
Division of Pediatric and Maternal Health	Jeanine Best

OPQ = Office of Pharmaceutical Quality
 OPDP = Office of Prescription Drug Promotion
 OSI = Office of Scientific Investigations
 OSE = Office of Surveillance and Epidemiology
 DEPI = Division of Epidemiology
 DMEPA = Division of Medication Error Prevention and Analysis
 DRISK = Division of Risk Management
 DIRM = Division of Imaging and Radiation Medicine
 OSM=Office of Speciality Medicine

Glossary

αFP	α-fetoprotein
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AI	aromatase inhibitors
BLA	biologics license application
DIRM	Division of Imaging and Radiation Medicine
ER	estrogen receptor
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose F 18
FES	fluoroestradiol F 18
FUL	fulvestrant
GLP	good laboratory practice
HER2	human epidermal growth factor receptor 2
hERG	human <i>ether-à-go-go</i> -related gene
IHC	immunohistochemical
IND	investigational new drug
IQR	interquartile range
MBq	megabecquerel
MBC	metastatic breast cancer
NCI	National Cancer Institute
NDA	new drug application
NPA	negative percent agreement
OCP	Office of Combination Products
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PET	positron emission tomography
PPA	positive percent agreement
PR	progesterone receptor
PK	pharmacokinetics
PREA	Pediatric Research Equity Act
SD	standard deviation
SHBG	sex-hormone binding globulin
SUV	standardized uptake value
TAM	tamoxifen

1. Executive Summary

1.1. Product Introduction

The Applicant submitted this original New Drug Application (NDA) seeking FDA approval to market Cerianna in the United States per authority granted under Section 505(b)(2) of the Food, Drug, and Cosmetic Act. The active drug substance in Cerianna is Fluoroestradiol F 18 (FES), a synthetic derivative of estradiol labelled with the radionuclide fluorine 18. After Cerianna is administered intravenously, FES binds to the estrogen receptor (ER) and thereby concentrates within ER-expressing cells, where fluorine 18 decay leads to release of positrons and emission of dual 511 keV photons that can be imaged for ER detection in vivo.

In vitro ER detection is part of the standard workup for patients with breast cancer prior to initial systemic therapy. In this population, the clinical value of ER detection is based on superior outcomes for anti-estrogen (hormone) therapy in ER-positive over ER-negative subgroups, with subgroups defined by in vitro ER testing. Assessment of ER status of tumor is critical in management, prognosis, and prediction of response to hormone therapy. Accordingly, when systemic therapy is indicated, hormone therapy is recommended for patients with breast cancer with ER-positive but not ER-negative primary tumors. Hormone therapy is also a first-line recommendation in ER-positive but not ER-negative patients with recurrent or metastatic breast cancer. However, in this population, detecting ER-positive tumors is more challenging because ER expression is heterogeneous between non-primary tumors and across time. In patients with recurrent or metastatic breast cancer, non-primary tumors may be multiple and inaccessible, so biopsy is generally recommended only for one lesion, in addition, biopsy may be infeasible in some patients. Adding ER imaging has the advantage of non-invasive view of multiple lesions. ER imaging is thus clinically meaningful because it has adjunctive value to tissue biopsy for patients with recurrent or metastatic breast cancer, for example, to detect ER positive lesions where biopsy is not feasible or to prioritize lesion sampling.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of Cerianna for detecting ER-positive non-primary breast cancer lesions was evaluated in published reports of FES studies in patients with recurrent or metastatic breast cancer. Among these reports, two studies are relied upon for the assessment of efficacy and are described in the clinical-studies section of the prescribing information. Additional supportive information is provided by another published study report in the indicated patient population, and by the Applicant's review of literature covering broader FES investigations. The review team finds substantial evidence that Cerianna performance exceeds clinically meaningful thresholds for detecting ER-positive lesions in patients with recurrent or metastatic breast cancer. In addition, the Applicant and the Agency have reached agreement on Cerianna labeling, with particular emphasis on Cerianna's adjunctive role to biopsy which is necessary to verify ER status of tumor by pathology assessment. The review team thus concludes that Cerianna is effective for its adjunctive use.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The review team finds that benefit-risk is favorable and recommends approval of Cerianna for detection of ER-positive lesions as an adjunct to biopsy (indicated use) in patients with recurrent or metastatic breast cancer (indicated population). The effectiveness of Cerianna for this indicated use was evaluated in published reports of FES studies in the indicated population. The review team finds substantial evidence that Cerianna performance exceeds clinically meaningful thresholds for detecting ER-positive lesions in patients with recurrent or metastatic breast cancer. The safety of Cerianna was evaluated in the same published reports, data from a phase 2 study of a different use in the same population, and the Applicant's summary of published study reports including other populations. The review team finds substantial evidence that Cerianna is safe, accounting for labeling changes to mitigate risks around misdiagnosis and radiation, to which Applicant has agreed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Breast cancer is the second leading cause of cancer death among women in the United States. Hormone therapy is recommended only in patients with ER-positive breast cancer. In patients with recurrent or metastatic breast cancer, there is known heterogeneity in ER expression among lesions and across time. Available in vitro diagnostic products for these patients may require selection among multiple candidate lesions.	In patients with recurrent or metastatic breast cancer, heterogeneity in ER expression may raise questions about a patient's ER status not fully addressable using available in vitro methods. Addressing these questions provides a rationale for development of new ER detecting products.
<u>Current Treatment Options</u>	In the United States, only in vitro diagnostic products are available, intended for ER detection and indicated as aids in management, prognosis, and prediction of response for hormone therapy. The review team is not aware of other marketed in vivo diagnostic products for ER detection. No other imaging agent has been approved for ER detection.	Cerianna is an imaging agent available for detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.
<u>Benefit</u>	Evidence: Study 1: Image reader performance for distinguishing between ER-positive and ER-negative FES status was compared to biopsy in 85 patients from the indicated population. Of the 47 patients with positive biopsy (Allred score ≥ 3, possible range 0-8), 36 were positive on imaging (majority reader score	Convergent evidence supports the review team's finding that Cerianna performance exceeds clinically meaningful thresholds for detecting ER-positive lesions in patients with recurrent or metastatic breast cancer. In addition, no instance of disagreement between

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	≥3, possible range 1-3). Of the 38 patients with negative biopsy, all 38 were negative on imaging. • Study 2: In another study with 13 patients from the indicated population (11 with positive biopsy), results were similar. • Another published report investigating indicated patients and the Applicant's review of literature covering broader FES investigation were supportive. Uncertainties: • Efficacy evaluation for this 505(b)(2) submission primarily relied on a published study report from an uninspected investigational site and without review of submitted patient- and reader-level data. • In this study, FES performance data in the following subgroups of special interest was not available for review: ○ Patients with ER-negative primary tumors and ER-positive recurrent or metastatic lesions. ○ Patients in whom only bone lesions could be sampled were excluded, since the performance-risk balance for in vitro biopsy is relatively low.	FES and pathology reader has been reported for FES-positive reads, a magnitude of positive agreement that supports extrapolation of the review team's finding to more uncertain subgroups.
Risk and Risk Management	• Cerianna targets neither human epidermal growth factor receptor 2 (HER2) nor the progesterone receptor (PR). • In Study 1, 10 of 11 patients with false negative imaging had Allred scores between 3 and 6. • The uptake of Cerianna is not specific for breast cancer and may occur in a variety of ER-positive tumors arising outside of the breast. • Estimated total effective radiation dose after administration of 222 MBq (6 mCi) Cerianna is 4.9 mSv. • No deaths or other serious adverse events (AEs) were reported among more than 1000 patients after FES administration in the clinical studies published.	The review team finds substantial evidence that Cerianna is safe, with the following mitigation advice for risks of misdiagnosis and radiation described in recommended labeling: • Do not use Cerianna in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer. • Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative Cerianna scan.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• Ensure safe drug handling and patient preparation procedures to protect patients and health care providers from unintentional radiation exposure.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient-reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☒	Patient experience data were not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

After skin cancer, breast cancer is the most commonly diagnosed cancer in American women. Currently, the risk of a woman in the United States developing breast cancer sometime in her life is about 13%, a 1 in 8 chance. According to the American Cancer Society's estimates, about 276,480 new cases of invasive breast cancer will be diagnosed and about 42,170 women will die from metastatic breast cancer in 2020 (American Cancer Society 2020). The treatment of breast cancer depends on the clinical subtype. Approximately 75% of newly diagnosed patients have estrogen receptor (ER)-expressing (ER-positive) breast tumors, which are associated with a more favorable prognosis. According to American Society of Clinical Oncology guidelines on endocrine therapy for ER-positive metastatic breast cancer (MBC), "Sequential hormone therapy is the preferential treatment for most women with ER-positive MBC. Except in cases of immediately life-threatening disease, hormone therapy, alone or in combination, should be used as initial treatment" (Rugo et al. 2016). Given the efficacy and low morbidity of endocrine therapy for ER-positive tumors, assay for ER expression plays an established role in the workup of patient with MBC.

Comment: In this review, when the abbreviation "MBC" is used in the context of diagnostic imaging, it refers to an overlap of concepts defined at both patient and lesion levels: first, to patients presenting with recurrence of previously treated breast cancer or initially with stage IV disease; and, second, to breast cancer lesions localized outside of the breast.

ER expression in breast cancer is assessed by in vitro assays on biopsied or surgically resected tissue, often with immunohistochemical (IHC) staining. Table 1 and Table 2 summarize IHC pathological scoring systems commonly used for clinical reporting and research, respectively (Dowsett et al. 2008; Fitzgibbons et al. 2014; Fitzgibbons; et al. 2014).

Table 1. Reporting Results of Estrogen Receptor Testing

Result	Criteria (% of Immunoreactive Cells Present)*
Positive	≥1%
Negative	<1%

*: The percentage of immunoreactive cells may be determined by visual estimation or quantitation. Quantitation can be provided by reporting the percentage of positive cells or by an Allred scoring system.

Table 2. Allred Score for Estrogen Receptor Evaluation*

Positive Cells (%)	Proportion Score	Intensity	Intensity Score
0	0	None	0
<1	1	Weak	1
1–10	2	Intermediate	2
11–33	3	Strong	3
34–66	4		
≥67	5		

* The Allred score combines the percentage of positive cells and the intensity of the reaction product in most of the carcinoma. The 2 scores are added together for a final score with 8 possible values. Scores from 0 to 2 are negative. Scores from 3 to 8 are positive.

ER status is routinely assessed in primary breast tumors at biopsy or resection. However, knowledge of ER status in the primary tumor at initial presentation may not predict ER status of

metastatic lesions because of genetic mutation and other causes of heterogeneity. It is rarely feasible to biopsy all metastatic lesions; therefore, a positron emission tomography (PET) imaging drug for ER detection may help as an adjunct to biopsy. The mechanism of action of FES is via ER binding.

Currently, there is no imaging drug approved in the United States for detection of ER.

Comment: In this review, the abbreviation “FES” is used to refer to Fluoroestradiol containing the radioactive fluorine-18 isotope and independent of the manufacturer. “Non-radioactive FES” is used to refer to decayed FES or Fluoroestradiol containing the stable fluorine-19 isotope. The tradename “Cerianna” specifically refers to the product the Applicant intends to market in the United States. For more detailed discussion, including of bridging issues, see separately documented OPQ review.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The following is a summary of the regulatory history of Cerianna relevant to this review:

- September 19, 2017: Pre-investigational new drug (Pre-IND) 135755 meeting for new drug application (NDA) submission with 505(b)(2) pathway; FDA requested a protocol for literature review.
- July 16, 2018: Pre-NDA 212155 meeting; FDA recommended focus on the use of FES in MBC.
- February 27, 2019: Received NDA 212155 with 505(b)(2) pathway submission for Cerianna. Proposed indication: “characterization of ER status [REDACTED] (b) (4) [REDACTED] breast cancer.”
- August 8, 2019: A post-mid-cycle meeting was held between the Agency and Applicant via teleconference.
- September 30, 2019: The Applicant’s response to the post-midcycle communication and information request was received by the FDA. It was subsequently declared a Major Amendment resulting in an extension of the review clock by three months.
- April 7, 2020: The Applicant cancels the Late Cycle teleconference after receiving agenda to focus on labeling.

3.2. Summary of Presubmission/Submission Regulatory Activity

See above.

3.3. Foreign Regulatory Actions and Marketing History

The Applicant received authorization to market FES in France on July 21, 2016, under the tradename Estrotep (Parikh et al. 2017). However, (b) (4), and Applicant reports that only 130 vials of Estrotep have been distributed in France as of July 20, 2018.

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

4.1. Office of Scientific Investigations (OSI)

The approvability of this NDA does not rely on sponsor-conducted studies, therefore no OSI review was conducted.

4.2. Product Quality

The quality review team from the Office of Pharmaceutical Quality (OPQ) consisted of Soumya Mitra, Dhanalakshmi Kasi, Xia Xu, Krishna Ghosh, Hansong Chen, Anika Lalmansingh, Donna Christner, Nandini Bhattacharya, Vidya Pai, Topash Ghosh, Eldon Leutzinger, and Danae Christodoulou. The quality review team recommended approval of this NDA. The following excerpts from their review highlight certain notable findings.

From page 12 of 142. Product Labeling: During review of the drug product labeling, the vial labels were found in need of revisions. This included an expiration date and time, storage condition, drug product composition, and total volume for the multi dose vial, and the statement, “do not use if it is cloudy or contains (b) (4) particulate matter” in the vial label. Microbiology: In summary, the drug product is (b) (4)

(b) (4) From the Microbiology review, all issues have been adequately addressed, and the final decision is an overall adequate. Biopharmaceutics: From the Biopharmaceutics review, “the Biopharmaceutics review focuses on the side-by-side comparison between the proposed product and the ones in the literature and assesses whether the bio-bridge between them is sufficient.” This determination for FES is adequate. Facility Inspections: There are two facilities associated with this NDA. (b) (4)

(b) (4) – responsible for the manufacture of FES, as well as its packaging, and controls. (b) (4) – ISO certified facility responsible for

(b) (4) The (b) (4) is deemed acceptable by PAI inspection and review of IR response to FDA 483. (b) (4) (manufacturer of precursor, packaging, release and stability testing is determined to be accepted by file review. In accordance to the facilities review, “a post-approval inspection will be recommended to ensure that all process and analytical assay related corrective actions have been completed adequately.”

From page 14 of 142. Comparability Protocol (CP):

(b) (4)

. These changes are the following, any one of which will necessitate submission of a Prior Approval Supplement (PAS):

-
-
-
-
-

(b) (4)

Zionexa has agreed to this plan and their response is acceptable to FDA.

(b) (4)

For additional information, see separately documented Integrated Quality Assessment.

4.3. Clinical Microbiology

Not applicable to this product.

4.4. Devices and Companion Diagnostic Issues

The review team identified no device and companion diagnostic issues.

4.5. Office of Oncologic Disease (OOD)

The review team consulted OOD for comment regarding major revisions recommended to the Applicant during the first round of labeling negotiation under the headings of Indication, Warning and Precautions, and Drug Interactions. OOD agreed with multiple revisions recommend by the review team and intended to ensure that Cerianna not be used to replace standard practice of confirming recurrent or metastatic breast cancer and verifying ER status by pathology. Based on OOD's recommendations for adding language to further define and emphasize these points in Indications and for clarifying Drug Interactions, the review team recommended additional labeling refinements in its second round of labeling negotiation.

The final approved labeling takes into account the limitations of the data in the application and provides the specific information needed for the safe and effective use of Cerianna. A claim of characterization of ER status (b) (4) was judged to be insufficiently supported by the imaging performance data; as a result, the language in the indication statement describes the use of Cerianna for detection of ER-positive lesions. Moreover, the Indications and Usage section of the PI includes a Limitations-of-Use statement to underscore the essential role of pathologic diagnosis to verify the recurrence of breast cancer and the ER status of the tumor in the indicated population. Finally, the Warnings and Precautions section (5.1 Risk of Misdiagnosis) of the PI further emphasizes the adjunctive role of a Cerianna scan. The consultant's recommendation to include in the labeling a more detailed description of the indicated population (e.g., patients who cannot undergo biopsy, and patients with multiple lesions) was not adopted because it was judged to be unduly prescriptive and to lack support from the data in the application.

For additional information, see separately documented consultative review from Dr. Preeti Narayan and sections 6.3.2, 8.3, and 11.1 below.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This NDA should be approved from a nonclinical perspective. The submission by the Applicant supports the marketing authorization of Cerianna for detection of ER-positive lesions as an adjunct to biopsy in patients with recurrent or MBC. An extended, single-dose toxicity study of non-radioactive FES (decayed) in Sprague Dawley rats conducted by the Applicant was not adequately designed to support the proposed dose. However, the Applicant is relying on nonclinical pharmacology and toxicology studies conducted by the (b) (4) and relevant published nonclinical literature to support safety. FES has been under clinical investigation as a diagnostic PET imaging agent in patients with breast cancer for more than 30 years (Mintun et al. 1988) with a well-established safety profile.

