CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217639Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multi-Disciplinary Review and Evaluation

In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	217639
Priority or Standard	Priority
Submit Date(s)	June 17, 2022
Received Date(s)	June 17, 2022
PDUFA Goal Date	February 17, 2023
Division/Office	DO1/OOD/OND/CDER
Review Completion Date	*Electronic Stamp Date*
Established Name	Elacestrant
(Proposed) Trade Name	Orserdu
Pharmacologic Class	Estrogen receptor antagonist
Code Name	RAD1901
Applicant	Stemline Therapeutics, Inc.
Formulation(s)	345 mg and 86 mg tablets
Dosing Regimen	345 mg orally once daily, with food
Applicant Proposed Indication(s)/Population(s)	Elacestrant (ORSERDU) is indicated for the treatment of postmenopausal women and men with (b) (4) positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Elacestrant (ORSERDU) is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

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- Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Amy Tilley
Pharmacology/Toxicology Reviewer(s)	Nikolett Biel, PhD
Pharmacology/Toxicology Team Leader(s)	Tiffany Ricks, PhD
Office of Clinical Pharmacology Reviewer(s)	Wentao Fu, PhD (OCP/DCP I), Fang Li, PhD (OCP/DPM), Jillian (Jielin) Sun, PhD (OCP/DTPM), Jianghong Fan, PhD (OCP/DPM)
Office of Clinical Pharmacology Team Leader(s)	Salaheldin Hamed, PhD (OCP/DCP II), Jerry (Jingyu) Yu, PhD (OCP/DPM), Robert Schuck, PharmD, PhD (OCP/DTPM), Manuela Grimstein, PhD (OCP/DPM)
Clinical Reviewer	Danielle Krol, MD, Hima (Bindu) Lingam, MD
Clinical Team Leader	Mirat Shah, MD
Safety Analyst (if applicable)	Ilynn Bulatao, MD
Safety AD	Abhilasha Nair, MD
Safety RPM	Stacie Woods
PROs	Vishal Bhatnagar, MD
Statistical Reviewer	Haley Gittleman, PhD, Xin (Cindy) Gao, PhD
Statistical Team Leader	Mallorie Fiero, PhD
Associate Director for Labeling (ADL)	William Pierce, PharmD, MPH
Cross-Disciplinary Team Leader	Mirat Shah, MD
Division Director (DHOT)	John Leighton, PhD
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Shenghui Tang, PhD
Division Director (OOD)	Laleh Amiri-Kordestani, MD
Office Director (or designated signatory authority)	Paul Kluetz, MD

- Additional Reviewers of Application

OPQ	RPM: Kristine Leahy DP/DS: Rajiv Agarwal, Sivakoteswara (Siva) Rao Mandadapu, Paresma (Pinky) Patel Facilities: Zhaoyang Meng, Huiquan Wu Biopharmaceutics: Anitha Govada, Qi Zhang Senior Quality Assessor: Xing Wang
OPDP	Koung Lee, Brantley Dorch
OSI	Yang-Min (Max) Ning, Min Lu, and Jenn Seller
DPV	Afrouz Nayernama, Kathleen Sullivan Graça Dores
OSE/DEPI	Fang Tian, Aida Kuzucan
OSE/DMEPA	Ashleigh Lowery, Janine Stewart
OSE/DRISK	Naomi Boston, Brad Moriyama
CDRH	Liuya Tang, Shyam Kalavar, Abdelrahmman Abukhdeir, Anand Pathak, Shyam Kalavar, Soma Ghosh
DMPP	Susan Redwood, Barbara Fuller

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

- Glossary

ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AI	aromatase inhibitor
AUC	area under the plasma concentration-time curve
BBB	blood brain barrier
BCRP	breast cancer resistance protein
BLA	biologics license application
CB	clinical benefit
CBR	clinical benefit rate
CDK4/6	cyclin-dependent kinase 4/6
CL/F	central apparent clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
CYP3A4	cytochrome P450 3A4
DDI	drug-drug interaction
DoR	duration of response
E2	17β-estradiol
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EPAR	European Public Assessment Report
E-R	Exposure response
ER+	estrogen receptor positive
ERα	estrogen receptor-alpha
ESR1	estrogen receptor 1 gene
ESR1-mut	*ESR1* mutation
ESR1-mut-nd	*ESR1* mutation not detected
FDA	Food and Drug Administration
FES	18F-fluoro-17β-estradiol
FES-PET/CT	16α-18F-fluoro-17β-estradiol positron emission tomography with low-dose computed tomography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HER2-	human epidermal growth factor receptor 2 negative
HR	hormone receptor
HRQOL	health-related quality of life
ICH	International Council for Harmonisation
IM	intramuscular

IND	Investigational New Drug
IQR	interquartile range
IRC	Imaging Review Committee
ISE	integrated summary of efficacy
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
LH	luteinizing hormone
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NDA	new drug application
NOAEL	no observed adverse effect level
OR	objective response
ORR	objective response rate
OS	overall survival
OVX	ovariectomized
PBPK	physiologically-based PK
PD	pharmacodynamics
PFS	progression-free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PopPK	population PK
PP	per protocol
PRO	patient reported outcome
PS	performance status
PT	preferred term
QD	once daily
Q/F	apparent intercompartmental clearance
QTc	heart rate-corrected QT interval
QTcF	QT interval corrected with Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SCS	Summary of Clinical Safety
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SOC	standard of care
$t_{1/2}$	elimination half-life
TK	toxokinetics
TEAE	treatment-emergent adverse event

USPI	United States Prescribing Information
Vc/F	apparent volume of distribution of the central compartment
Vp/F	apparent volume of distribution of the peripheral compartment

1 Executive Summary

1.1. Product Introduction

Elacestrant is an oral estrogen receptor antagonist. It does not have approval for any indication worldwide.

The Applicant proposed the following indication for NDA 217639:

Elacestrant (ORSERDU) is indicated for the treatment of postmenopausal women and men with (b) (4) *-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer who have progressed following at least one line of endocrine therapy.*

The recommended indication for regular approval is:

Elacestrant (ORSERDU) is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

The recommended dosage for elacestrant is 345 mg taken orally, once daily, with food.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends granting regular approval for elacestrant for the treatment of postmenopausal women or adult men with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer in accordance with 21 Code of Federal Regulations (CFR) 314.126(a)(b).

Substantial evidence of effectiveness for this application is based on efficacy and safety results from Study RAD1901-308 (EMERALD), a randomized, active-controlled, open-label, multicenter trial in 478 patients with ER-positive, HER2-negative advanced or metastatic breast cancer with disease progression following 1-2 prior lines of endocrine therapy, including 1 line containing a CDK4/6 inhibitor. Patients were randomized to receive elacestrant or standard-of-care (SOC) endocrine therapy with either fulvestrant or an aromatase inhibitor (AI). The family of primary endpoints included progression-free survival (PFS) assessed by independent review committee (IRC) according to RECIST v1.1 in the *ESR1*-mut subpopulation and ITT population. Overall survival (OS) in the *ESR1*-mut subpopulation and ITT population was a key secondary endpoint. The Applicant used the Guardant360 CDx assay to evaluate for *ESR1* mutations in patients enrolled to Study RAD1901-308.

Study RAD1901-308 demonstrated a statistically significant improvement in PFS based on IRC in the *ESR1*-mut subpopulation. Median PFS was 3.8 months (95% confidence interval (CI): 2.2,

7.3) in the elacestrant arm compared to 1.9 months (95% CI: 1.9, 2.1) in the SOC arm (HR 0.55, 95% CI: 0.39-0.77, p=0.0005). This PFS improvement was robust to multiple sensitivity analyses. The OS endpoint was not met in the *ESR1*-mut subpopulation, but there was no trend towards OS detriment with a HR of 0.90 (95% CI: 0.63, 1.30).

Study RAD1901-308 also statistically met its PFS endpoint in the ITT population with a median PFS of 2.8 months (95% CI: 1.9, 3.8) in the elacestrant arm compared to 1.9 months (95% CI: 1.9, 2.1) in the SOC arm (HR 0.70, 95% CI: 0.55-0.88; p= 0.0018), however the FDA considered these results to be primarily driven by the 48% of patients in the *ESR1*-mut subpopulation. The FDA concluded that a clinically meaningful improvement in PFS had not been demonstrated for patients in the *ESR1*-mut-not detected (nd) subpopulation (52% of ITT). A variety of PFS sensitivity analyses to evaluate issues such as early censoring in the *ESR1*-mut-nd subpopulation consistently indicated no clear benefit for the elacestrant arm. Across Study RAD1901-308, the performance of the control arm was poor with respect to PFS. In the setting of a poorly-performing control arm, the marginally favorable PFS HR trend in the *ESR1*-mut-nd subpopulation was not considered clinically meaningful, particularly in the context of additional symptomatic gastrointestinal (GI) toxicities noted in the safety evaluation.

Results from secondary endpoints also did not show evidence of clinical benefit with elacestrant in the *ESR1*-mut-nd subpopulation. In an exploratory OS analysis in the *ESR1*-mut-nd subpopulation, the OS HR was 0.92 (95% CI: 0.65, 1.31). Although this HR point estimate seemed to indicate no trend towards OS detriment, there was uncertainty in this OS estimate due to asymmetric withdrawal of consent between the elacestrant and SOC arms in the *ESR1*-mut-nd subpopulation. In addition, although ORR was low overall in this trial (as would be expected for endocrine therapies), the ORR estimate was numerically lower on the elacestrant arm compared to SOC arm in the *ESR1*-mut-nd subpopulation: 2.1% (95% CI: 0.3%-7.5%) vs. 4.2% (95% CI: 1.1%-10.3%).

Additionally, publicly available data external to Study RAD1901-308 for other oral selective estrogen receptor degraders (SERDs) suggest that these products may have greater activity in patients with *ESR1* mutation(s). Therefore, the apparent lack of benefit in the *ESR1*-mut-nd subpopulation repeatedly observed in multiple trials is unlikely due to chance.