Pharmacology

FES is a fluorinated synthetic derivative of the endogenous sex steroid, 17 β -estradiol (estradiol or ES). Binding studies conducted with FES demonstrate competitive, high-affinity binding to estrogen receptors alpha and beta (ER- α and ER- β), and moderate affinity to the plasma proteins sex-hormone binding globulin (SHBG), and α -fetoprotein (α FP). The greatest extent of binding and uptake occurs in ER-positive tissues, (e.g., uterus, ovaries, liver), as well as xenograft models of primary and MBC.

PK/ADME

The Applicant cited published literature for studies characterizing distribution, metabolism, and elimination of FES. FES uptake in ER-positive tissues and tumors is higher following intravenous administration as compared to other routes of administration (Downer et al. 2001); plasma albumin and SHBG increase metabolic stability, resulting in greater specific uptake (Jonson et al. 1999). FES undergoes rapid hepatic metabolism to inactive, low-affinity sulfate and glucuronide conjugates (Mankoff et al. 2001) that are eliminated in the urine and bile (approximately 20% of injected dose is present in circulation by 20 minutes).

Safety Pharmacology

No significant effects on central nervous system behavior, as measured by the modified Irwin test in rats, were observed following a single intravenous dose of FES at 0.62 µg/kg. FES did not significantly inhibit human *Ether-à-go-go*-related gene (hERG) current in vitro and the IC50 value was >8 ng/mL (approximately 10 times maximal peak plasma levels). No clinical cardiovascular events were observed with FES.

Toxicology

In a 14-day repeat-dose toxicity study conducted by the (b) (4), Sprague Dawley rats received vehicle, 13 µg/kg FES, or 51 µg/kg FES. No significant toxicity findings (observations, hematology, clinical chemistry, or histopathology) were observed following intravenous administration of up to 51 µg/kg FES; corresponding to 100 times the clinical dose.

In an extended single-dose toxicity study conducted by the Applicant, Sprague Dawley rats received a single intravenous administration of vehicle, or 0.62 µg/kg FES corresponding to 1.2x the clinical dose. No toxicity was observed at 1- or 14-days following administration.

Genotoxicity

Mutagenicity of FES was evaluated by in vitro and in vivo studies conducted by the (b) (4). FES was negative for mutagenicity in a bacterial reverse mutagenesis assay (Ames test) at up to 1.25 µg/plate and in a L5178Y/TK^{+/−} mouse lymphoma assay at 8 ng/mL. In an in vivo rat micronucleus assay, the incidence of micronucleated polychromatic erythrocytes remained unaffected following repeated exposure at up to 51 µg/kg/day for 14 days. Published carcinogenicity studies were not evaluated because the product is intended for use as a diagnostic radiopharmaceutical.

Reproductive and Developmental Toxicity Studies

Reproductive and developmental toxicity studies were not conducted for FES. The Applicant's request of a waiver for conducting reproductive and developmental toxicity studies was granted based on the proposed single-use indication, target population, and microdose.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Published literature submitted by Applicant included studies characterizing FES binding to ER α and ER β , serum proteins α FP and SHBG, and biodistribution in rats and mice including xenograft models of breast cancer.

FES is a synthetic analog of the endogenous steroid hormone, estradiol (17 β -estradiol or ES) (Kiesewetter et al. 1984) with very high, selective uptake in the reproductive organs (uterus and ovaries) of immature female rats. FES binds competitively to ER α and ER β with nanomolar affinity (Yoo et al. 2005; Antunes et al. 2017). FES has moderate affinity to plasma sex steroid-binding proteins α FP and SHBG (VanBrocklin et al. 1992), whose expression can vary across species (Petra 1991), affecting metabolic stability and target tissue uptake (Tewson et al. 1999).

The Applicant cited several biodistribution studies conducted in xenograft mouse models of breast cancer to compare the relative uptake of FES with that of other ES ligands, and the relevance of ER status to therapeutic response. Overall, most FES uptake occurs in ER-positive tissues, e.g., uterus, ovaries, and liver. Studies performed in male nude mice implanted with ER+ SKOV (ovarian-derived adenocarcinoma) tumors demonstrated higher ER α -dependent uptake when challenged with ES or genistein (an ER β agonist) (Antunes et al. 2017). PET imaging studies in Balb/c mice implanted with ER-positive (MC7-L1 mouse breast carcinoma) and ER α -negative (ER α knockdown in MC4-L2 mouse breast carcinoma) tumor cell lines demonstrated a strong correlation between FES uptake and ER α status (Paquette et al. 2012). Furthermore, FES uptake was much greater in ER β knockout mice, with a 6.3-fold greater preference in ER α mice (Yoo et al. 2005). PET imaging studies with FES and fluorodeoxyglucose F 18 (FDG) were conducted to monitor ER status and response to fulvestrant (FUL) (a selective estrogen receptor degrader) therapy in a mouse xenograft model of MBC (MCF7 adenocarcinoma); FES uptake mirrored dose-dependent changes in functional ER expression (Heidari et al. 2015). In another PET imaging study comparing FES uptake with FDG and fluoromisonidazole F 18 in a mouse xenograft model of metastatic breast cancer (ZR-75-1 carcinoma), FES uptake correlated with tumor response to FUL treatment (He et al. 2016).

In vitro and in vivo studies cited by Applicant demonstrate high affinity and specific uptake in ER-expressing tissues and xenograft models of breast cancer, supporting efficacy of FES for the proposed indication.

Secondary Pharmacology

No secondary pharmacology study reports of FES were submitted by Zionexa.

Safety Pharmacology

No safety pharmacology studies with FES were conducted by the Applicant. The Applicant submitted an in vitro safety pharmacology study report (Study # 080912.SUJ), performed by (b) (4), evaluating the effects of FES on hERG channel current (a surrogate for the delayed rectifier cardiac potassium current).

Study 080912.SUJ “Effects of 16- α -Fluoroestradiol on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells”, (b) (4)

Human embryonic kidney cells (HEK293) stably expressing the hERG gene were treated with FES, vehicle (HEPES-buffered physiological saline supplemented with 0.3% ethanol), positive control (60nM terfenadine), or 500nM E-4031 (reference substance to subtract non-hERG current). Channel inhibition by FES was evaluated at a single concentration, 8 ng/mL. FES inhibited hERG potassium channel current by $1.4 \pm 0.2\%$ (mean $\pm$ SD, n=3) at 8 ng/mL compared to $0.3 \pm 0.1\%$ with vehicle control. The positive control, 60nM terfenadine, inhibited hERG potassium current by $80.4 \pm 0.1\%$ (mean $\pm$ SD, n=2). The IC₅₀ for the inhibitory effect of FES on hERG potassium current was not determined due to solubility limitations of the formulation but was estimated to be greater than 8 ng/mL.

5.4. ADME/PK

Table 3. ADME/PK Summary

Type of Study	Major Findings
<i>Absorption</i>	
“Effect of administration route on FES uptake into MCF-7 tumors” (Downer et al. 2001)	Intravenous administration of fluoroestradiol (FES) results in greater tumor uptake compared to intraperitoneal administration in a xenograft mouse model of breast cancer (MCF-7).
<i>Distribution</i>	
“Breast cancer models to study the expression of estrogen receptors with small animal PET imaging” (Aliaga et al. 2004)	Biodistribution studies in xenograft transplant models of human breast cancer and murine mammary carcinoma demonstrated specific uptake of FES. Greatest non-tumor uptake was observed in the ovaries, uterus, and liver.
“Interactions of 16 α -[¹⁸ F]-Fluoroestradiol (FES) with sex steroid binding protein (SBP)” (Tewson et al. 1999)	FES uptake in PET imaging studies is significantly affected by plasma levels of SHBG that facilitate cellular uptake of the tracer.
“Biodistribution and breast tumor uptake of 16 α -[¹⁸ F]-Fluoro-17 β -estradiol in rat” (Sasaki et al. 2000)	Endogenous levels of estrogens may reduce FES uptake in ER-positive tissues based on biodistribution studies in immature and mature Sprague-Dawley rats.
<i>Metabolism</i>	
“Characterization of the uptake of 16 α -([¹⁸ F]Fluoro)-17 β -estradiol in DMBA-induced mammary tumors” (Mathias et al. 1987)	FES is metabolized rapidly in Sprague Dawley rats with only 25% intact by 15 min post-dose. The majority of the activity in the blood pool and non-target tissues is from metabolites.

Type of Study	Major Findings
"Analysis of blood clearance and labeled metabolites for the estrogen receptor tracer [F-18]-16 alpha-Fluoroestradiol (FES)" (Mankoff et al. 1997)	FES is metabolized to a similar extent in humans, with 20% of the injected dose in plasma circulation by 20 min. Clearance was rapid with a plateau by 30 min (primarily metabolites) due to similar clearance rates from the liver and urine.
"Comparative breast tumor imaging and comparative in vitro metabolism of 16alpha-[18F]Fluoroestradiol-17beta and 16beta-[18F]Fluoromoxestrol in isolated hepatocytes" (Jonson et al. 1999)	In vitro metabolism studies in hepatocytes from rat, baboon, and humans, demonstrated that the absence of SHBG in rat hepatocytes contributes to increased metabolism rate for FES. FES binding to SHBG results in increased metabolic stability and tumor uptake in vivo.
Excretion	
"Rapid liver metabolism, urinary and biliary excretion, and enterohepatic circulation of 16 alpha-radioiodo-17 beta-estradiol" (Scharl et al. 1991)	Elimination studies of 125I-estradiol in juvenile swine demonstrated rapid liver metabolism with primary urinary and biliary excretion.
"Characterization of the uptake of 16 alpha-([18F]Fluoro)-17 beta-estradiol in DMBA-induced mammary tumors" (Mathias et al. 1987)	FES is metabolized rapidly within 2 hours in rats; re-injection of 2-hour blood samples lacked specific binding and accumulated in non-target tissues with greatest uptake in blood.
Toxicokinetic data from general toxicology studies <i>Study not conducted</i>	N/A
Toxicokinetic data from reproductive toxicology studies <i>Study not conducted</i>	N/A
Toxicokinetic data from carcinogenicity studies <i>Study not conducted</i>	N/A

5.5. Toxicology

5.5.1. General Toxicology

Study (b) (4) -1059, 0211886.001.001: 14-Day Intravenous Repeat Dose Toxicology Study in Rats with Micronucleus Assessment

- Rats received daily intravenous administration of 0, 13, or 51 µg/kg FES for 2 weeks. No adverse toxicological findings were observed.
- The no-observed-adverse-effect-level was 51 µg/kg, the highest dose tested.

Conducting laboratory and location: (b) (4)

Good laboratory practice (GLP) compliance: Yes

Table 4. Methods

Method	Details
Dose and frequency of dosing:	0, 13, 51 µg/kg; daily
Route of administration:	Intravenous
Formulation/vehicle:	15% Ethanol in saline
Species/strain:	Rat/Sprague Dawley CD® (SD)IGS BR

Method	Details
Number/sex/group:	5
Age:	6 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Table 5. Observations and Results: Changes from Control

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	No drug-related clinical signs noted.
Body weights	No drug-related effects on body weights or body weight gains.
Hematology	MD and HD: +57% mean absolute eosinophil counts in males; non-adverse as changes were not observed in % eosinophil counts or absolute or % eosinophil counts in females.
Clinical chemistry	No toxicology significant drug-related findings.
Gross pathology	No drug-related macroscopic findings.
Organ weights	MD and HD: higher mean absolute (+39% and +30%) and relative pituitary weights (+35% and +29%) in males; differences were attributed to low vehicle control and not considered drug-related. HD: higher mean relative kidney weight (+15%) in males; not considered drug-related because mean absolute kidney weight was comparable to vehicle control and there were no body weight changes observed.
	No toxicology significant drug-related findings
Histopathology	No drug-related microscopic findings.

Abbreviations: MD = mid dose; HD = high dose.

5.5.1.1. Additional General Toxicology Studies**Study 20110311TRP: Extended Single-Dose Toxicity Study in the Rat by the Intravenous Route**

Ten male and 10 female Sprague Dawley rats per group were dosed with vehicle (sodium ascorbate 0.5% w/v, 3.5% ethanol v/v, in 0.9% sodium chloride) or 0.62 µg/kg non-radioactive FES (decayed) by intravenous administration. Toxicity was evaluated by mortality, clinical observation, modified Irwin test, body weight and body weight gains, food consumption, ophthalmic examination, clinical (hematology, coagulation, and chemistry), and gross macroscopic and histopathology evaluation. No significant drug-related toxicology findings were observed in main and recovery animals. The no-observed-adverse-effect-level for this study was 0.62 µg/kg; equivalent to 1.2-fold higher than the recommended human dose (based on body surface area scaling).

The dose selected for the study was not adequate to support the proposed clinical dose of not more than 5 µg. The Applicant relies on findings of safety from a 14-day, repeat dose toxicity study conducted in Sprague Dawley rats.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study ^{(b) (4)}-1059: Bacterial Reverse Mutation Assay

Key Study Findings:

- Up to 1.25 µg FES per plate was negative for mutagenicity in the absence or presence of S9 microsomal activation (defined by at least a 2-fold increase in bacterial revertants).
- Positive control (2-aminoanthracene + S9 activation) and diagnostic mutagens (2-nitrofluorene, sodium azide, 9-aminoacridine, and methyl methanesulfonate) demonstrated expected S9- and strain-dependent increases in bacterial revertants.

GLP compliance: Yes

Test system: *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and *Escherichia coli* (WP2 uvrA) treated for 48 hours with up to 1.25 µg/plate with or without S9 metabolic activation.

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study 211886.001: In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK[±] Mouse Lymphoma Assay)

Key Study Findings:

- There were no concentration-dependent increases in mutant frequency in the absence or presence of S9 microsomes.
- The positive controls, methyl methanesulfonate (-S9), and 7,12-dimethyl-benz(a)anthracene (7,12-DMBA, +S9) increased the mutant frequency relative to vehicle control.

GLP compliance: Yes

Test system: Mouse lymphoma cell line L5178Y (clone 3.7.2C); up to 8 ng/mL; with or without S9 metabolic activation.

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study ^{(b) (4)}-1059: Micronucleus Assessment (as part of 14-Day Intravenous Repeat Dose Toxicology Study in Rats with Micronucleus Assessment)

Key Study Findings:

- FES did not affect the proportion of polychromatic erythrocytes (PCEs) to total erythrocytes in bone marrow, nor did it induce a statistically significant increase in the incidence of micronucleated PCEs relative to vehicle or historic control.

- The positive control, cyclophosphamide (30 mg/kg by single intraperitoneal injection), induced a statistically significant increase in the incidence of PCEs relative to control.

GLP compliance: Yes

Test system: Rat, bone marrow micronuclei, single intravenous dose of 13 or 51 µg/kg/day FES for 14 days.

Study is valid: Yes

Other Genetic Toxicity Studies

None.

5.5.3. Carcinogenicity

Carcinogenicity studies are not required for microdose radiopharmaceuticals and were not submitted.

5.5.4. Reproductive and Developmental Toxicology

The Applicant requested a waiver for reproductive and developmental toxicology studies. The waiver request was justified because FES is a radiopharmaceutical diagnostic drug that will be administered as a single dose at no more than 5 µg, corresponding to a sub-pharmacologic dose level. The pharmacokinetic (PK) properties of FES include a short half-life and rapid elimination from organs and tissues. The radiation dose to the developing fetus is considered when evaluating the radiation dosimetry and is detailed in the label. The waiver request was granted based on the proposed single-use indication, mass dose, and intended clinical population.

5.5.5. Other Toxicology Studies

None.

6. Clinical Pharmacology

6.1. Executive Summary

This NDA is approvable from a clinical pharmacology perspective. There were no clinical pharmacology studies performed by the Applicant. Published literature was used to support the clinical pharmacology section of this NDA.

The recommended dose of FES (b) (4) is 222 megabecquerel (MBq) and may range between 111 MBq to 222 MBq (3 mCi to 6 mCi). (b) (4). Although most published studies have not reported the mass of the drug, the maximum administered mass was typically less than 5 µg, and the maximum reported mass was 8.4 µg.

No formal dose finding studies for FES were conducted by the Applicant. However, the Applicant listed several literature articles that have used FES with average doses ranging from 111 MBq to 296 MBq (3 mCi to 8 mCi). The proposed dose is justified based on the extensive use of the tracer in multiple published studies.

In humans, 95% of FES is bound to plasma proteins (either SHBG or albumin). At equilibrium, 45% of the non-metabolized FES is bound to plasma SHBG. Since this fraction remains stable over time, it could theoretically allow delivery of enough tracer to image ER-positive tissues. The suggested time to start image acquisition is (b) (4) -minute post-injection (b) (4)

The uptake of FES could be altered in patients undergoing FES PET scan if they are on common antiestrogen therapies such as tamoxifen (TAM), fulvestrant (FUL), or aromatase inhibitors (AI).

The effect of TAM on FES uptake in patients with MBC was first described by McGuire et al. (McGuire et al. 1991). The mean lesion uptake of $2.22 (\pm 1.23) \times 10^{-3} \% \text{ID/mL}$ at baseline was reduced to $0.8 (\pm 0.42) \times 10^{-3} \% \text{ID/mL}$ after antiestrogen therapy.

Similarly, Linden et al. (Linden et al. 2011) measured regional estrogen-ER binding by using FES PET prior to and during treatment with AI, TAM, or FUL in a series of patients with MBC. FES PET measured in vivo estrogen binding at all tumor sites in heavily pretreated women with metastatic bone soft tissue-dominant breast cancer. Tumor FES uptake declined more markedly with ER modulators/blockers (TAM/FUL, average 54% decline) compared with a less than 15% average decline with estrogen-depleting AIs.

Therefore, it is recommended that patients undergo FES PET imaging prior to taking ER modulators such as TAM or ER blockers such as FUL.

The radiation absorbed effective dose associated with 222 MBq (6 mCi) of injected activity of FES is approximately 4.9 mSv (0.49 rem) in an adult weighing 70 kg. This is comparable to the radiation exposure caused by the administration of a standard dose of FDG.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. General Dosing and Therapeutic Individualization

See Section 6.1 above.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The pharmacology of FES is best understood by analogy to estradiol, a naturally occurring steroid. Estradiol is highly lipophilic and is generally present in higher concentration in tissues with higher fat content. Circulating estradiol is largely protein-bound with high-affinity low-capacity to SHBG and low-affinity high-capacity to albumin.

There are three naturally occurring estrogens in women: estrone (E1), estradiol (E2), and estriol (E3). The predominant estrogen during pregnancy is estriol, whereas in postmenopausal women estrone is the primary form of estrogen. Estrogens are established growth factors for endometrial and breast cancers. Approximately 60% to 80% of breast cancers express ER, estradiol and other estrogens provide a key stimulus for tumor growth and an opportunity for endocrine-based therapy.

In humans, 95% of FES is bound to plasma proteins (either SHBG or albumin). Even though most FES initially binds to albumin immediately after intravenous administration, within less than 20 seconds, the tracer is transferred to SHBG. At equilibrium, 45% of the non-metabolized FES is bound to plasma SHBG, and remains stable over time, which theoretically would allow delivery of enough tracer to image ER-positive tissues. (b) (4)

Comment: The review team recommends the following labeling under 2.4 Image Acquisition Guidelines. For additional rationale, see also Table 6 and the “PET imaging start time after FES administration” row, indicating a start time of 80 minutes for the primary clinical study relied upon, and 60 minutes for the other clinical studies:

The recommended start time for image acquisition is 80 minutes after the intravenous administration of CERIENNA. Scan duration adapted from the range of 20 minutes to 30 minutes and imaging start times adapted within the range of 20 minutes to 80 minutes may be customized according to the equipment used and patient and tumor characteristics for optimal image quality.

Pharmacodynamics: Quantitative estimates of FES uptake in human tumors show that FES uptake measured by PET is proportional to tumor ER expression and correlates with in vitro assays of ER expression. This was first demonstrated in 13 patients with primary breast masses; there was a 0.96 correlation between FES uptake within the primary tumor and the tumor ER concentration measured in vitro after excision (Mintun et al. 1988).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Efficacy of FES is not based directly on pharmacokinetics (exposure-response/imaging). However, FES uptake in tumors occurs due to binding to ER expressed on breast cancer. As stated above, a good correlation was observed between FES uptake within the primary tumor and the tumor ER measured in vitro after excision. Clinical pharmacology information provides limited supportive evidence of effectiveness.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No alternative dosing regimen is required for subpopulation based on intrinsic factors.

A retrospective study (Peterson et al. 2011) evaluated the effect of patient characteristics on uptake of FES, by reviewing the results of the 10 years of investigational experience, including 312 scans from 239 patients. Most scans (96%) were from female patients with Stage III or IV disease (advanced stage breast cancer). Factors evaluated for a potential effect on standardized uptake value (SUV) included patient characteristics (age, sex, menopausal status, disease stage, human epidermal growth factor receptor 2 (HER2) status, presence of FES-negative lesions, body mass index), treatment history (prior chemotherapy, radiation, or use of TAM, current chemotherapy), blood assays (serum estradiol, testosterone, albumin, serum SHBG, rate of FES metabolism), and dosing details (dose in MBq, specific activity, mass dose/kg, fractional binding of FES to SHBG). The average FES dose injected was 185 MBq (5.0 mCi) with a range of 103.6 MBq to 296 MBq (2.8 mCi to 8.0 mCi).

Of these, concurrent chemotherapy and the presence of one or more FES-negative lesions were each associated with lower average SUV than without these findings. Other significant findings included an increase in SUV with increasing body mass index, and a decrease in SUV with higher SHBG and increased binding to SHBG. No significant differences were reported for age, sex, menopausal status, disease stage, or HER2 status.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There were some clinically relevant drug-drug interactions. The patients undergoing FES PET may be on anti-estrogen therapy (ER blocking agents targeting the receptor, and estrogen depleting agents targeting production of the ligand). ER blockers include selective ER modulators such as TAM, which have both ER agonist and antagonist properties, working primarily as antagonists in tumors. A second class of ER blockers includes FUL, which is a selective ER downregulator and a pure ER antagonist. These patients could also be on AI. Estrogen-lowering AIs target aromatase, the enzyme that converts androstenedione and testosterone to estrogen, and result in lower estrogen levels both in the plasma and at the tumor site.

In the study first describing the effect of TAM on FES uptake in patients with metastatic breast cancer (McGuire et al. 1991), 11 patients received anti-estrogen therapy (10 were on TAM and 1 was on toremifene). Of these, seven patients, who had a total of 34 analyzable lesions, underwent FES PET before and after the start of therapy. The mean lesion uptake at baseline was $2.22 (\pm 1.23) \times 10^{-3} \% \text{ID/mL}$, while the mean lesion uptake after antiestrogen therapy was $0.8 (\pm 0.42) \times 10^{-3} \% \text{ID/mL}$. Thus, a decrease of about 64% was observed in FES after the anti-estrogen therapy.

Regional estrogen-ER binding by using FES PET prior to and during treatment with AI, TAM, or FUL was measured in patients with metastatic breast cancer (Linden et al. 2011). FES PET measured in vivo estrogen binding at all tumor sites in heavily pretreated women with metastatic bone soft tissue-dominant breast cancer. In patients with preserved uterus (n=16), changes in uterine FES uptake were also measured.

Tumor FES uptake declined more markedly with ER blockers (TAM and FUL, average 54% decline) compared with a less than 15% average decline with estrogen-depleting AIs. The rate

of complete tumor blockade (FES SUV 1.5) following TAM (5/5 patients) was greater than the blockade rate following FUL (4/11). Percent FES SUV change in the uterus showed a strong association with tumoral change.

Therefore, the review team recommends that patients undergo FES PET imaging prior to taking ER modulators such as TAM or ER blockers such as FUL.

Comment: *The review team recommends the following labeling under 7 Drug Interactions Image Acquisition Guidelines, based on quantification of ~ 5 half-lives from the approved PI for Faslodex (fulvestrant) and published literature evaluating the half-life of high affinity (short half-life) and low affinity (long half-life) metabolites for tamoxifen:*

Certain classes of systemic endocrine therapies, including ER modulators and ER down-regulators, block ER, reduce the uptake of fluoroestradiol F 18, and may reduce detection of ER-positive lesions after administration of CERIANNA. Drugs from these classes such as tamoxifen and fulvestrant may block ER for up to 8 and 28 weeks, respectively. Do not delay indicated therapy in order to administer CERIANNA. Administer CERIANNA prior to starting systemic endocrine therapies that block ER.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant has submitted an original NDA for FES. The Applicant is seeking approval through the 505(b)(2) regulatory pathway and is relying on findings of safety and effectiveness from published literature. The originally proposed indication was “for characterization of estrogen receptor status (b) (4) breast cancer.”

FES exhibited the highest uptake selectivity and target to background ratio among several estrogens labeled with F 18 in 1984 (Kiesewetter et al. 1984). Since then, there have been more than 35 clinical studies of FES reporting on more than 1000 subjects. However, a search for investigations aimed at the MBC population yielded three relevant papers submitted by the Applicant. For additional discussion of relevant regulatory history and terminology, see Section 2. The Applicant also submitted data from ESTROTEPREDIC (ClinicalTrials.gov 2012), an exploratory study of FES to predict response to hormone therapy. See Table 6 for summary:

Table 6. Listing of the Clinical Trials Relevant to This NDA

Category	Study 1 (Chae et al. 2019)	Study 2 (Peterson et al. 2014)	Study 3 (Venema et al. 2017)	Estrotepredic (ClinicalTrials.gov 2012)
Study code	NCT 01986569	NCT 00602043	NCT 01988324	NCT 01627704
Phase	3	2	2	2
Design	Prospective	Prospective	Prospective	Prospective
Study population	MBC patients	MBC patients	MBC patients	MBC patients
Endpoint	PET imaging/IHC	PET imaging/IHC	PET imaging/IHC	PET imaging/IHC
SOT	IHC	IHC	IHC	6-month response rate
Dose (MBq)	204 (192–211)	2.6/kg, ≤222	200	2–4/kg, ≤400
Dose (mCi)	5.5 (5.2–5.7)	0.07/kg, ≤6	5.4	0.05–0.11/kg, ≤10.8
Mass dose	NA	≤2.8 µg	NA	NA
Volume	NA	20 mL	NA	NA
Duration of IV administration	1–2 mins	NA	NA	Infusion, rate 1 mL/sec
Volume/duration/time of post-FES flushing	NA	Duration: 2 mins	NA	NA
PET imaging start time after FES administration	80 mins	~60 mins (w/ additional dynamic acquisition)	60 mins	60 mins
Total scan time	NA	NA	NA	20 mins
Prior endocrine therapy washout period before FES PET	At least 60 days	6 months for prior endocrine therapy and 6–8 weeks more for tamoxifen	NA	>3 weeks
Subjects completed FES PET (n)	90	19	21	72
Subjects for efficacy (n)	85	15	13	61
Subjects with known ER status for primary breast tumor (n)	51 (15 POS, 36 NEG)	15 (all POS)	13 (all POS)	61 (all POS)
ER conversion occurred	Yes	Yes	Yes	NA
Sex	All female	All female	11 female, 2 males	All female
Age	55 (46–60)	62 (38–77)	64	62±15.8
Race	All Korean	16 white, 2 black, 1 American Indian	NA	NA
FES scan blinded readers (n)	3	3	NA	1

Abbreviations: MBC = metastatic breast cancer; SOT = standard of truth; IHC = immunohistochemistry; POS = positive; NEG = negative; NA = not available

Among the four studies listed above, Study 1 (Chae et al. 2019) is most relevant to the population of intended use and provides estimates of FES performance from the largest sample size.

7.2. Review Strategy

The Applicant submitted a trial (ESTROTEPREDIC) to support this NDA. The review team mainly relied on Study 1 (Chae et al. 2019), Study 2 (Peterson et al. 2014) and Study 3 (Venema et al. 2017) for efficacy assessment. For safety, the review team relied on the Applicant's summary of the literature, which included Studies 1, 2, 3, and Estrotepredic as well.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 1 (Chae et al. 2019)

Study Title

Diagnostic accuracy and safety of 16 α -[¹⁸F]Fluoro-17 β -estradiol PET-CT for the assessment of estrogen receptor status in recurrent or metastatic lesions in patients with breast cancer: a prospective cohort study (Chae et al. 2019).

Trial Design

Phase 3, prospective, non-randomized, single-center cohort study.

Enrollment

Inclusion criteria:

- Patient is ≥ 19 years of age and male or female of any race/ethnicity.
- Patient has first recurrence of breast cancer or stage IV disease as defined by the American Joint Committee on Cancer staging system for breast cancer.
- Patients had histologically confirmed invasive breast carcinoma, and the result of histology is available.
- Patients are scheduled to undergo core needle biopsy or surgery for histological confirmation and determination of ER status of recurrent or distant metastatic cancer within 15 days after FES scan; or patients already underwent core needle biopsy of recurrent or distant metastatic cancer within 30 days before FES scan and biopsy specimens are available for determination of ER status.
- Patient discontinued selective ER modulators or fulvestrant for at least 60 days prior to FES scan.

- Patient has Eastern Cooperative Oncology Group performance status of ≤ 2 . See table 7 for description of categories.

Table 7. ECOG Performance Status Categories (Oken et al. 1982)

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

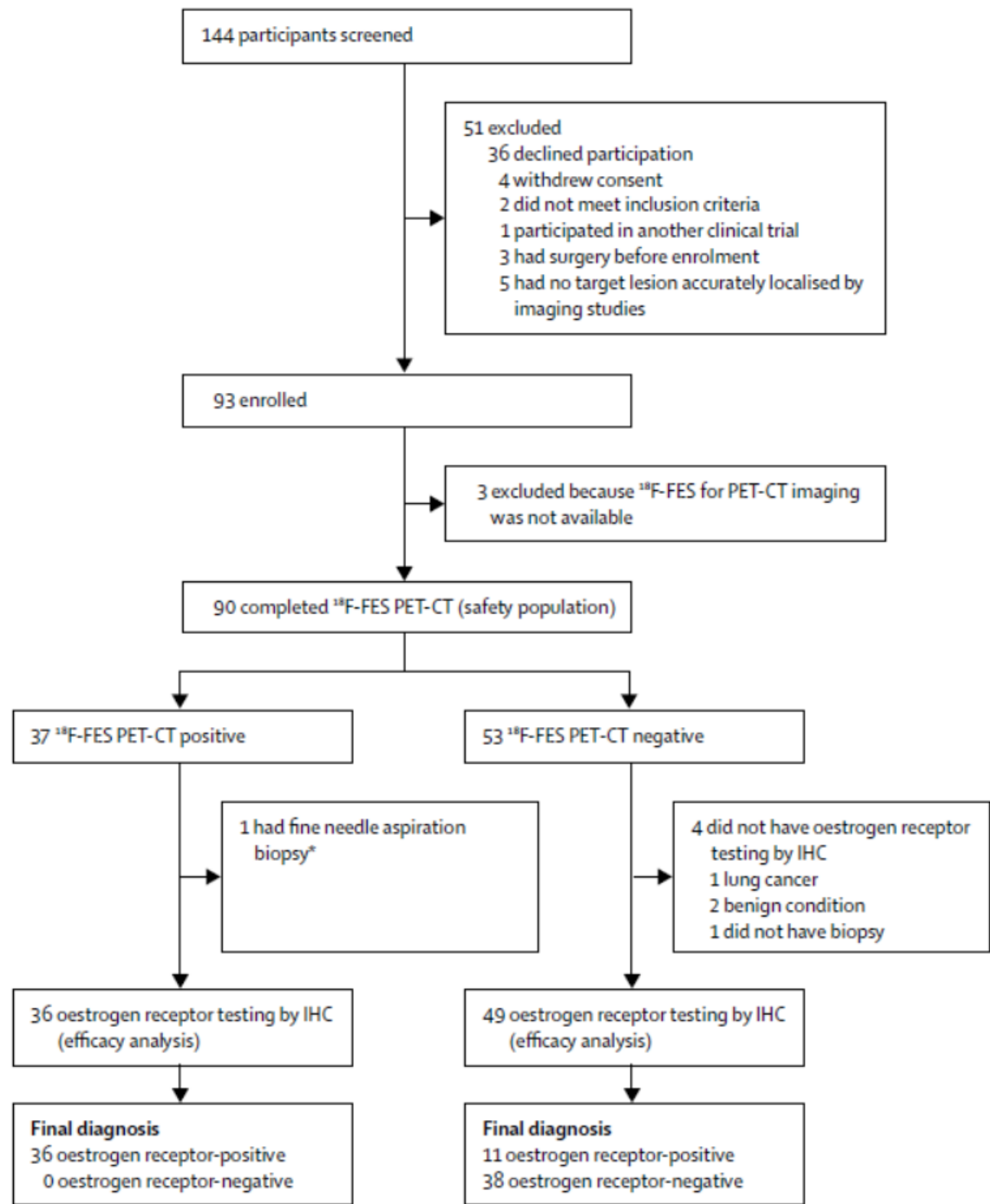
Abbreviation: ECOG = Eastern Cooperative Oncology Group

Comment: *ER-positive primary breast cancer was not required for enrollment.*

Major exclusion criteria:

- Chemotherapy, radiation therapy, or immune/biologic therapy is scheduled before the histologic confirmation or FES scan.
- Patient has concurrent severe and/or uncontrolled and/or unstable medical disease other than cancer (e.g., congestive heart failure, acute myocardial infarction, pulmonary disease, chronic renal or hepatic disease) which could compromise participation in the study.