Finally, as would be expected for an endocrine therapy, most adverse reactions (ARs) associated with elacestrant were Grade 1-2 in severity. However, there was increased GI toxicity in patients receiving elacestrant, which is orally administered, compared to SOC, including nausea: 35% vs. 19%, vomiting: 19% vs. 9%, decreased appetite: 15% vs. 10%, and dyspepsia: 10% vs. 2.6%. The FDA review team notes that even Grade 1-2 GI toxicity may have a negative impact on a patient's quality of life and potentially affect patient adherence. Elacestrant was also associated with increased cholesterol and increased triglycerides compared to SOC: 30% vs. 17% and 27% vs. 15%, respectively. The FDA labeled dyslipidemia under Warnings and Precautions.

While Study RAD1901-308 met its PFS endpoint in the ITT population and in the subgroup of

patients with *ESR1* mutations, efficacy was uncertain in patients without *ESR1* mutations (*ESR1*-mut-nd subpopulation). The review team concluded that elacestrant did not demonstrate a favorable benefit-risk profile for patients in the *ESR1*-mut-nd subpopulation. The GI toxicity and dyslipidemia associated with elacestrant were not justified because based on assessment of PFS, OS, and ORR, these patients did not appear to derive clinical benefit from elacestrant and the results in ITT was mainly driven by the subgroup of patients with *ESR1* mutations.

In contrast, the review team concluded that elacestrant demonstrated a favorable benefit-risk profile for patients in the *ESR1*-mut subpopulation. Although the PFS improvement was modest, the result demonstrated superiority in a replacement design with elacestrant directly compared to SOC. Furthermore, efficacy results were robust to multiple sensitivity analyses and supported by OS results having no trend towards detriment. Overall, the safety profile was acceptable for a patient population with a serious and life-threatening condition. The GI toxicity and risk of dyslipidemia were acceptable, as clinical benefit was demonstrated. Finally, the oral route of delivery offers another SERD alternative to those not wishing to receive IM administration.

Therefore, the review team recommends granting regular approval to elacestrant in the *ESR1*-mut subpopulation. This represents a new oral endocrine treatment option for patients who experience disease progression following treatment with a CDK4/6 inhibitor and will be the first FDA-approved therapy specifically for patients with *ESR1* mutation(s). The indication for approval is:

Elacestrant (ORSERDU) is an estrogen receptor antagonist indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

A supplemental Pre-Market Approval (PMA) Application (sPMA P200010/S010) was submitted to CDRH for the Guardant360 CDx assay. The sPMA will receive contemporaneous approval with this NDA as a companion diagnostic device for elacestrant.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Breast cancer is the most common cancer in women worldwide. In the U.S., there are 297,790 new cases of breast cancer and 43,170 deaths from breast cancer estimated for 2023. Although rare, male patients can also develop breast cancer and may present at a higher stage than female patients. Histopathological subtypes of breast cancer are defined by expression of the estrogen receptor (ER), progesterone receptor (PR), and/or human epidermal growth factor receptor 2 (HER2). Approximately 70% of patients with breast cancer will have ER-positive, HER2-negative disease. Although associated with a better prognosis than the other breast cancer subtypes, if ER-positive, HER2- breast cancer is advanced (and surgically unresectable) or metastatic, it is incurable and associated with a limited life expectancy.

The preferred first-line treatment for patients with ER-positive, HER2-negative advanced or metastatic breast cancer in the U.S. is a CDK4/6 inhibitor in combination with endocrine therapy (an AI or fulvestrant). At disease progression, FDA-approved options for second and later-line treatment include endocrine monotherapy with fulvestrant, an AI, or tamoxifen (if not received as first-line treatment); everolimus in combination with endocrine therapy; alpelisib in combination with fulvestrant in patients with a *PIK3CA*-mutated tumor; and chemotherapy such as capecitabine. Sequential endocrine therapy is preferred because it is typically associated with less toxicity than chemotherapy. Endocrine monotherapy is associated with less toxicity than combinations with targeted agents. It is unknown which treatment(s) offer patients the most clinical benefit following treatment with a CDK4/6 inhibitor.

Acquired resistance to endocrine therapy, particularly AIs, can occur due to activating missense mutations in the ligand-binding domain (LBD) of *ESR1*. It is estimated that approximately 20-40% of patients exposed to an AI for treatment of metastatic breast cancer will acquire tumor *ESR1* mutation(s), and there are no FDA-approved treatments specifically for patients with ER-positive, HER2-negative, *ESR1*-mutated breast cancer. There is unmet medical need for therapies to improve clinical outcomes in all patients with ER-positive, HER2-negative advanced or metastatic breast cancer, including patients with *ESR1* mutations.

The efficacy and safety assessment for elacestrant is primarily based on data from Study RAD1901-308 (EMERALD), a randomized, active-controlled, open-label, multicenter clinical trial in 478 patients with ER-positive, HER2-negative advanced or metastatic breast cancer who experienced disease progression following 1-2 prior lines of endocrine treatment, including 1 line containing a

CDK4/6 inhibitor. Patients received either elacestrant 345 mg orally daily or investigator's choice SOC endocrine treatment with fulvestrant or an AI. Patients continued treatment until disease progression or unacceptable toxicity. Tumor assessments occurred every 8 weeks. The family of primary endpoints included PFS assessed by IRC according to RECIST v.1.1 in the *ESR1*-mut subpopulation and ITT population. OS in the ESR1-mut subpopulation and ITT population was a key secondary endpoint.