Figure 1. Study Profile



Source: from (Chae et al. 2019)

*Fine needle aspiration specimens do not have enough cells for immunohistochemical stains; patients who had only core needle biopsy or surgery were included (specified in the eligibility criteria)

Abbreviations: ¹⁸F-FES, 16 α -[¹⁸F]Fluoro-17 β -estradiol; IHC, immunohistochemical assay

Radioactive Dose

Per protocol: 111 MBq to 222 MBq (3 mCi to 6 mCi), IV bolus over 1 min to 2 min, single dosing.

Imaging Procedure

PET imaging from the skull base to the upper thigh for 2 min acquisition time per bed position for each patient, started at 80 to 100 min post-FES injection. A lower dose CT primarily for anatomic localization and attenuation correction of PET images was also acquired.

Imaging Interpretation

Three central, independent nuclear medicine physicians were blinded to patient medical records, including pathology results. However, they were unblinded to study eligibility criteria and to the location of the largest lesion scored by pathologists.

Comment: *Mismatch between the scope of ascertainment between image reading (here from skull base to upper thighs) and the standard used for image performance quantification (here pathology from largest biopsied lesion, with typically only one lesion biopsied per patient) is a recurring issue in the design of studies for new diagnostic imaging drugs. The solution reported in Study 1 has the advantage of feasibility and simplicity, and it is not clear that tradeoffs involved with alternative design choices would have been preferable. Nevertheless, a key disadvantage of this design is that while pathologists were fully independent of image readers, the converse was only partially true: image readers selected one lesion per subject for study interpretation with prior knowledge of the location of the largest biopsied lesion (“reference lesion”). This key methodological limitation constrains generalizability of the primary endpoints (see also “Study Endpoints” below and under Section 8.3). It also explains the study authors’ and review team’s preference for descriptive terminology “positive/negative percent agreement” (PPA/NPA) and “positive/negative predictive agreement” over the identically calculated “sensitivity/specificity” and “positive/negative predictive value.” The latter more familiar terms are most meaningfully reserved for study designs that provide for greater independence between image reading and the standard used for performance quantification.*

Criteria for FES-Positive Scans

Excerpted from Chae et al. 2019: “Based on the knowledge of normal FES biodistribution, intensity was assessed on a three-point scale (0, decreased uptake; 1, equivocal uptake; 2, increased uptake) in relation to the background activity. When a focus of increased FES uptake was present in the reference lesion, it was interpreted as positive. If the intensity was equivocal or decreased, the lesion was interpreted as negative.”

For each patient with three blinded FES reads of positive or negative for the reference lesion, if two or more (majority) were positive, the patient was classified as FES-positive; otherwise, as FES-negative. Per-reader FES interpretations were not reported.

Standard of Truth

The largest MBC lesion biopsied per patient was defined as the reference lesion and immunostained for ER. Semiquantitative ER expression was assessed according to the Allred score by blinded breast pathologists. Proportion of positive cells (0 to 5) and staining intensity scores (0 to 3) were summed for a total score of 0 to 8. For patients with Allred scores of 0 to 8, their ER status was positive if the Allred score of their reference lesion was 3 or higher; otherwise, their ER status was negative.

Safety Monitoring

Vital signs were monitored, and physical exam was conducted before and two hours post-FES injection. Adverse events (AEs) were continuously recorded, beginning with patient enrollment until the last patient contact between 1 and 10 days after FES administration.

Study Endpoints

The primary objective was to show agreement between qualitative FES scan interpretation and pathologically based ER status.

Statistical Analysis Plan

Not applicable for this literature-based review.

Protocol Amendments

Not mentioned.

8.1.2. Study Results

Compliance with Good Clinical Practices

Excerpted from Chae et al. 2019: “The institutional review board (IRB) approved the study protocol. The study was done in accordance with the Declaration of Helsinki and institutional guidelines. All patients provided written informed consent before participating in the study.”

Financial Disclosure

Excerpted from Chae et al. 2019: “The study was sponsored by the Asan Foundation from South Korea and funded by the Ministry of Health and Welfare, South Korea (grant number, HI06C0868). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.”

Patient Disposition

Table 8. Baseline Characteristics of Patients with Completed FES Scan

Individualized treatment effect	Participants
Menopausal status, n (%)	
Premenopausal	35 (39)
Postmenopausal	55 (61)
Body mass index (kg/m ²), median (IQR)	23 (21 – 26)
ECOG performance status, n (%)	
0	84 (93)
1	6 (7)
Pathology of the primary carcinoma, n (%)	
Invasive ductal carcinoma	88 (98)
Invasive lobular carcinoma	2 (2)
Previous treatment for breast cancer, n (%)	
Surgery	86 (96)
Chemotherapy	73 (81)
Hormonal therapy	50 (56)
Radiotherapy	47 (52)
Reason for inclusion in the study, n (%)	
Locoregional and distant recurrence	86 (96)
Stage IV metastatic breast cancer	4 (4)
Time interval from surgery to recurrence, months*, median (IQR)	52 (19 – 108)
Pathological diagnosis of recurrence or metastasis†, n (%)	
Regional lymph node‡	40 (47)
Distant lymph node	14 (16)
Lung	18 (21)
Chest wall	13 (15)
Pleura	1 (1)

Source: from (Chae et al. 2019)

Data are median (IQR) or n (%).

* Patients with pathologically confirmed recurrence (n=83).

† Patients with pathologically confirmed recurrence or metastasis (n=86).

‡ Metastases in ipsilateral axillary, internal mammary, supraclavicular, or infraclavicular lymph node(s).

Abbreviations: FES = Fluoroestradiol F 18; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range;

Protocol Violations/Deviations

Not mentioned.

Table of Demographic Characteristics

Table 9. Demographic Characteristics of Patients with Completed FES Scan

Parameters	Participants n (%)
Sex	
Female	90 (100)
Age (years)	55 (46 – 60)
Race	
Asian (Korean)	90 (100)

Source: from (Chae et al. 2019)

Comment: Study 1 was conducted at a single center, limiting generalizability.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

None. Patients with concurrent severe and/or uncontrolled and/or unstable disease other than cancer (e.g., congestive heart failure, acute myocardial infarction, pulmonary disease, chronic renal or hepatic disease), which could compromise participation in the study, were excluded.

Efficacy Results – Primary Endpoint

A total of 93 patients were enrolled over a three-year period. Of the 85 patients included in the efficacy analysis, 47 (55%) were ER-positive (Allred score 3 to 8) and 38 (45%) ER-negative (Allred score 0 to 2). Biopsy samples were most commonly taken from lymph nodes (54/85, 64%) and lung (18/85, 21%). FES scan was positive in 36 of 47 ER-positive patients, yielding a PPA of 76.6%. All 38 ER-negative patients had negative FES PET, yielding an NPA of 100%. With the same 2x2 tabulation data analyzed based on proportion of positive and negative FES scans, positive predictive agreement was 100% and negative predictive agreement was 77.6%. See table below.

Table 10. Performance of FES PET/CT (N=85)

	SOT, ER Status by IHC		Predictive Value
	ER Positive n=47	ER Negative n=38	
FES scan			
Positive	36	0	PPrV, 100%
Negative	11	38	NPrV, 77.6%
PPA (%)	76.6		
NPA (%)		100	

Source: from (Chae et al. 2019)

Abbreviations: FES = Fluoroestradiol F 18; ER = estrogen receptor; IHC = immunohistochemical assay; NPA = negative percent agreement; NPrV= negative predictive value; PPA = positive percent agreement; PPrV = positive predictive value; SOT = standard of truth

Since there were three blinded readers for PET scan interpretation, individual reader performance is of interest. The inter-rater agreement among the three readers was 0.90 (Chae et al. 2019). The paper concludes, “In this study, qualitative FES PET-CT interpretation was robust, with high interobserver concordance.”

The review team requested that the Applicant obtain and submit reader-level performance data (per reader and per lesion line-item data) supporting this conclusion. Based on the response, although the Applicant was able to contact study authors, they were unable to obtain and submit the requested information.

Data Quality and Integrity

The Applicant was unable to submit any unpublished data from Study 1. No data quality or integrity issues were identified in the published report.

Efficacy Results – Secondary and Other Relevant Endpoints

Secondary endpoint measures included association between SUVmax from the FES scan and the pathological Allred score Median SUVmax values were 4.6 (IQR 2.1 to 7.9) for ER-positive

reference lesions and 1.2 (1.0 to 1.5) for ER-negative reference lesions (Table 11). The correlation between SUVmax and Allred score was positive ($p=0.83$). See Figure 2.

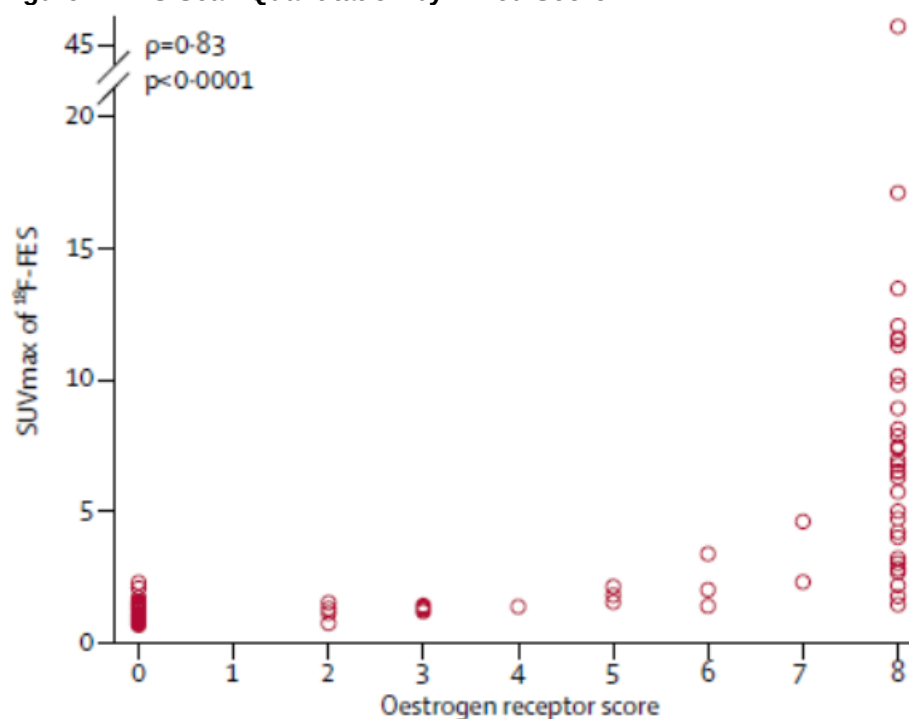
Table 11. FES Scan Quantitation by ER Status

Category	SOT, ER Status by IHC	
	Positive (n=47)	Negative (n=38)
SUVmax (median)	4.6	1.2
	IQR 2.1 – 7.9	IQR 1.0 – 1.5

Source: from (Chae et al. 2019)

Abbreviation: FES = ¹⁸F-fluoroestradiol; IQR = interquartile range; SOT = standard of truth; SUVmax = maximum standardized uptake value

Figure 2. FES Scan Quantitation by Allred Score



Source: from (Chae et al. 2019)

All patients with FES PET-CT and immunohistochemical IHC assay available are shown (n=85)

Abbreviation: FES, fluoroestradiol F 18; SUVmax = maximum standardized uptake value

Dose/Dose Response

The median administered activity of FES was 204 MBq, 5.5 mCi (IQR 192–211 MBq).

8.1.3. Assessment of Efficacy Across Trials

In comparison to Study 1 (Chae et al. 2019), Study 2 (Peterson et al. 2014) and Study 3 (Venema et al. 2017) investigated similar patient populations with more exploratory study objectives and smaller sample sizes.

Study 2 was a single-center study that evaluated agreement between FES PET and biopsy results. Eligible patients were pre- and post-menopausal women with pathologically confirmed ER-positive invasive primary breast cancer and stage IV disease. Nineteen patients underwent FES imaging and 17 had at least one biopsied metastatic lesion. The median age was 62, and 17

patients were post-menopausal. Quantitatively evaluated FES scans were also evaluated qualitatively by three blinded readers. All three FES scan readers agreed with one another on whether the patient had any metastatic lesions that were FES-negative (6 Yes, 13 No). Thirteen patients had both quantitative FES scan and biopsy evaluation of the same or regionally co-located lesion. Based on the reported analysis using SUVmean ≥ 1.5 and pathological Allred score ≥ 2 to define FES-positive and ER-positive patients, respectively, all 11 ER-positive patients were FES-positive and both ER-negative patients were FES-negative.

The study reported by Venema and colleagues also evaluated agreement between FES scan and biopsy results. Male and post-menopausal female patients with MBC and a previous ER-positive primary tumor were eligible if they had metastasis outside of the liver that was safe to biopsy. The mean age was 64, and 11 of the 13 evaluable patients were female. While all evaluable patients had an ER-positive primary tumor, two patients had ER-negative MBC lesions. Using SUVmax > 1.5 to define FES-positive patients, all 11 ER-positive patients were FES-positive and both ER-negative patients were ER-negative.

Table 12 provides additional detail comparing studies. See also Table 6.

Table 12. Additional Comparison Across Efficacy Studies

Category	Study 1	Study 2	Study 3
Qualitative reading	Yes	Partial	No
Quantitative reading	Yes	Yes	Yes
Prospectively powered for pre-specified endpoint and win criteria	Yes	No	No
One vs. one or more lesions evaluated per patient per reported FES scan evaluation	One (target location pre-specified)	One or more	One or more
Liver lesion eligible for the reads	No	No	No
Bone lesions eligible for qualitative FES reads	No	Yes	Yes

Abbreviations: FES = Fluoroestradiol F 18

ER conversions, defined as changes from ER-positive to -negative status or verse visa, were reported in all three efficacy studies. In Study 1, the ER status of primary tumors was available from medical records in 51 of 85 patients (15 ER-positive and 36 ER-negative). Of the 15 patients with ER-positive primary breast cancer, two (13%) had ER-negative recurrent breast cancer, whereas of the 36 patients with ER-negative primary breast cancer, two (6%) had ER-positive recurrent breast cancer. Table 13 summarizes these and comparable results across studies.

Table 13. ER Status Conversions

	Study 1				Study 2				Study 3							
Subjects completed FES PET (n)	90				19				21							
Subjects for efficacy (n)	85				15				13							
Subjects with ER status of original breast tumor (n)	51				15				13							
Tumor ER status																
Original (primary)	POS: 15				NEG: 36				All 15 POS							
Treatment or time between evaluations	Surgery, chemotherapy, hormonal therapy, and radiotherapy				3 months to 29 years				All 13 POS							
Recurrent (metastasis)	POS: 13		NEG: 2		POS: 2		NEG: 34		POS: 12		NEG: 3		POS: 11		NEG: 2	
FES PET	P	N	P	N	P	N	P	N	P	N	P	N	P	N	P	N
	UK	UK	0	2	UK	UK	0	34	11	0	0	2	11	0	0	2

Source: from (Peterson et al. 2014; Venema et al. 2017; Chae et al. 2019)]

The methodology of PET reading in Chae study was qualitative, POS or NEG.

The methodology of PET reading in Peterson study was quantitative and converted to POS: SUV >1.5 and NEG: SUV ≤1.5.

The methodology of PET reading in Venema study was quantitative and converted to POS: SUV_{max} >1.5 and NEG: SUV_{max} ≤1.5.

Abbreviations: FES = Fluoroestradiol F 18; PET = positron emission tomography ER = estrogen; IHC = immunohistochemical assay; POS = positive; NEG = negative; UK = unknown

There are multiple published reports addressing heterogeneity in ER status across time at the patient-level based on biopsy. Table 14 and Table 15 provide example results from two reports.

Table 14. Estrogen Receptor Conversion of Breast Cancer (N=231, (Yang et al. 2018))

Table 2. Estrogen Receptor: Subclassification of Breast Cancer (N = 221, (May 2010))				
Tumor	ER Status			
Original tumor	Positive		Negative	
	221		10	
Treatment between evaluations	Neoadjuvant chemotherapy (NAC)			
Residual tumor	Positive	Negative	Positive	Negative
	173	48	7	3

Table 15. Estrogen Receptor Conversion of Breast Cancer (N=627, (Meng et al. 2016))

Tumor		ER Status		
Original tumor	Positive 346	Negative 281		
Treatment between evaluations		Detailed treatment unknown		
Metastatic tumor	Positive 240	Negative 106	Positive 59	Negative 222

Comment: In patients with MBC, it is not feasible to biopsy all lesions, nor to biopsy lesions repeatedly. Combined with ER-status heterogeneity i) across lesions and ii) across time, this provides the essential rationale for the clinical utility of detecting ER-positive lesions using non-invasive, whole-body PET, even as an adjunct to biopsy (e.g., as a guide for which lesions to biopsy when feasible or as a fallback, when biopsy is infeasible). Table 14 and Table 15 and the design of Study 1 restrict focus only to ii and thus likely underestimate potential benefit. On the other hand, in Table 12, while the subgroup analysis of performance in the 15->2 converters is supportive, the value of P in the 36->2 converters is unknown, yet of interest. However, even acknowledging PPA in this subgroup is likely less than the overall reported PPA of 77%, detecting ER-positive lesions in any patient with MBC when none are suspected is likely of particular clinical value, given the favorable profile of anti-estrogen therapy. The review team thus recommended (b) (4)

Efficacy Conclusions Across Trials

The reported design of Study 1 is mostly consistent with relevant FDA guidance for industry *Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications* (June 2004) for phase 3 investigation of medical imaging drugs for new disease or pathology detection or assessment indications. In response to information requests, the Applicant submitted limited reader data from Study 2. The review team has identified no discrepancy between this submitted data and the reported performance for Study 2, nor between reported FES performance across studies. Such convergence mitigates against added uncertainty shared by all members of the review team, given that Applicant proposes to rely primarily on published reports, as authorized under 505(b)(2) of the FD&C, and review flexibility, as discussed in recent FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) on substantial evidence of effectiveness. In summary, relying primarily on Study 1 plus confirmatory evidence from Study 2, the review

team finds substantial evidence that PPA and NPA exceed clinically meaningful thresholds for detecting ER-positive lesions in patients with recurrent or metastatic breast cancer.

8.2. Review of Safety

Safety Review Approach

The ESTROTEPREDIC study conducted by Applicant showed that the drug was tolerated by all patients with no adverse reactions. The clinical investigation of FES has been conducted by multiple independent investigators over many years. There was no overall plan for the evaluation of safety, nor were any studies undertaken solely for the purpose of evaluating the safety of FES.

8.2.1. Review of the Safety Database

Overall Exposure

To date, approximately 1,506 patients have received FES, including 1,279 patients with or suspected to have breast cancer, and 227 patients have received FES for other indications (primarily ovarian and uterine imaging).

Race was not reported in most of these studies. All 90 participants in Study 1 (Chae et al. 2019) were Korean women. Three U.S. studies involving a total of 110 patients (Mortimer et al. 2001; Dehdashti et al. 2009; Peterson et al. 2014) included 89 patients identified as white, 20 identified as black or African American, and one identified as American Indian or Alaskan Native. Other studies in the literature had at least 662 patients recruited from the United States or Canada. Across all indications, ten studies representing 299 patients were reported from China, Japan, or Korea (Mortimer et al. 2001; Dehdashti et al. 2009; Peterson et al. 2014).

In most breast cancer studies, FES was administered in a dose of approximately 185 – 222 MBq (5–6 mCi), with the mass dose being typically <5 µg. The maximum dose reported in the literature is 8.4 µg.

As expected for a product with affinity for the ER, most of the patients (98%) studied were female. Patients ranged in age from 21 to 91 years, with a weighted mean age of 55.3 years across the various studies. Consistent with both the weighted mean age and the age distribution of breast cancer, more than half of the women were postmenopausal.

Adequacy of the Safety Database

The sample size of more than 1,500 is adequate.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The safety data were from clinical studies, database, or literature available. There are no data integrity issues identified.

Categorization of Adverse Events

No clinical study was conducted to specifically address FES safety and the published sources do not provide information regarding FES safety. However, some studies provide information regarding AEs associated with the administration of FES, as summarized in the table below:

Table 16. Studies Reporting Safety Information

Study	Patient #	Safety Info Assessed	Result
(Mankoff et al. 2001)	49	AEs	"No chemotoxicity from FES was expected, nor has it been noted in our experience."
(Kumar et al. 2007)	20	AEs	"No adverse reactions were recorded to any of the FES injections."
(Peterson et al. 2014)	19	Vital signs, AEs	"During this study, there were no adverse events related to FES administration or FES imaging."
(Vatsa et al. 2017)	5	AEs	"Radiopharmaceutical was well tolerated by patients."
(Chae et al. 2019)	90	AEs	"No AEs were related to the study drug except injection site pain in one (1%) patient. No serious AEs were recorded."
ESTROTEPREDIC*	72	Vital signs, AEs	"No adverse reaction to FES was observed."

*Source: from the submission.

Abbreviations: AE = adverse event; FES = Fluoroestradiol F 18

Routine Clinical Tests

Not applicable.

8.2.3. Safety Results

Deaths

No deaths due to FES have been documented in the available literature.

Serious Adverse Events

No serious adverse events due to FES have been documented in the available literature.

Dropouts and/or Discontinuations Due to Adverse Effects

No dropouts or discontinuation due to AEs from FES have been documented in the available literature.

Significant Adverse Events

"Alcohol taste" was listed as an AE of FES based on the Richtlijnen database Federatie medisch specialisten of Netherlands (Guidelines database of Federation of medical specialists). It states that "Other than infrequent transient intravenous site discomfort and an "alcohol taste", there have been no adverse events related to FES administration" (Knöspel et al. 2016).

Dysgeusia is listed as an AE with possible relationship to FES by Comprehensive Adverse Events and Potential Risks List from NCI, National Institutes of Health, with unknown rate and intensity.

One of the objectives of Study 1 was FES safety. It reported that “The most common adverse event was procedural pain in nine (10%) of 90 patients injected with FES. No adverse events occurred that were related to the study drug except injection site pain in one (1%) patient. No serious adverse events occurred during the study and there were no treatment-related deaths...FES PE-CT was well tolerated and no serious adverse events were recorded” (Chae et al. 2019).

Table 17. Adverse Events in Study 1, Safety Population (N=90)

Patients With TEAE(s) Preferred Term*	Grade 1 n (%)	Grade 2 n (%)
Patients with ≥1 TEAE	10 (11)	5 (6)
Nausea	3 (3)	0
Injection site pain‡	1 (1)	0
Viral URTI	0	1 (1)
Procedural pain	5 (6)	4 (4)
Dizziness	1 (1)	0
Headache	0	1 (1)
Skin irritation	1 (1)	0

Source: See reference (Chae et al. 2019)

*: Adverse events are listed by preferred terms (Medical Dictionary for Regulatory Activities version 20.0) and graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). All events are presented irrespective of association with study drug. There were no grade 3, 4, or 5 events.

‡: One adverse event was considered to be possibly treatment-related.

Abbreviations: TEAE = treatment-emergent adverse events; URTI = upper respiratory tract infection

As with other IV administered agents, it is possible that FES could cause a potentially life-threatening allergic reaction. However, this has not been observed in the limited human exposure to date.

Based on the FDA Document Archiving, Reporting, and Regulatory Tracking System, a total of 12 active IND studies with FES. None of the studies had AEs severe enough to trigger Agency’s decision of clinical hold, or Applicant’s withdrawal, or inactivation of the IND.

Treatment-Emergent Adverse Events and Adverse Reactions

No FES-related treatment-emergent AEs or adverse reaction have been documented in the literature.

Laboratory Findings

No studies included a clinical laboratory evaluation in the study design. No clinically significant changes in any parameters have been reported.

Vital Signs

According to the ESTROTEPREDIC study, there were no remarkable changes in any patient for any parameter of the vital signs.

Table 18. Effect of FES on Vital Signs*

Parameter	Baseline		45-60 Min Post-Injection		Prior to Discharge	
	n	Median (Range)	n	Median (Range)	n	Median (Range)
Systolic BP (mm Hg)	42	131 (80–198)	38	130 (80–198)	38	130 (80–198)
Diastolic BP (mm Hg)	42	76 (47–97)	38	76 (42–97)	38	73 (46–97)
Pulse rate (bpm)	38	78 (58–130)	38	77 (58–130)	34	79 (58–130)

Source: from ESTROTEPREDIC, submitted.

* Vital signs were not collected in all patients (72). According to the report, because no remarkable changes were observed, and none expected, vital signs collection was stopped to limit the radiation exposure of study personnel.

Abbreviations: BP = blood pressure; bpm = beats per minute; FES = Fluoroestradiol F 18

Electrocardiograms

No electrocardiogram data in subjects receiving FES is available in the literature.

QT

No evaluation of QT intervals in subjects receiving FES is available in the literature.

Immunogenicity

FES is a radiopharmaceutical consisting of an estradiol analogue radiolabeled with ¹⁸F and unknown immunogenicity. No immunogenicity studies involving FES have been documented in the literature.

Radiation Exposure

As with all PET imaging agents, FES is a radiopharmaceutical that decays with positron emission. As such, FES poses an intrinsic radiation exposure risk. The table “Radiation Absorbed Doses in Various Organs/Tissues in Adults” in labeling for 2.6 Radiation Dosimetry reflects published literature (Mankoff et al. 2001; Talbot et al. 2015). The effective dose of FES is 0.022 mSv/MBq. The effective dose resulting from the administration of the maximal recommended activity of 222 MBq (6 mCi) of FES Injection for an adult weighing 70 kg is about 4.9 mSv, which is acceptable for the indicated population of patients with MBC. For an administered activity of 222 MBq (6 mCi), the typical radiation doses delivered to the critical organs, (i.e., liver and gallbladder, are 28 mGy and 23 mGy, respectively. Whole-body and organ absorbed doses of radiation associated with FES PET imaging are comparable to or lower than doses associated with other radiopharmaceuticals widely used clinical nuclear medicine.

8.2.4. Analysis of Submission-Specific Safety Issues

Not applicable.

8.2.5. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable.

8.2.6. Safety Analyses by Demographic Subgroups

See discussion under Section 8.2.1.

8.2.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.8. Additional Safety Explorations

Not applicable.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

According to the Applicant, Estrotep (FES) was granted a marketing authorization in France on July 26, 2016. As of July 20, 2018, a total of 130 vials of Estrotep have been distributed to nuclear medicine pharmacies in France, representing exposure to 130 patients. No AEs have been reported to the Applicant. No regulatory actions have been taken because of safety concerns with Estrotep.

Expectations on Safety in the Postmarket Setting

The clinical review team does not anticipate any significant safety issue after drug approval.

8.2.10. Integrated Assessment of Safety

The review team finds that Cerianna is safe for its intended use. The following description summarizes the adverse reactions under labeling section 6.1 Clinical Trials Experience.

The safety of FES was evaluated from published clinical studies of 1207 patients with breast cancer receiving at least one FES administration. The following adverse reactions occurred at a rate <1%:

- *General disorders:* injection-site pain
- *Neurological and gastrointestinal disorders:* dysgeusia

8.3. Statistical Issues

Statistical issues regarding benefit involve considerations such as whether to draw inference regarding the statistical strength of evidence for characterization of ER status for FES.

Statistical findings are as follows. This application is 505(b)(2) with three relevant papers from the clinical literature. Since Study 1 (Chae et al. 2019) was well-documented at the time of NDA submission, FDA requested this study be submitted at the midcycle communication. Results for patient-level qualitative FES scan data from this published single-center study can be summarized as follows:

Table 19. Patient-Level Qualitative FES PET Data (N=85)

Imaging/Truth Standard	IHC ER-Positive	IHC ER-Negative
FES PET positive	36	0
FES PET negative	11	38

Abbreviations: ER = estrogen receptor; FES = ¹⁸F-fluoroestradiol; IHC = immunohistochemical assay; PET = positron emission tomography

Readers of test imaging were blinded, and results were not reported per reader, but inter-reader kappa was reported to be 0.9 (95% CI 0.78,1.0). The authors claimed that interpretation of qualitative FES scan finding is robust with high inter-reader concordance (measured by kappa).

Results for patient-level quantitative FES PET data from this single-center study extracted from the publication are as follows:

Table 20. Patient-Level Quantitative FES PET Data (N=85)

Imaging/Truth Standard	IHC ER-Positive	IHC ER-Negative
FES PET positive (SUVmax ≥ 1.5)	40	8
FES PET negative (SUVmax < 1.5)	7	30

Abbreviations: ER = estrogen receptor; FES = ¹⁸F-fluoroestradiol; IHC = immunohistochemical assay; PET = positron emission tomography; SUVmax = maximum standardized uptake value

The authors cited a previous report of tumor size affecting SUVmax of FES PET scan and raised concern about limited applicability of quantitative assessment of ER-status due to variations in technical factors affecting SUV.

The authors cited some limitations of this study such as single-center participation and enrollment of the last five patients with primary ER-negative status for target enrollment purposes. More patients had locoregional recurrence than distant metastatic disease (lymph nodes, lung, chest wall, and pleura), and patients with recurrent or a metastatic lesion located in the breast, bone, liver, ovary, or uterus were excluded thereby limiting the generalizability of the results. The absence of fully blinded central review of test imaging is another study limitation.

As stated by the authors, a tissue sample obtained for IHC testing might not be representative of the whole tumor lesion. Discordant results might simply reflect inherent differences between the IHC assay and FES PET scan.

The ER status of one metastatic or recurrent lesion can be positive and ER status of another lesion can be negative in the same patient. Therefore, lesion-level data analyses are needed to adequately and fully characterize the ER status. However, lesion-level data cannot be available and truth standard at the patient-level cannot be complete and depends on tissue sample obtained for IHC testing. Sensitivity and specificity computations require that “independently determined complete (lesion level) truth standard” be available. Therefore, the authors use, fittingly, the terminology of positive and negative percent agreements, which are pre-specified coprimary endpoints of the study.

This study provides the statistical evidence in support of a FES indication for detection of ER positive metastatic/recurrent lesions via high PPrV and high NPA (both 100% with (approx.) 95% CI (90%, 100%)). Study 2 and Study 3 (Peterson et al. 2014; Venema et al. 2017) offer supportive information.

As per the authors, lesion-level data cannot be made available, making truth standard at the patient-level incomplete. High false negative results in this study (23.4%, 95% CI (12.3%, 38%)) raise concerns about the need to not rely on a discordant Cerianna scan.

Comment: *To address these limitations of the data, the review team recommends that the label add “as an adjunct to biopsy” to 1 INDICATIONS AND USAGE and “Risk of Misdiagnosis - Inadequate Tumor Characterization and Other ER-Positive Pathology” and “False Negative CERIANNA scan” under a “Risk of Misdiagnosis” subsection in 5 WARNING AND PRECAUTIONS, as follows in the indented text below:*

1. Cerianna is indicated for use with positron emission tomography (PET) imaging for detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer.

Limitations of Use

Tissue biopsy should be used to confirm recurrence of breast cancer and to verify ER status by pathology. Cerianna is not useful for imaging other receptors, such as human epidermal growth factor receptor 2 (HER2) and the progesterone receptor (PR).

5.1 Risk of Misdiagnosis

Inadequate Tumor Characterization and Other ER-Positive Pathology

Breast cancer may be heterogeneous within patients and across time. Cerianna targets neither human epidermal growth factor receptor 2 (HER2) nor the progesterone receptor (PR). The uptake of Cerianna is not specific for breast cancer and may occur in a variety of ER-positive tumors that arise outside of the breast, including from the uterus, ovaries, prostate, and meninges. Do not use Cerianna in lieu of biopsy when biopsy is indicated in patients with recurrent or metastatic breast cancer.

False Negative Cerianna Scan

A negative Cerianna scan does not rule out ER-positive breast cancer [see Clinical Studies (14)]. Pathology or clinical characteristics that suggest a patient may benefit from systemic hormone therapy should take precedence over a discordant negative Cerianna scan.

8.4. Conclusions and Recommendations

The review team finds that the benefit-risk of Cerianna is favorable for detection of estrogen receptor (ER)-positive lesions as an adjunct to biopsy in patients with recurrent or metastatic breast cancer. Applicant has agreed to major recommended labeling revisions, and the review team therefore recommends approval of this NDA.