Regarding baseline characteristics, in the ITT population, 1.5% of patients were male. There were 71% of patients who were White, 7% of patients who were Asian, and 2.7% of patients who were Black; race was unknown or not reported for 19 % of patients. Due to the large amount of missing race data, it was not clear if the patient population enrolled to RAD1901-308 was representative of a US-based population with ER-positive, HER2-negative advanced or metastatic breast cancer with respect to race. Due to this uncertainty, the FDA issued a PMC for the Applicant to characterize the safety and efficacy of elacestrant in patients from racial and ethnic minority groups. There were 67% of patients with visceral metastases. Fifty-seven percent of patients had received 1 prior line of endocrine treatment and 43% of patients had received 2 prior lines of endocrine treatment in the metastatic setting. All patients had received a CDK4/6 inhibitor, 30% of patients had received prior fulvestrant, 22% of patients had received prior chemotherapy in the advanced or metastatic setting, and 4% of patients had received a prior targeted therapy in the metastatic setting.

Study RAD1901-308 demonstrated a statistically significant improvement in PFS in the *ESR1*-mut subpopulation. Median PFS was 3.8 months in the elacestrant arm compared to 1.9 months in the SOC arm (HR 0.55, 95% CI: 0.39-0.77, p=0.0005). This PFS improvement was robust to multiple sensitivity analyses. The OS endpoint was not met in the *ESR1*-mut subpopulation, but there was no l trend towards OS detriment with a HR of 0.90 (95% CI: 0.63, 1.30).

The PFS endpoint was also met in the ITT population, however the FDA considered these results to be driven by the 48% of patients in the *ESR1*-mut subpopulation. In exploratory PFS analysis in the *ESR1*-mut-not detected (nd) subpopulation, median PFS was 1.9 months on the elacestrant arm compared to 2.0 months on the SOC arm (HR 0.86, 95% CI: 0.63-1.19). In the setting of a poorly- performing control arm across Study RAD1901-308, there was uncertainty related to efficacy in this subgroup, and the marginally favorable PFS HR trend in the *ESR1*-mut-nd subpopulation was not considered clinically meaningful. Furthermore, multiple sensitivity analyses in the *ESR1*-mut-nd subpopulation cast further doubt regarding PFS improvement as the KM curves for the elacestrant arm and SOC arm were overlapping. Results from the secondary endpoints OS and ORR also pointed to a lack of clinical benefit in the ESR1-mut-nd subpopulation. The OS HR was 0.92 (95% CI: 0.65, 1.31) which seemed to indicate no trend towards potential OS detriment. However, there was uncertainty in this estimate due to asymmetric withdrawal of consent between the elacestrant and SOC arms in the *ESR1*-mut-nd subpopulation. In addition, the ORR estimate was numerically lower

on the elacestrant arm compared to SOC arm in the *ESR1*-mut-nd subpopulation: 2.1% (95% CI: 0.3%-7.5%) vs. 4.2% (95% CI: 1.1%-10.3%).

There are also publicly available external data which suggest that patients with *ESR1* mutations may derive greater benefit from oral SERDs compared to patients without ESR1 mutations. Emerging clinical data from three other oral SERDs, summarized in Section 2.2 showed these products may have better activity in patients with tumors with *ESR1* mutations.

The safety profile of elacestrant was generally reflective of an endocrine therapy with mostly Grade 1-2 ARs. Fatal ARs were low and balanced between the two groups, occurring in 1.7% of patients who received elacestrant and 2.6% of patients who received SOC. Fatal ARs in patients who received elacestrant were due to cardiac arrest, septic shock, diverticulitis, and an unknown cause. Serious adverse reactions (SARs) were balanced between the two groups, occurring in 12% of patients who received elacestrant and 11% of patients who received SOC. SARs occurring in more than 1% of patients who received elacestrant were musculoskeletal pain (1.7%) and nausea (1.3%). Grade 3 ARs and all grade ARs were slightly higher in patients receiving elacestrant compared to SOC: 27% vs. 21% and 93% vs. 85%, respectively. The most common (>10%) adverse reactions, including laboratory abnormalities, were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.

Dosage interruptions were more common in patients who received elacestrant compared to SOC: 15% vs. 5%. The most common (>1%) reason for dosage interruptions in patients who received elacestrant were nauseas (3.4%), musculoskeletal pain (1.7%) and increased ALT (1.3%). Dose reductions were low in patients who received elacestrant (3%) and not permitted in patients who received SOC. Drug discontinuations were low in patients who received elacestrant compared to SOC: 6% vs. 4.3%.

An important safety signal for elacestrant was GI toxicity. The following ARs occurred more commonly in patients receiving elacestrant compared to SOC: nausea: 35% vs. 19%, vomiting: 19% vs. 9%, decreased appetite: 15% vs. 10%, and dyspepsia: 10% vs. 2.6%. Although most of these GI toxicities were Grade 1-2 in severity, the FDA notes that even lower grade GI toxicities can require use of concomitant medications and negatively impact quality of life for patients.