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting or other external consultations for this NDA review.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

The Applicant requested a full waiver for pediatric studies for FES on the basis that the incidence of breast cancer in the pediatric population is very rare and further that breast cancer lesions in pediatric patients do not typically present as estrogen receptor bearing tumors. As such, use of FES imaging in this population would not be indicated and if performed, would not provide any clinically relevant information.

The clinical review team agrees that the justification for the PREA waiver request is and acceptable. The Agency has determined that the proposed NDA application would not trigger PREA.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

An important revision is in the indication and usage section, in which the indicated population has been changed to all patients with MBC and with suspicious ER positive lesion(s), no matter the ER status of their primary breast cancer. In addition, based on the performance data the claim of characterization was changed to the one of detection. Importantly, the adjunctive role of Cerianna to biopsy is A limitation-of-use statement underscores the essential role of pathological diagnosis to confirm the identity and ER status of the tumor. Moreover, the warnings and precautions section provides additional information to mitigate the risk of misdiagnosis

Other Prescription Drug Labeling

In the section 14 clinical studies, only Study 1 (Chae et al. 2019) is fully described because it is the only phase 3 prospective trial for the indicated population with sufficient study sample size.

Study 2 is cited. The data from the other studies was relied upon for assessment of safety of the drug.

In the Lactation section, the information was based on the report prepared by the Division's Health Physicist, Dr. Stanley Stern, and appended to this review document as an Appendix 16.3.

12. Risk Evaluation and Mitigation Strategies (REMS)

According to the review of the Division of Risk Management (DRISK), "There is substantial safety information concerning this product. A risk evaluation and mitigation strategy are not needed."

13. Postmarketing Requirements and Commitment

There are no post-marketing requirements or commitments for this application.

14. Division Director (OCP) Comments

None.

15. Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the review team to approve NDA 212155 for the use of Cerianna, F18 Fluoroestradiol (FES), with PET imaging to detect estrogen receptor (ER)-positive lesions in patients with recurrent or metastatic breast cancer as an adjunct to biopsy. This is a 505 (b)(2) application relying on published data alone. The product comparison between the applicant's drug and the drug's versions used in the relevant publications indicated that no further bridging studies were necessary. Multiple review issues surrounding product quality have been adequately addressed resulting in the approval recommendation. Other disciplines contributing to this review document, including clinical pharmacology, statistics and pharmacology-toxicology, recommend approval as well.

Despite some issues with published clinical data verification and generalizability the clinical team is also recommending approval. Determination of efficacy has been based on two main publications. The primary efficacy analyses of positive and negative percent agreement, with lesion biopsy as a reference standard and blinded image interpretation, revealed almost no false positive images in lesion detection. False negatives, although of concern, have been addressed in labeling. Additional analyses were supportive. Clinical review also included

additional smaller studies in the proposed patient population as well as multiple other smaller studies providing supportive efficacy data and a significant safety database. There are no safety signals. Risks related to a wrong diagnosis or radiation exposure are low and mitigated by labeling. Concerns about the drug's clinical utility expressed by the Oncology colleagues have been acknowledged and addressed in the review and to some degree in the prescribing information. Most importantly Cerianna-PET is not to replace tissue biopsy in confirming recurrence of breast cancer and verifying ER status by pathology.

The totality of reviewed information on the use of Cerianna in the indicated population is sufficient for providing substantial evidence of its safety and effectiveness. Clinical benefits of its indicated use outweigh its risks and favor the approval.

16. Appendices

16.1. References

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16.2. Financial Disclosure

Applicant obtained rights to the study findings of a phase 2 clinical study that involved the administration of ¹⁸F-Fluorestradiol Injection to patients with known breast cancer. This study was initially designed and conducted by the investigator and as a result neither the design nor the outcome was influenced or controlled by Applicant.

There were two principal investigators in the study:

Principal investigator: Dr. Khaldoun KERROU
 Scientific supervisor: Prof. Jean-Noël TALBOT
 Service de Médecine Nucléaire
 Hôpital TENON
 4 rue de la Chine, 75020 Paris

Applicant certified that the two listed clinical investigators, who were required to disclose to Applicant whether they had a proprietary interest in this product or a significant equity in Applicant as defined in 21 CFR 54.2(b), did not disclose any such interests. Applicant further certified that no listed investigators were recipients of other significant payments as defined in 21 CFR 54.2(f). An FDA Form 3455 is submitted for the application.

Table 21. Covered Clinical Study

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>2</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>2</u>		
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)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (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 ☒	No ☐ (Request explanation from Applicant)

16.3. Radiation Dosimetry Regarding Prescribing Information on Pregnancy and Lactation

**** This section is available for long term use and can also be accessed in [SharePoint](#) or [ECMS](#) when necessary. ****

Pregnancy

1. During FDA review and discussion, there was a suggestion that as part of the section-8.1 risk summary in the proposed prescribing information, it would be beneficial to specify an estimated value of the radiation absorbed dose to the embryo and fetus. This suggestion included an assertion that during the first trimester of pregnancy, as radiation risk is most significant during organogenesis occurring in the early fetal period and, as risk lessens as pregnancy progresses, the embryo/fetal absorbed-dose value could be approximated by the uterus absorbed-dose value. While this assertion was attributed to recommendations of the International Commission on Radiological Protection (ICRP), there are problematic aspects:

- 1.1 ICRP Publication 88 [1] is nuanced in its delineation of the timeframe in which the embryo/fetus absorbed dose could be reasonably assumed to be approximated by the absorbed dose to the uterus. ICRP characterizes this timeframe as limited from conception to the second month of gestation, not the entire first trimester:

..".Very limited data are available on the accumulation of radionuclides by the developing embryo. It has, therefore, been assumed in this document, in the absence of more specific information, that the dose to all tissues of the embryo, from conception up to the end of the second month of gestation (56 days after conception), can be approximated by the dose to the uterus. All embryonic tissues thus receive the same dose. Up to this age the embryo weighs less than about 10 g and is closely associated with the tissues of the uterus...."

..".The fetal period is taken to last from the beginning of the 9th week after conception (57 days post conception) to birth at 38 weeks (266 days). Sources of radiation exposure of the fetus are radionuclides deposited in fetal tissues, in the placenta and in maternal tissues. For a number of elements considered in this report there are sufficient data to enable the development of specific models. This applies to tritiated water, cesium, iodine, and the alkaline earth elements. The models consider, inter alia, changes in transfer during the fetal period and distribution within the fetus. Where sufficient information for the development of specific

models is not available, a generic modelling approach has been used, based largely on data from studies with experimental animals.”

- 1.2 A recent study [2] concerning particular sources of irradiation external to a pregnant woman raises the possibility of problems with the accuracy of applying uterine absorbed dose to estimate embryonic/fetal absorbed dose: Especially when (as usually done) a uterine absorbed-dose estimate is derived from a *non-pregnant* computational model (mathematical phantom), the uterine absorbed-dose might underestimate the embryonic/fetal absorbed dose. The problems identified in this study [2] emerge from analyses and simulations modeled [2] according to 1945 Japanese morphometry data applied in conjunction with the 2002 update to the dosimetry system “DS02” and associated atomic-bomb radiation fields. DS02 has been previously applied in longitudinal radiation-epidemiology studies of the cohorts of surviving women who were pregnant and their surviving children exposed *in utero* to the radiation fields of the atomic bombs exploded over Hiroshima and Nagasaki. The following excerpt from the abstract summarizes study-[2] methods and findings. Were the results to be applied in an epidemiological analysis of the outcomes of the cohort of children who survived in utero exposure, they hold promise for a refined understanding of absorbed dose throughout fetal development as it might affect potential cancer incidence, adverse bioeffects, genetic heritability of radiation-attributable disease in surviving progeny:

..”.Here we present a new J45 (Japanese 1945) series of high-resolution phantoms of the adult pregnant female at 8-, 15-, 25- and 38-weeks post-conception. These models, which were derived from the University of Florida (UF) series of ICRP Publication 89 compliant reference phantoms, have been rescaled to approximate the pregnant mother using 1945 Japanese morphometry data. Fetal and maternal organ doses were estimated by computationally exposing the pregnant female phantom series to DS02 free-in-air photon and neutron fluences at three distances from the hypocenter at both Hiroshima and Nagasaki under frontal (AP) and isotropic (ISO) particle incidence. As for the fetal organ doses, our results indicate that the uterine wall of the non-pregnant female generally underestimates fetal organ dose within the pregnant female. The magnitude of these differences varies with both radiation type and irradiation geometry, with the smallest differences (5–7%) seen for ISO photon fields and the largest differences (20–30%) seen for AP neutron fields. Significant discrepancies were seen in fetal brain dose and its uterine wall surrogate, particularly for photon AP fields (ratio of uterine wall to brain dose varied from 0.9 to 1.3) and neutron AP fields (dose ratios from 0.75 to 2.0). As for the maternal organ doses, the use of organ doses in a non-pregnant female was shown, in general, to overestimate the corresponding organ doses in the pregnant female, with greater deviations seen at later stages of pregnancy (12–16% for AP photons and 44–53% for AP neutrons). The one exception was the uterine wall dose in pregnancy which was seen to be underestimated by that in the non-pregnant female phantom, particularly for ISO and AP neutron fields. These results demonstrate that the J45 pregnant female phantom series offers the opportunity for

significant improvements in both fetal and maternal organ dose assessment within this unique cohort of the atomic bomb survivors.”

2. During FDA review and discussion, another suggestion put forward was that the section-8.1 risk summary of the proposed prescribing information could include a statement that “Fetal adverse effects have not been reported with cumulative radiation exposures less than 50 mGy.” As follows, this assertion is analyzed with reference to some of the relevant guidelines that were also suggested. The analysis concludes with particular consideration of a hypothetical value estimated for uterine/embryo/fetal dose and associated risk for cancer incidence.

- 2.1 We summarize as follows the ICRP Publication 103 [3] brief review of adverse events associated with fetal absorbed doses below approximately 100 mGy:

- Embryonic susceptibility to lethal effects of irradiation in the pre-implantation period of embryonic development is infrequent for this dose range.
- There are gestational age-dependent patterns of *in-utero* radiosensitivity, where maximum sensitivity is expressed during major organogenesis, and animal data suggest a true threshold of approximately 100 mGy to induce malformations.
- A threshold of at least 300 mGy in the most sensitive pre-natal period (8 – 15 weeks post conception) can induce severe mental retardation, whereas “associated data on IQ losses estimated at around 25 points per Gy are more difficult to interpret and the possibility of a non-threshold dose response cannot be excluded. However, even in the absence of a true dose threshold, any effects on IQ following in-utero doses under 100 mGy would be of no practical significance.”
- Accounting for all of the information discussed in Section 3 (“Biological Aspects of Radiological Protection”) of ICRP Publication 103 [3], for equivalent doses below approximately 100 mSv the ICRP continues to base its system of radiation protection on the assumption that the incremental probability of incurring cancer or heritable effects attributable to radiation is directly proportional to the incremental dose.

- 2.2 ACOG guideline [4] delineation of dose thresholds for adverse bioeffects following in-utero irradiation of an embryo/fetus is generally consistent with that reviewed in ICRP Publication 103 [3]. Based on a tabulation of data in a review by Patel et al. [5], the guideline [4] includes a statement that “Fetal risk of anomalies, growth restriction, or abortion have not been reported with radiation exposure of less than 50 mGy, a level above the range of exposure for diagnostic procedures.” However, the guideline [4] includes scant mention of cancer induction or heritable effects in progeny after birth, and there are not practicable recommendations concerning interruption of breast-feeding following administration of radiopharmaceuticals to lactating women.

- 2.3 With one exception, CDC information [6] for clinicians about radiation and pregnancy is an excellently presented and accurate resource for information, generally consistent with previous guidelines and detailed in its delineation of potential non-cancer health

effects resulting from prenatal radiation exposure. The exception is an outdated reference (absent CDC follow-up) to a 2008 study by Preston et al. [7] that concluded:

“Both the in utero and early childhood groups exhibited statistically significant dose-related increases in incidence rates of solid cancers. The apparent difference in EARs [excess absolute rates] between the two groups suggests that lifetime risks following in utero exposure may be considerably lower than for early childhood exposure, but further follow-up is needed.”

A 2016 follow-up paper [8] clarified:

“Cancer incidence in survivors exposed prenatally is remarkably similar to incidence among those exposed in early childhood, though observed outcomes have been too few to provide conclusive results... On the other hand, no increased risk of cancer incidence or cancer mortality associated with parental radiation dose has been observed in children of atomic bomb survivors, although these subjects were still relatively young when these results were established, and a longer period of follow-up is necessary.”

A 2019 follow-up review [9] elaborated:

“Associations between in utero exposure and excess cancer mortality and incidence were not detected until the 1980s, probably due to the need to accumulate sufficient data among the small cohort [of persons exposed in utero]. The risks of solid cancer mortality and incidence were comparable to those observed in survivors who were exposed at young ages (Yoshimoto et al. 1988; DeLongchamp et al. 1997; Preston et al. 2008). Potential difference in cancer risk by exposure in different gestational periods will be focused from the viewpoint of radiosensitivity based on development of tissue stem cells. Excess occurrences of leukemia have not been observed in this cohort probably because of small number of subjects. Note that collection of cancer incidence data was initiated in 1958 and some subjects were not recruited until 1960 although mortality was followed up from birth for the original group, so outcomes were mostly adulthood malignancies.”

“Significant dose effects were observed for the prevalence of systolic hypertension as well as systolic blood pressure in adolescence among survivors exposed in the second trimester of pregnancy through annual medical examinations (Nakashima et al. 2007). On the other hand, there was no significant dose-response relationship for incidence of adult-onset hypertension, hypercholesterolemia or cardiovascular disease (myocardial infarction and stroke) in utero-exposed survivors (Tatsukawa et al. 2008). No significant dose-response relationships for prevalence of cataracts as well as thyroid diseases such as solid thyroid nodules, cysts and autoimmune thyroid disease were observed in survivors under 60 years of age exposed in utero (Nakashima et al. 2006; Imaizumi et al. 2008).”

- 2.4 Mindful of the preceding comments in this memo, for a *hypothetical* scenario one can calculate an embryonic/fetal absorbed dose of **8.7 mGy**, approximated by the product

of the estimated adult uterine absorbed dose per unit activity (0.039 mGy/MBq) [28] and the recommended amount activity (222 MBq) [28] that could be administered to a pregnant woman. For an embryonic/fetal absorbed dose of 8.7 mGy, the only significant risk is that for prospective incidence of radiation-attributable cancer over the course of the child's lifetime. The epidemiological data [8, 9] suggest that this risk is comparable to that for a child exposed in her or his year of birth. For simple expedience, we assume that this absorbed dose is uniformly distributed through the embryo/fetus, and we estimate cancer risk with the NCI Radiation Risk Assessment Tool (RadRAT) [10].

For females, the mean lifetime risk for cancer incidence attributable to 8.7 mGy radiation absorbed dose in the year of birth is 0.46% with the following 90-percent range of uncertainty: (0.25%, 0.78%). For males, the mean lifetime risk for cancer incidence attributable to 8.7 mGy radiation absorbed dose in the year of birth is 0.28% with the following 90-percent range of uncertainty: (0.14%, 0.49%). The lifetime **baseline** values of mean risk for cancer incidence (including skin cancer) **not** attributable to radiation are much larger than those attributable to radiation: 41% risk and 48% risk, respectively for females and males, where the 90-percent uncertainty range for baseline risk is less than $\pm 1\%$ difference from each mean.

Lactation

3. (b) (4) "ACMUI guidance... [11]...recommends to have 10 physical half-lives of the radiopharmaceutical as the radioactive waiting time" for interrupting breast feeding following administration of a radiopharmaceutical to a lactating woman. This assertion is misleading in several respects:
 - (i) The document [11] cited is a *draft report*. It is not "guidance." The draft report [11] was submitted by a *sub-committee* to an NRC *advisory committee* (ACMUI), and, furthermore, this draft report [11] was superseded by a final report [12] that was endorsed unanimously [20] by ACMUI. A number of values recommended in the final report [12] for interruption of breast feeding were ultimately adopted in the current NRC regulatory guide RG 8.39 [21].
 - (ii) The draft report [11] mentions "ten physical half-lives" in two contexts, neither of which involves a *recommendation* from the ACMUI subcommittee for interruption of breast feeding:
 - The first context ([11], p. 2 of 27) is an elaboration of the nature of radionuclide decay with a simple statement of physical law: "Ten physical half-lives of a radionuclide approximate 0.001 of the original radioactivity or 99.999% of a radioisotope's radioactive decay...."
 - The second context ([11], pp. 2-3 of 27) pertains to *waiting time for storage of expressed breast milk before using it for feeding*:

"Since many radiopharmaceuticals are secreted into her breast milk, during this interruption period, the mother may also express and store her milk to be used after the milk is no longer radioactive.... This radioactive waiting time is usually

10 physical half-lives of the radiopharmaceutical.... Alternatively, the nursing mother may choose to discard expressed milk.”

The interval for storing radio-decaying milk is not necessarily the same as an interval for interrupting breast feeding. In any case, citation no. 11 (see [11], p. 3 of 27) of the ACMUI sub-committee draft report [11] associates ten physical half-lives waiting time for storage of expressed breast milk with a practice recommendation of an ¹³¹I-**therapy** task force of the American Thyroid Association. Milk storage for 10 half-lives might be an appropriately conservative radiation-protection safeguard in the context of ¹³¹I *therapy* – with the relatively large doses of administered activity in the therapeutic context – and for the avid uptake of iodine by thyroid tissue. But such a long storage interval is not necessarily needed for other isotopes administered in the context of diagnostic imaging, where the amounts of activity administered are relatively low compared to those for therapy, and where radioisotope uptake is not dominated by one particular organ.

- (iii) The explicit ACMUI subcommittee recommendation of the draft report [11], and also the final report [12], is that “To the extent that is practical, expressed radioactive milk can be held for decay in storage for the same length of time as the recommended interruption period and then used for feeding the child,” with no mention of 10 physical half-lives.

4. An FDA suggestion [13] to change (b) (4) interrupting breast feeding after Cerianna administration from a duration of (b) (4) hours to 4 hours was based on the ACMUI sub-committee *final report* [12]. A subsequent examination of some of the changes between the final [12] and draft report [11] relevant to ¹⁸F-radiolabeled products indicates that whereas the draft report ([11], pp. 11-12 of 27) had recommended a 12-h cessation for ¹⁸F-fluorodeoxyglucose (FDG) *and for other ¹⁸F-labeled radiopharmaceuticals*, the final report [12] refers explicitly only to “FDG,” dropping its reference altogether to “¹⁸F-labeled” radiopharmaceuticals as a class. In other words, except for FDG, a 4-h interval for interruption of breast feeding is not necessarily appropriate in general for *all* ¹⁸F-labeled radiopharmaceuticals because that interval is based *solely* on findings and analysis for ¹⁸F-FDG. Moreover, when we compared estimates for Cerianna organ-dose per unit administered activity (from Table 1 of the sponsor’s proposed label, Radiation Dosimetry section 2.6) to corresponding estimates [25] for FDG, for many organs we found differences between FES and FDG on the order of a factor of two. In other words, the biodosimetric distributions of FES and FDG can differ considerably from each other. Therefore, more detailed analysis is needed to justify using the FDG recommendation [12] for interruption of breast-feeding following administration of FES.
5. The final report [12] of the ACMUI subcommittee is problematic in a fundamental respect, especially for radiopharmaceuticals as internal sources of radiation, with regard to the meaning and intent of the following assertion [12, p. 11 of 30], which is a primary underpinning of the report:

“Existing recommendations for nursing mothers promulgated by the NRC⁵⁴, the International Commission on Radiological Protection (ICRP)⁵⁵, and others⁵⁶ are based on a maximum dose (i.e., dose equivalent) to the nursing child of 0.1 rad.”

The assertion is ambiguous and unclear. Current national [16] and international [17, 18] recommendations specify circumstances and associated application of dose limits to the **effective dose**,¹³ (formerly designated **effective dose equivalent**^{1,2}) that would be incurred by a person. These national and international recommendations [16 – 18] **do not** pertain to *average whole-body absorbed dose* associated with internal radiation sources. In addition to **effective dose**, recommendations [16, 17] also specify dose limits to **equivalent dose** that would be incurred by particular tissue — e.g., the eye lens or the skin — but **not** the thyroid. There are crucial distinctions between these dosimetric parameters: Only *absorbed dose*¹ represents the fundamental physical aspect of radiant energy absorbed per unit mass of absorbing medium. *Effective dose*, on the other hand, is actually a metric of radiation detriment, i.e., a population-averaged index of prospective cancer incidence, severity, lethality, and prospectively heritable genetic disease.³ *Equivalent dose* is a metric of how various types of radiant energy — e.g., alpha-, beta-particles, x-and gamma-rays, neutrons, protons, atomic ions, etc. — multiply the biological impact of mean absorbed dose in an organ or tissue. For the internal sources of radiation associated with radiopharmaceutical biodistributions, average, whole-body absorbed-dose numerical values would tend to *underestimate* corresponding numerical values of effective dose (or effective dose equivalent) because whole-body averages integrally include energy absorbed within a large mass of tissue not particularly radiosensitive, i.e., tissue not explicitly associated with tissue-weighting factors, factors which are based on radiation detriment within the effective-dose schema. *Such underestimation would bias a value imputed to be “effective dose” (or*

¹ The dosimetric parameter “effective dose” is quantified in units of “millisievert,” abbreviated “mSv;” “equivalent dose” is also quantified in units of “mSv;” and “absorbed dose” is quantified in units of “milligray,” abbreviated “mGy.” The legacy unit quantifying values of “effective dose” (previously designated “effective dose equivalent”²) and values of “equivalent dose” (previously designated “dose equivalent”) is the “rem.” The legacy unit quantifying values of “absorbed dose” is the “rad.”

² “**Effective dose equivalent**” is a former version of the dosimetric quantity “**effective dose**” and is conceptually similar to “effective dose” — albeit with a different set of tissue-weighting factors ([17], section B.2.1) — modeling prospective risk of radiation detriment. Current ICRP recommendations ([17], p. 78, paragraph 168) elaborate that “Despite changes in dosimetric modelling, as well as differences in the computation of effective dose, previous assessments of equivalent dose or effective dose should be considered adequate. In general, the Commission does not recommend re-computation of existing values with the new models and parameters.” In other words, for purposes of radiation protection, values of either effective dose or of effective dose equivalent estimated according to the ICRP paradigm that had been developed and recommended in any previous era should be considered adequate currently.

³ In the calculation of *effective dose*, tissue weighting-factors, which are multipliers of tissue-respective equivalent doses, account for fractional amounts that tissues contribute to “radiation detriment,” the index of stochastic risk of radiation-attributable cancer incidence, severity, lethality, and genetically heritable disease.

“effective dose equivalent”) **erroneously low** compared to the limiting safeguard value of 1 mSv. Hence, for internal sources of radiation, the ACMUI subcommittee adoption [12] of either **whole-body absorbed dose** or **thyroid absorbed dose** as a metric to which a “0.1-rad” (1-mGy) limit would apply is conceptually inconsistent with the conventionally recommended approach adapted in U.S. government guidance supporting its regulations.

6. The current NRC regulatory guide RG 8.39 [21]⁴ provides recommendations for compliance with 10 CFR 35.75 [22], which comprises a radiation-protection safeguard for the public — including nursing infants — required of medical licensees in releasing individuals administered radioactive materials:

“§ 35.75 Release of individuals containing unsealed byproduct material or implants containing byproduct material.

(a) A licensee may authorize the release from its control of any individual who has been administered unsealed byproduct material or implants containing byproduct material if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 mSv (0.5 rem).

(b) A licensee shall provide the released individual, or the individual’s parent or guardian, with instructions, including written instructions, on actions recommended to maintain doses to other individuals as low as is reasonably achievable if the total effective dose equivalent to any other individual is likely to exceed 1 mSv (0.1 rem). If the total effective dose equivalent to a nursing infant or child could exceed 1 mSv (0.1 rem) assuming there were no interruption of breast-feeding, the instructions must also include—

- (1) Guidance on the interruption or discontinuation of breast-feeding; and
- (2) Information on the potential consequences, if any, of failure to follow the guidance.

(c) A licensee shall maintain a record of the basis for authorizing the release of an individual in accordance with § 35.2075(a)....”

7. Based on the criterion that the maximum **effective dose equivalent**² to a breast-feeding newborn infant be less than **1 mSv** (0.1 rem) [21 – 24], Table 3 of RG 8.39 ([21], pp. 11 and 12) delineates activities of radiopharmaceuticals administered to breast-feeding mothers above which medical licensees are required to provide instructions to patients that include information on the interruption or discontinuation of breast-feeding and are required to maintain records of the basis for patient release. Table 3 of RG 8.39 also includes examples of recommended durations of interruption of breast-feeding.

⁴ While the current version of RG 8.39 [21] includes aspects of the ACMUI final report [12], for the most part it is based on the methodology and data of a comprehensive report dating to 1997 [23] and is cited in updated NRC guidance [24] to which medical licensees are referred.

8. However, as no ¹⁸F-labeled radiopharmaceuticals other than FDG are listed in Table 3 of NRC RG 8.39 [21], RG 8.39 cites NUREG-1492 [23] in reference to detailed calculations that could be applied to evaluate requirements. In the following paragraphs we adapt aspects of the NUREG-1492 [23] approach and aspects of the ACMUI subcommittee report [12] approach to the proposed Cerianna label section 8.2 by incorporating several more recent modeling assumptions, data, and new analysis applying scaling factors which can be related to results of measurements [14, 18] of FDG excreted into breast milk:

- 8.1. Our understanding of the ACMUI subcommittee final report [12] recommendation for 4 hours interruption of breast-feeding following administration of FDG is that it was based on the following assumption, among others, regarding FDG biodistribution as an internal source of radiation in lactating women: making reference to a study [14] that had measured the standardized uptake value (SUV) from PET imaging of the breasts of lactating women *one hour post FDG injection*, the final report [12] associated the SUV with a maximum 4% (total) of the injected FDG activity that notionally could be excreted to the breast milk and then cumulatively ingested by a breast-feeding child over the course of multiple feedings [see ref. 12, Table 3, $f_{\text{breast milk}} = 0.04$ for FDG]. From the perspective of developing a radiation safeguard — namely, interruption of breast-feeding — this assumption [12] is conservative in that it would yield a relatively large effective dose requiring a correspondingly long interval of interruption of breast-feeding to reduce it below the 1-mSv ceiling recommended [16 – 18] for safety and associated [21 – 24] with regulatory guidance and requirements. However, according to a comparison [14] of imaging-based breast-to-background ¹⁸F-activity ratios before and after expression of milk from one breast in two patients, the value [12] $f_{\text{breast milk}} = 0.04$ seems to have been a gross overestimate of the cumulative fraction that an infant might ingest of the FDG activity administered to a breast-feeding woman. The particular study [14] (published in 2001) cited in the ACMUI subcommittee final report [12] found that

..”no change in breast activity was demonstrable after expression of breast milk. A 200-mL sample of breast milk placed in the PET field view with the breasts could not be visualized. In 1 case SUV calculations were performed for each breast before and after expression of breast milk. There was no significant change in SUV in either breast on this evaluation (Table 1)...The lack of change in the absolute activity or the distribution of radiotracer after expression of milk would independently suggest low excretion of FDG, which is supported by the low activity measured in expressed milk. This was documented in all 4 cases where the patient was able to express a milk sample. Given the metabolically inert nature of phosphorylated FDG which leads to intracellular trapping of this agent, low excretion into milk is not unexpected....Based on the scan appearances we suspect that the high uptake and retention of FDG in the breast even after expression of breast milk suggests intracellular trapping of the radiotracer in active glandular tissue.”

From measurements [14] of FDG activity concentration in expressed breast milk, the study [14] found that “allowing for decay, the concentration...appeared to peak at 3 h after administration.” Based on the value 5.6 Bq/mL/MBq administered activity measured 3.25 h following administration [14], and applying the breast-feeding model schedule [27] to which the study [14] refers (feeding starting 3 h post-administration and then every 4 h thereafter, 142 mL per feeding, approximately 850 mL per day) we estimate a cumulative effective dose of 0.025 mSv (i.e., to the infant from this internally ingested source of radiation) associated with 106 MBq of administered activity, i.e., approximately $2.4 \times 10^{-4} \text{ mSv}_{\text{infant}}/\text{MBq}_{\text{mother}}$ (see **Note** to [14]). Using the value of breast-milk activity concentration measured at 3.25 h post-administration [14] and the same breast-feeding schedule [14, 27], we calculate that a cumulative fraction $f_{\text{breast milk}} = 0.00102$ (= 0.10%) of the activity administered to the lactating woman could be ingested by a breast-feeding infant, a value much less than the 4% value [12, Table 3] that the subcommittee report [12] based on the SUV data of [14].

The concentration of FDG activity in breast milk measured in the 2001 study [14] is consistent with values measured independently in a 2016 study [18]. The 2016 study [18] measured an effective half-life of 1.7 hours breast-milk excretion in one of two lactating women, and it presumed the ^{18}F physical half-life of 1.83 hours for the second woman. Applying a different model [19] of infant feeding (starting 4 h post-administration and then every 4 h thereafter, 133 mL per feeding, approximately 800 mL per day), the study [18] found a cumulative fraction $f_{\text{breast milk}} = 0.00070$ of administered activity that could be ingested by a breast-feeding newborn; and it estimated an effective dose = $6.7 \times 10^{-4} \text{ mSv}_{\text{newborn}}/\text{MBq}_{\text{mother}}$. However, when we recalculate $f_{\text{breast milk}}$ by (i) retaining the 1.7-h effective half-life but assuming the same feeding schedule as that of study [14], namely, (ii) starting the feeding schedule at 3.25 h rather than 4 h post-administration, and (iii) assuming that 142 mL of breast milk rather than 133 mL are consumed at each feeding, we estimate [15] a value $f_{\text{breast milk}} \approx 0.00098$ close to the value $f_{\text{breast milk}} = 0.00102$ inferred from study [14]. (An expected correlate is that under the study-[14] feeding schedule, the study-[18] value of effective dose would be reduced to $4.8 \times 10^{-4} \text{ mSv}_{\text{newborn}}/\text{MBq}_{\text{mother}}$, i.e., in inverse proportion to the ratio 0.000981/0.00070.) Hence, while the measured [14, 18] concentrations of FDG activity in breast milk are consistent with each other, one infers that various estimates of the amount of activity actually ingested by a nursing infant are highly dependent on respectively associated models of breast-feeding schedule: in the case of FDG, two studies [14, 18] applying somewhat different models yield a factor of at least 0.00102/0.00070 ≈ 1.5 in the spread of values associated with differing models of breast-feeding schedules.

- 8.2 To address radioisotope-activity excretions in breast milk for ^{18}F -radiolabeled pharmaceuticals *other* than FDG, i.e., *where there are no measured milk-activity data*, we approximate the maximum **fraction** of administered radiopharmaceutical activity that could be cumulatively ingested from breast milk as the **ratio** of the *energy absorbed in the breasts* of an adult (mathematical phantom) to the *total energy absorbed* in all of the organs/tissue of the adult (phantom). Albeit an overestimation,

this approximation is expedient. Organ absorbed-energy is the product of organ mass [25, 26] and organ absorbed-dose [25]. Starting with the following values for FDG parameters as “controls” to bridge to corresponding parameters for other ¹⁸F-radiolabeled pharmaceuticals, we approximate [15] $f_{\text{breast milk (FDG)}}|_{\text{max}} \approx \text{absorbed-energy ratio (FDG)} = \mathbf{0.0028}$. The effective dose per unit activity ingested by a newborn can be extrapolated [15] from the FDG dosimetry tabulation [25] for one-year-olds: $E \text{ (FDG) per unit newborn-ingested activity} = \mathbf{0.21 \text{ mSv/MBq}_{\text{newborn}}}$. Hence $E|_{\text{max}} \text{ (FDG, newborn) per unit activity administered to the breast-feeding mother} = 0.21 \text{ mSv}_{\text{newborn}}/\text{MBq}_{\text{newborn}} \times 0.0028 [\text{MBq}_{\text{newborn}}/\text{MBq}_{\text{mother}}] = \mathbf{5.8 \times 10^{-4} \text{ mSv}_{\text{newborn}}/\text{MBq}_{\text{mother}}}$.