Another important safety signal for elacestrant was dyslipidemia. Elevated cholesterol and elevated triglycerides were more common in patients who received elacestrant: 30% vs. 17% and 27% vs. 15%, respectively. The FDA included dyslipidemia under Warnings and Precautions in labeling and recommended monitoring at baseline and periodically thereafter for patients receiving

elacestrant.

The FDA review team concluded that for patients in the *ESR1*-mut subpopulation, the benefit-risk assessment for elacestrant was favorable given the statistically significant improvement in PFS which was robust to multiple sensitivity analyses and supported by a positive OS HR trend. The GI toxicity and risk of dyslipidemia were acceptable given that clinical benefit was demonstrated.

The FDA review team concluded that for patients in the *ESR1*-mut-nd subpopulation, the benefit-risk assessment for elacestrant was not favorable. There was uncertainty regarding clinically meaningful improvement in PFS, OS assessment added further uncertainty, and ORR was numerically lower in the elacestrant arm compared to the SOC arm. External data also suggest that patients with *ESR1* mutations may receive greater benefit from oral SERDs.

Based on the overall benefit-risk assessment, the review team recommends regular approval for the following indication:

Elacestrant (ORSERDU) is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

Eligibility criteria for Study RAD1901-308 allowed for inclusion of both males and females. In the ITT population, 1.5% of patients were male. The safety of elacestrant appeared to be similar in females and males. Although there were no male patients in the *ESR1*-mut subpopulation in Study RAD1901-308, the FDA included male patients in the indication based on extrapolation of data from female patients and biologic rationale that there are no expected safety or efficacy differences in male and female patients with *ESR1* mutations. This is aligned with FDA guidance for industry entitled: “Male Breast Cancer: Developing Drugs for Treatment.”

Elacestrant will be the first FDA-approved treatment specifically for patients with *ESR1* mutations. Patients should be selected for treatment using the Guardant360 CDx assay. The Guardant360 CDx assay is a qualitative next generation sequencing (NGS)-based *in vitro* diagnostic device which uses targeted high throughput hybridization-based capture technology for detection of molecular alterations in circulating cell-free DNA. The sPMA P200010/S010 for the Guardant360 CDx will be approved by CDRH contemporaneously with this NDA for elacestrant.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	● Breast cancer is the most common cancer in women, with 297,790 new cases estimated and 43, 170 deaths estimated from breast cancer in the U.S. in 2023. ● Although rare, breast cancer can also occur in male patients. ● Approximately 70% of patients with breast cancer will have ER+HER2- disease. ● Advanced or metastatic breast cancer is incurable.	**ER-positive, HER2-negative advanced or metastatic breast cancer is a serious and life-threatening condition.**
Current Treatment Options	● ER-positive, HER2-negative advanced or metastatic breast cancer is not curable. Treatment is palliative with the aims of reducing cancer-related symptoms, delaying disease progression, and prolonging survival. ● Following treatment with a CDK4/6 inhibitor in combination with endocrine therapy, treatment options may include endocrine monotherapy with fulvestrant, an AI, or tamoxifen; everolimus in combination with endocrine therapy; alpelisib in combination with fulvestrant in patients with a *PIK3CA*-mutated tumor; and chemotherapy such as capecitabine. ● Activating missense mutations in tumor *ESR1* are a common cause of acquired tumor resistance to endocrine therapies, particularly AIs. Tumor *ESR1* mutations occur in 20-40% of patients following exposure to an AI.	**All treatment options are palliative. There is an unmet medical need to improve outcomes in patients with ER-positive, HER2-negative advanced or metastatic breast cancer.** **There are no FDA-approved therapies specifically for patients with ER-positive, HER2-negative, *ESR1*-mutated breast cancer.**
Benefit	● Study RAD1901-308 enrolled 478 patients with ER-positive, HER2-negative advanced or metastatic breast cancer who had disease progression following 1-2 lines of endocrine therapy, including a CDK4/6 inhibitor. ● There were 228 patients (48%) in the *ESR1*-mut subpopulation. ● In the *ESR1*-mut subpopulation, median PFS was 3.8 months in the elacestrant arm compared to 1.9 months in the SOC arm	**For patients in the *ESR1*-mut subpopulation, elacestrant demonstrated a statistically significant improvement in PFS, which was supported by a favorable trend in OS.** **For patients in the *ESR1*-mut-nd subpopulation, there was uncertainty**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(HR 0.55, 95% CI: 0.39-0.77, p=0.0005). In the ITT population, median PFS was 2.8 months in the elacestrant arm compared to 1.9 months in the SOC arm (HR 0.70, 95% CI: 0.55-0.88; p= 0.0018) ● The OS endpoint was not met but demonstrated a trend favoring the elacestrant arm in both the *ESR1*-mut subpopulation and ITT population, HR 0.90 (95% CI: 0.63, 1.30) and HR 0.91 (95% CI: 0.71, 1.18), respectively. ● In the *ESR1*-mut-nd subpopulation, exploratory analysis demonstrated a median PFS of 1.9 months on the elacestrant arm compared to 2.0 months on the SOC arm (HR 0.86, 95% CI: 0.63-1.19). This marginally favorable HR trend was not robust to multiple sensitivity analyses. ● Exploratory OS analysis in the *ESR1*-mut-nd subpopulation demonstrated a HR of 0.92 (95% CI: 0.65, 1.31). However, there was uncertainty in this estimate due to asymmetric withdrawal of consent specifically in this subpopulation. ● The ORR estimate was numerically lower on the elacestrant arm compared to SOC arm in the *ESR1*-mut-nd subpopulation: 2.1% (95% CI: 0.3%-7.5%) vs. 4.2% (95% CI: 1.1%-10.3%). ● Emerging publicly available clinical data from other oral SERDs show that these products may have better activity in patients with tumors with *ESR1* mutations.	**regarding efficacy with elacestrant. There was no clinically meaningful improvement in PFS; and OS and ORR results added further uncertainty regarding clinical benefit in this subpopulation. Additionally, there are external data to suggest that oral SERDs may have better activity in the presence of tumor *ESR1* mutation(s).**
Risk and Risk Management	● The safety profile for elacestrant was similar in the ITT population and *ESR1*-mut subpopulation. Results are presented for the ITT population. ● All-grade ARs and Grade 3 ARs were slightly increased in patients who received elacestrant compared to SOC: 93% vs. 85% and 27% vs. 21%, respectively. There were no Grade 4 ARs on Study RAD1901-308.	**For patients with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer, elacestrant had an acceptable safety profile. Overall, the benefit-risk assessment is favorable. Safe use of elacestrant can be managed with labeling.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	● SARs were balanced between the two arms: 12% vs. 11%, and fatal ARs were low and balanced between the two arms: 1.7% vs. 2.6%. ● Elacestrant was associated with increased GI toxicity compared to SOC, including nausea: 35% vs. 19%, vomiting: 19% vs. 9%, decreased appetite: 15% vs. 10%, and dyspepsia: 10% vs. 2.6%. ● Elacestrant was also associated with elevated cholesterol and elevated triglycerides compared to SOC: 30% vs. 17% and 27% vs. 15%, respectively. ● The most common (≥ 10%) TEAEs, including laboratory abnormalities, in patients who received elacestrant were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.	**Dyslipidemia and Embryo-Fetal Toxicity are included under Warnings and Precautions. There is no indication for REMs.** **For patients with ER-positive, HER2-negative, *ESR1*-mut-nd advanced or metastatic breast cancer, the increased GI toxicity and risk of dyslipidemia are not justified as clinical benefit was uncertain for this group. Overall, the benefit-risk assessment is not favorable for patients in the ER-positive, HER2-negative, *ESR1*-mut-nd population.**

1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			Section 8.1.1, Section 8.2
			X	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 was not submitted in the application but was considered in this review.		

X

Mirat Shah
Cross-Disciplinary Team Lead

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Disease Background

Breast cancer is the leading cause of cancer in women and the leading cause of cancer deaths in women (Bray et al, 2018). The incidence and prevalence of patients with invasive breast cancer as well as estimates for the prevalence of subjects with estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2-) breast cancer, are presented in Table 1.

Table 1: Epidemiology of ER+/HER2- Breast Cancer (× 1,000)

	US	EU[a]	Japan[a]	Global[a]
Incidence: New yearly cases of invasive breast cancer	253[a], 282[b]	531	92	2,261
Prevalence of invasive breast cancer	1,071[a]	2,138	328	7,791
Prevalence of ER+/HER2- breast cancer (approximately 70% of invasive breast cancer)	750	1,497	230	5,454

Abbreviations: ER+=estrogen receptor positive; EU=European Union; HER2-=human epidermal growth factor receptor 2 negative; SEER=Surveillance, Epidemiology, and End Results; US=United States.

[a] International Agency for Research on Cancer and World Health Organization, 2021

[b] National Cancer Institute and Surveillance, Epidemiology, and End Results (SEER) Program, 2021

In the United States (US), 43,600 women were estimated to have died from breast cancer in 2021 (Surveillance, Epidemiology, and End Results [SEER] Program 2021). Mariotto and colleagues estimated that by January 2017, there were 154,794 women living with metastatic breast cancer (mBC) in the US, with 3 in 4 initially diagnosed with stage I-III breast cancer who later progressed to mBC (Mariotto et al, 2017). In Europe, Ferlay and colleagues estimated that 157,100 women died from breast cancer in 2020 (Ferlay et al, 2021).

In comparison, breast cancer in men is very rare: less than 1% of the total number of cancer cases. Nevertheless, the American Cancer Society estimates that there will be 2,620 new cases of invasive breast cancer in men and nearly 520 men will die from breast cancer in 2020 (Breastcancer.org, 2020).