In sum, the values derived via this absorbed-energy approximation for FDG are nearly consistent as upper bounds to respective estimates (calculated in [15]) of the cumulatively-ingested fraction of administered FDG activity and effective dose (per maternal-administered activity) to a breast-feeding infant. These estimates are based on independent measurements of activity in expressed breast milk and differing models of breast-feeding schedules, namely, $\{f_{\text{breast milk}} \approx \mathbf{0.0010}; E \approx \mathbf{2.4 \times 10^{-4} \text{ mSv}_{\text{infant}}/\text{MBq}_{\text{mother}}}\}$ [14], and $\{f_{\text{breast milk}} \approx \mathbf{0.00070}; E \approx \mathbf{6.7 \times 10^{-4} \text{ mSv}_{\text{infant}}/\text{MBq}_{\text{mother}}}\}$ [18]. Moreover, when the breast-feeding schedule applied in study [18] is normalized to that of study [14], study-[18] values are calculated [15] as $\{f_{\text{breast milk}} \approx \mathbf{0.00098}; E \approx \mathbf{4.8 \times 10^{-4} \text{ mSv}_{\text{infant}}/\text{MBq}_{\text{mother}}}\}$, each value less than the respective upper bound estimated according to the absorbed-energy approximation: $\{f_{\text{breast milk (FDG)}}|_{\text{max}} = \mathbf{0.0028}, E|_{\text{max}} \text{ (FDG)} = \mathbf{5.8 \times 10^{-4} \text{ mSv}_{\text{newborn}}/\text{MBq}_{\text{mother}}}\}$.

- 8.3 Applying the absorbed-energy approximation (described in the preceding paragraph) for newborn ingestion of breast milk following administration of Cerianna (Fluoroestradiol ¹⁸F, FES) to a breast-feeding woman, we calculate [15, 28] $f_{\text{breast milk (FES)}}|_{\text{max}} = \mathbf{0.0015}$ and $E|_{\text{max}} \text{ (FES)} = \mathbf{0.25 \text{ mSv}_{\text{newborn}}/\text{MBq}_{\text{newborn}}}$, which imply that $E|_{\text{max}} \text{ (FES)} = \mathbf{3.8 \times 10^{-4} \text{ mSv}_{\text{newborn}}/\text{MBq}_{\text{mother}}}$.

Hence, for the recommended amount of FES activity (222 MBq [28]) that could be administered via injection into a breast-feeding woman, through multiple subsequent feedings a newborn could cumulatively incur an effective dose of $E|_{\text{max}} \text{ (FES)} = \mathbf{0.085 \text{ mSv}_{\text{newborn}}}$ from the internal biodosimetric distribution of FES.

- 8.4 To estimate the contributions to the newborn’s effective dose from external sources of irradiation (namely, from the breast and the rest of the body of the breast-feeding woman), we apply [15] the external-radiation modeling developed in the ACMUI subcommittee report [12].⁵ Since the radiant energy is primarily that of the 511-keV gamma rays arising from positron-electron annihilation, it is reasonable to approximate that energy as homogeneously penetrant throughout the habitus of a

⁵ In our calculations [15] to evaluate absorbed dose (mGy) from estimated exposure (in roentgens, R), we multiply the radionuclide specific gamma ray constant Γ by a factor 8.76 mGy/R, a factor that was not included in the external-irradiation modeling [12].

newborn and therefore contributing uniformly to absorbed dose. In this circumstance, the numerical value of the newborn whole-body absorbed dose per unit administered activity estimated with the external irradiation model [12]⁴ would numerically equal that of the newborn effective dose (or effective dose equivalent) per unit administered activity. Furthermore, the presumed uniformity of the absorbed dose (per unit administered activity) throughout the newborn means that the effective dose (per unit administered activity) depends only on the external source of radiant gamma-ray energy arising from the radioisotope (¹⁸F) distribution **within the woman, not** on a biodosimetric distribution of the pharmacophore within the newborn. In other words, this external-irradiation modeling [12]⁴ would hold for any ¹⁸F-radiolabeled pharmaceutical.

We calculate [15] that for the recommended amount of FES activity (222 MBq [28]) that could be administered via injection into a breast-feeding woman, through multiple subsequent feedings a newborn could cumulatively incur an effective dose of $E_{\text{ext}}(\text{FES}) = 0.275 \text{ mSv}_{\text{newborn}}$ from the external radiant energy emitted by the breast-feeding woman.

- 8.5 We calculate [15] that for the recommended amount of FES activity (222 MBq [28]) that could be administered via injection into a breast-feeding woman, through multiple subsequent feedings a newborn could cumulatively incur a **total effective dose** of $E_{\text{tot}}(\text{FES}) = 0.360 \text{ mSv}_{\text{newborn}}$ from the internal biodosimetric distribution of FES ingested plus from the external radiant energy emitted by the breast-feeding woman. Although this estimated value is less than the 1-mSv threshold [21 – 24] that would necessitate instructions for interruption of the infant's breast-feeding schedule, there is significantly large modeling uncertainty. As a conservative safety precaution, we therefore suggest that following radiopharmaceutical administration, breast feeding be interrupted for an interval of four hours, which in models of breast-feeding schedules is the upper range characterizing the interval between feeding sessions for newborn infants.

References and Notes

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- [3] ICRP Publication 103, *The 2007 Recommendations of the International Commission on Radiological Protection*, approved by the Commission in March 2007, *Annals of the ICRP*,

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- [12] Vasken Dilsizian et al., *Advisory Committee on Medical Uses of Isotopes (ACMUI) Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials*, Report dated February 1, 2018; revised June 19, 2018; submitted June 26, 2018; re-revised September 20, 2018; endorsed [20] in a unanimous vote by ACMUI September 20, 2018; final report submitted January 31, 2019; <https://www.nrc.gov/docs/ML1903/ML19038A498.pdf>; accessed May 11, 2020.
- [13] FDA email (with labeling suggestions attached) to Zionexa US Corporation, DARRTS reference i.d. 4572669, March 9, 2020.

- [14] Rodney J. Hicks, David Binns, and Michael G. Stabin, "Pattern of Uptake and Excretion of FDG in the Lactating Breast," *The Journal of Nuclear Medicine*, Vol. 42, No. 8, pp. 1238-1242, Aug 2001.

Note:

The feeding schedule in ref. [14] is based on that of ref. [27]: this model assumes a first feeding 3 h post-administration, then every 4 h thereafter, 142 mL of breast milk per feeding. At the nominal "3 h" (actually reported [14] as 195 min = 3.25 h) after FDG administration (at $t = 0$), the authors measured an activity concentration in milk of 5.6 Bq/mL per MBq administered activity [14]. When one accounts for radioisotope physical decay from $t = 0$, the value measured at 3.25 h post-administration represents the peak concentration of breast-milk activity, 19 Bq/mL per MBq administered activity. Starting at $t = 3.25$ h after administration and for successive 4-hour intervals, we summed [15] the contributions of multiple feedings and obtained a total fraction $f_{\text{breast milk}} = 0.00102$ of administered activity that would be cumulatively ingested by the breast-feeding infant.

Using a "dose factor" of "0.23 mGy/MBq" activity ingested, which we construe as implicitly assuming uniform internal irradiation throughout the infant corresponding to an effective dose of 0.23 mSv/MBq activity ingested, the paper [14] estimates a cumulative effective dose to the infant of approximately "0.085 mSv" from ingested activity. We checked the consistency of this reported value (0.085 mSv) as follows: $0.085 \text{ mSv} / (0.23 \text{ mSv per MBq infant-ingested}) = 0.37 \text{ MBq infant-ingested activity}$. The value we estimated, $f_{\text{breast milk}} = 0.00102$, implies that $0.37 \text{ MBq} / 0.00102 = 363 \text{ MBq}$ of FDG activity was administered to the woman. However, 363 MBq is discrepant from the range of administered FDG activity, 50 – 160 MBq reported for the sodium-iodide-detector PET scanner actually used in the study [14] rather than the more conventional bismuth-germanate-detector PET scanners requiring administered doses in the range 300 – 500 MBq [14]. One can resolve the discrepancy with an assumption that the authors [14] erroneously applied the $t = 0$ milk-activity concentration (19 Bq/mL per MBq administered activity) instead of the value (5.6 Bq/mL per MBq administered activity) actually measured at 3.25 h after administration. Applying (erroneously) the value 19 Bq/mL per MBq administered activity at 3.25 h, one would obtain [15] a fraction 0.0035 of administered activity that could be cumulatively ingested and implying that $0.37 \text{ MBq} / 0.0035 = 106 \text{ MBq}$ of FDG activity would have been administered to the woman, a value within the reported range of activity actually administered. In other words, identifying this presumed error yields an expected amount of administered activity actually administered in study [14]. The upshot of this analysis is that the estimated value 0.085 mSv [14] is erroneously too high. If we apply the fraction $f_{\text{breast milk}} = 0.00102$, appropriately calculated from the reported milk-activity concentration, to the estimated 106 MBq of administered activity, we estimate that 0.108 MBq would be ingested by an infant and, with the study's assumption of an effective dose of 0.23 mSv/MBq infant-ingested, we estimate that the effective dose to the infant would be approximately **0.025 mSv**, and the infant effective dose per

administered activity to the breast-feeding woman would be 0.025 mSv/106 MBq = **2.4×10^{-4} mSv/MBq_{administered}**.

- [15] Calculations for these *Comments on Radiation Dosimetry Regarding Prescribing Information on Pregnancy and Lactation for Women Administered Cerianna (Fluoroestradiol ¹⁸F, FES)* are done via the Excel workbook file *FDG-FES-FTP-Dosimetry.xlsx*.
- [16] NCRP Report No. 180, *Management of Exposure to Ionizing Radiation: Radiation Protection Guidance for the United States (2018). Recommendations of the National Council on Radiation Protection and Measurements*, Dec 31, 2018.
- Note 1** [bolded italics added]: Section 5.3 (“Public Exposure”), sub-section 5.3.1 (“Protection Against Stochastic Effects”), p. 57 of this NCRP report states “NCRP recommends that the **annual effective dose** to a member of the public from the continuous or reasonably anticipated presence of a source should not exceed **1 mSv**. This recommendation is suitable for use as a regulatory dose limit when the source is stable, characterized, and subject to an advance control program.”
- Note 2:** The National Council on Radiation Protection and Measurements (NCRP) is a non-profit corporation chartered by Congress in 1964.
- [17] ICRP Publication 103, *The 2007 Recommendations of the International Commission on Radiological Protection*, approved by the Commission in March 2007, *Annals of the ICRP*, Vol. 37, Nos. 2 – 4, Apr – Jun 2007.
- Note** [bolded italics added]: Section 6.5 (“Comparison of radiological protection criteria”), p. 116, Table 8 of this publication presents the following individual dose limits applicable for planned public exposure: an **effective dose of 1 mSv in a year**; an **equivalent dose of 15 mSv/year** to the lens of the eye; and an **equivalent dose of 50 mSv/year** to the skin. There is no equivalent-dose limit for any other organ or tissue.
- [18] Sigrid Leide-Svegborn et al., “Excretion of radionuclides in human breast milk after nuclear medicine examinations. Biokinetics and dosimetric data and recommendations on breastfeeding interruption,” *European Journal of Nuclear Medicine and Molecular Imaging*, Vol. 43, No. 5, pp. 808-821, May 2016.
- Note** [bolded italics added]: Page 810 of this paper includes the following statement: “The proposed recommendations on breastfeeding interruption were based on an **effective dose limit of 1 mSv** to the infant, which is the general limit recommended by the ICRP for protection of members of the general public” (where the statement cites the preceding ref. [17]).
- [19] ICRP Publication 95, *Doses to infants from radionuclides ingested in mothers’ milk*, approved by the International Commission on Radiological Protection in November 2004, *Annals of the ICRP*, Vol. 34, Nos. 3 – 4, paragraphs (30) – (33), (B4), 2004; ICRP Publication 95 errata are published in ICRP Publication 100, *Annals of the ICRP*, Vol. 36, Nos. 1 – 2, pp. 329-336, 2006.

- [20] *Meeting Summary* (<https://www.nrc.gov/docs/ML1828/ML18288A691.pdf>), Meeting of the NRC Advisory Committee on the Medical Uses of Isotopes (ACMUI), September 20 – 21, 2018.

Note 1: “The Committee endorsed the report” [12] “of the Subcommittee on the Nursing Mother Guidelines for the Medical Administration of Radioactive Materials with added language that this document reflects the FDA approved radiopharmaceuticals on the market at this time and that licensees are obligated to carefully evaluate radiopharmaceuticals that are not encompassed in this report to keep exposures ALARA to patients, staff, and members of the public. The recommendation passed unanimously with thirteen votes.”

Note 2: A number of values recommended in the final report [12] for interruption of breast feeding were ultimately adopted in the current NRC regulatory guide RG 8.39 [21].

- [21] U.S. Nuclear Regulatory Commission, Regulatory Guide 8.39 Revision 1, *Release of Patients Administered Radioactive Materials*, April 2020, accessed May 11, 2020 via <https://www.nrc.gov/docs/ML1923/ML19232A081.pdf>.
- [22] Code of Federal Regulations, Title 10, Part 35, Section 75, *Release of individuals containing unsealed byproduct material implants containing byproduct material* (10 CFR 35.75). Also see 10 CFR 20.1301, *Dose limits for individual members of the public*.
- [23] S. Schneider and S.A. McGuire, *Regulatory Analysis on Criteria for the Release of Patients Administered Radioactive Material*, NUREG-1492, U.S. Nuclear Regulatory Commission, Feb 1997.
- [24] U.S. Nuclear Regulatory Commission, *Consolidated Guidance About Materials Licenses. Program-Specific Guidance About Medical Use Licenses*, Final Report, NUREG-1556, Vol. 9, Rev. 3, Appendix U: “Release of Patients or Human Research Subjects Administered Radioactive Materials,” p. U-1, Sep 2019, accessed via <https://www.nrc.gov/docs/ML1925/ML19256C219.pdf>, May 12, 2020.
- Note:** While the current NUREG-1556 Revision 3 Appendix U [24] advises that “Licensees should use the most current version of RG 8.39 when developing procedures for the release of patients who are administered radioactive materials,” the hyperlink to RG 8.39 in the ML19256C219 pdf accessed May 12, 2020, retrieves the original 1997 version of RG 8.39, not the most recent version (<https://www.nrc.gov/docs/ML1923/ML19232A081.pdf>) per ref. [21].
- [25] ICRP Publication 128, *Radiation Dose from Radiopharmaceuticals: A Compendium of Current Information Related to Frequently Used Substances*, approved by the International Commission on Radiological Protection in July 2014, *Annals of the ICRP*, Vol. 44, No. 2S, Sage Journals, 2015.

Note: See section C.15. (FDG), pp. 107-109 of ICRP Publication 128, for FDG radiation dosimetry biokinetic modeling, references, and organ absorbed-dose and effective-dose estimates. See Annex section A.1 (Organ and tissue masses for different ages)

p. 39, and Table A.1 (Masses of models of selected organs and tissues at different ages) pp. 40-41: The masses of the phantom used for calculation of S values are those presented by M.G. Stabin and J.A. Siegel, “Physical Models and Dose Factors for Use in Internal Dose Assessment,” *Health Physics*, Vol. 85, No. 3, pp. 294-310, Sep 2003. For our calculations, age-dependent organ masses were adopted mostly from ICRP Publication 128 [25] and some from ICRP Publication 110 [26].

- [26] ICRP Publication 110, *Adult Reference Computational Phantoms*, *Annals of the ICRP*, Vol. 39, No. 2, pp. 48-51, April 2009.

Note: Male and female body masses for the computational phantoms are listed in Table 5.1 (Main characteristics of the adult male and female reference computational phantoms), p. 39; adult endosteal masses: Table 4.2, p. 36. For our calculations, age-dependent organ masses were adopted mostly from ICRP Publication 128 [25] and some from ICRP Publication 110 [26].

- [27] Michael G. Stabin and Hazel B. Breitz, “Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings, and Radiation Dosimetry,” *The Journal of Nuclear Medicine*, Vol. 41, No. 5, pp. 863-873, May 2000.

- [28] Cerianna (Fluoroestradiol ¹⁸F, FES) draft label, March 9, 2020.

Note: The basis of our calculations [15] was the radiation dosimetry table of the Cerianna draft label. The values of that table are the same as those in a preceding publication by David A. Mankoff et al., “[¹⁸F]Fluoroestradiol Radiation Dosimetry in Human PET Studies,” *The Journal of Nuclear Medicine*, Vol. 42, No. 4, pp. 679-684, April 1, 2001. The abstract of the paper by Mankoff et al. includes the following **misattribution** of *effective dose equivalent*, a former version of a metric of radiation detriment: “**Effective dose equivalent was calculated using International Commission on Radiological Protection Publication 60 weights for the standard woman. Results: The effective dose equivalent was 0.022 mSv/MBq (80 mrem/mCi).**” In fact, ICRP Publication 60 introduced a new metric, **effective dose** (updating its preceding version, *effective dose equivalent*). *Effective dose* is calculated with tissue-weighting factors provided in Publication 60 that are different than those for *effective dose equivalent* (which had been previously defined in ICRP Publication 26, issued in 1977). Hence, what the paper by Mankoff et al. mischaracterizes as “effective dose equivalent” is actually *effective dose*. This mischaracterization was included in the Cerianna draft label of March 9, 2020.

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