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of breast cancer with several clarifications. FDA notes that advanced or metastatic ER-positive, HER2-negative breast cancer is incurable, and the goal of therapy is palliative.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Currently, recommended first-line standard of care (SOC) for locally advanced or metastatic ER+/HER2- breast cancer is endocrine therapy, with either aromatase inhibitors (AIs) or fulvestrant, plus a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (NCCN, 2021; Bentzon et al, 2008; Burstein et al, 2021; Gennari et al, 2021). Once the disease progresses, there are limited therapeutics options. Treatment guidelines, when the pivotal trial (Study RAD1901-308) was initiated in 2018 and still currently, recommend the use of sequential endocrine therapy in the absence of visceral crisis until all endocrine therapy options have been exhausted (NCCN, 2018; NCCN, 2022; Gennari et al, 2021). Endocrine therapy includes endocrine monotherapy, such as fulvestrant, if the first-line therapy contained an AI-based therapy, or AIs if the first-line therapy applied a fulvestrant-based therapy (NCCN, 2021; Burstein et al, 2021; Gennari et al, 2021).

(b) (4)

Fulvestrant is currently the only approved selective estrogen receptor degrader (SERD) for the treatment of subjects with ER+/HER2- mBC (Niikura et al, 2014). Fulvestrant effectively degrades ER and has demonstrated clinical benefit in ER+/HER2- mBC. A 500 mg monthly dose of fulvestrant, after a biweekly dose during the first month, in subjects with ER+/HER2- mBC who failed previous endocrine therapy was associated with a median progression-free survival (PFS) of 6.5 months (Di Leo et al, 2010). However, these data were generated prior to the approval of CDK4/6 inhibitors. Recently, data on fulvestrant monotherapy post-CDK4/6 inhibitor treatment are starting to emerge.

- In a recent Phase 2 trial of second-/third-line venetoclax + fulvestrant versus fulvestrant alone in ER+/HER2- mBC who experienced disease recurrence/progression during/after CDK4/6 inhibitor therapy (VERONICA study), treatment with fulvestrant as a single agent was associated with a median PFS of 1.94 months with a clinical benefit rate (CBR) of 13.7% (Lindeman et al, 2021).
- In the MATCH Phase 2 clinical trial, high-dose fulvestrant was associated with a median PFS of 2.2 months and a CBR of 16% among subjects with a detectable estrogen receptor 1 gene (*ESR1*) mutation (*ESR1*-mut), where few subjects received prior CDK4/6 inhibitors (Turner et al, 2020).

In addition to the need for effective treatment options for patients with ER+/HER2- mBC after progression on CDK4/6 inhibitors, the intramuscular (IM) route of administration of fulvestrant underscores the need for novel oral ER antagonists in this setting. Although a long-acting IM formulation of fulvestrant was approved that can be administered monthly after 3 biweekly doses, the total volume of the injections per dose is 10 mL, a volume that is difficult to tolerate by some patients (Wardell et al, 2015; Bihani et al, 2017).

Available second-line combination therapy options are everolimus + exemestane and everolimus + fulvestrant. For subjects with *PIK3CA*-mutant breast cancer, the combination of

fulvestrant and alpelisib is another option. These combinations are associated with approximately 25% treatment discontinuation rate because of adverse events (AEs) in clinical trials (everolimus US Prescribing Information [USPI]; alpelisib USPI).

(b) (4) Use of these combinations among patients with prior exposure to CDK4/6i is estimated to be approximately (b) (4)% patient share, based on claims reviewed through (b) (4) (internal analysis for Menarini Stemline, by (b) (4), 2022)

In this context, next-generation, orally bioavailable SERDs with improved pharmacokinetic (PK) properties have garnered significant interest as novel therapies for ER+/HER2-mBC (Bentzon et al, 2008; Glück, 2014; McDonnell and Wardell, 2010; Osborne and Schiff, 2011). SERDs include a class of endocrine agents that induce the degradation of the ER, in addition to their antagonistic activities of the ER, and have demonstrated antitumor activity against ER+ breast cancers that are both endocrine sensitive and resistant (Gombos, 2019). Although several molecules are under development, IM fulvestrant is the only one currently approved. The low-level enteral bioavailability in part due to presystemic metabolism makes oral administration an inappropriate route for fulvestrant. Therefore, a long-acting IM formulation was developed that can be administered monthly after 3 biweekly doses. The total volume of the injections per dose is 10 mL, a volume that is difficult to tolerate for some patients. The PK properties of fulvestrant and IM route of administration underscore the need for novel ER antagonists (Wardell et al, 2015; Bihani et al, 2017).

Recent data suggest that mutations in the *ESR1* encoding estrogen receptor-alpha (ERα) play a significant role in resistance to endocrine therapy (Chandarlapaty et al, 2016; Nardone et al, 2015; O'Leary e al, 2018). Two commonly described mutations are Y537S and D538G. Y537S-specific *ESR1* mutations are reported as drivers of resistance to fulvestrant plus palbociclib combination therapy (O'Leary et al, 2018; Dustin et al, 2019).

The FDA's Assessment:

Current Treatment Landscape

The FDA generally agrees with the Applicant's description of the current treatment landscape. Endocrine therapy (AI or fulvestrant) in combination with a CDK4/6 inhibitor is the preferred first-line treatment. Second and later line treatment options include endocrine monotherapy with fulvestrant, an AI, or tamoxifen; everolimus in combination with endocrine therapy; alpelisib in combination with fulvestrant in patients with a *PIK3CA*-mutated tumor; and chemotherapy such as capecitabine. Sequential endocrine therapy (including in combination with targeted agents) may be preferred because it may cause less toxicity than chemotherapy. It is unknown which treatment option(s) offer the most clinical benefit following a CDK4/6 inhibitor.

The FDA also generally agrees that some emerging data suggest that fulvestrant may be associated with a shortened PFS when used following treatment with a CDK4/6 inhibitor.

However, FDA notes that one paper referenced by the Applicant cannot support this conclusion as only 10% of patients received a prior CDK4/6 inhibitor (Turner, 2020). [In addition, the reference listed by the Applicant is incorrect, and FDA has listed the corrected reference for (Turner 2020) in FDA References in Section 19.1.]

The FDA disagrees with the Applicant's assessment that the volume for a dose of fulvestrant is difficult to tolerate as neither reference provided by the Applicant support this conclusion. In addition, although it may be beneficial for patients to have an oral therapeutic option, oral therapies are not inherently superior to IM/IV therapies as they may come with their own set of challenges such as GI toxicity and issues with adherence.

The FDA also disagrees with the Applicant's use of marketing data to determine current treatment options. The FDA does not rely on marketing databases because patient characteristics are unknown, and it is unclear for which therapies the patients may be eligible. In addition, depending on when the data were collected, the database may not reflect current therapeutic options.

***ESR1*-mutated ER+HER2- Breast Cancer**

The FDA notes that the Applicant provided limited information on *ESR1*-mutated ER+HER2- breast cancer and adds the following information.

Activating mutations in the *ESR1* gene are a common cause of acquired tumor resistance to endocrine therapies, particularly AIs, in patients with ER+HER2- metastatic breast cancer. It is estimated that approximately 20-40% of patients who have received an AI for treatment of metastatic breast cancer will develop an *ESR1* mutation (Brett et al, 2021). The prevalence of *ESR1* mutations may depend on prior duration of endocrine therapy and treatment setting (adjuvant or metastatic). Most *ESR1* resistance mutations are in the ligand-binding domain of the ER receptor. The most common missense mutations are D538G and Y537S; other missense mutations include Y537N, Y537C, L536H, L536P, L536R, S463P, and E380Q. **Currently, there are no approved drugs to specifically treat ER+ HER2- *ESR1*-mutated metastatic breast cancer.**

Testing for *ESR1* mutation(s) is not standard-of-care for patients planning to receive subsequent endocrine therapy following first-line endocrine treatment for metastatic disease. However, certain guidelines recommend obtaining this information for patients being considered for an AI as an AI is considered an inferior treatment option in presence of an *ESR1* mutation (Gennari, 2021).

Oral SERDs

Although the FDA agrees that fulvestrant is the only approved SERD, several oral SERDs are in clinical development for second and later line treatment of locally advanced or metastatic ER+HER2- breast cancer. Emerging clinical data show that oral SERDS may have better activity in

patients with tumors with *ESR1* mutations. Publicly available data from the oral SERDs in development are summarized below:

- Amcenestrant (SAR439859): The AMEERA-3 trial [NCT04059484] compared amcenestrant to physician's choice of endocrine therapy (fulvestrant, AI or tamoxifen) in 290 patients with ER+HER2- metastatic breast cancer with disease progression following endocrine therapy. There were 79% of patients who received prior treatment with a CDK4/6i. The primary endpoint was PFS per independent central review (ICR) in the ITT population which was not met (median PFS 3.6 months v 3.7 months; HR 1.05). Approximately 40% of patients had an *ESR1* mutation, and there was a trend towards improvement of PFS with amcenestrant in patients with tumors with an *ESR1* mutation (median PFS 3.7 months v 2.0 months) (Tolaney, 2022).

- Giredestrant (GDC-9545): The acelERA trial [NCT04576455] compared giredestrant to physician's choice of endocrine therapy (fulvestrant or AI) in 303 patients with ER+HER2- locally advanced or metastatic breast cancer who had received 1-2 prior lines of systemic therapy in the locally advanced or metastatic setting. The primary endpoint was PFS per investigator in the ITT population which was not met (median PFS 5.6 months v 5.4 months; HR 0.81). Among patients who had an *ESR1* mutation, there was a trend towards improvement of PFS with giredestrant (5.3 months v 3.5 months; HR 0.60) (Jimenez, 2022).

- Camizestrant (AZD9833): The SERENA-2 trial [NCT04214288] compared one of three doses of camizestrant: 75 mg, 150 mg, or 300 mg (300 mg was later discontinued) to fulvestrant in patients with advanced ER+HER2- breast cancer with disease recurrence or progression on at least one line of endocrine therapy. There were ~50% of patients who received a prior CDK4/6i. The primary endpoint was PFS per investigator in the ITT population, and the trial was designed to be exploratory with an alpha of 0.10 and no multiplicity adjustments for multiple comparisons. In the ITT population, median PFS was 7.2 months on the 75 mg arm and 7.7 months on the 150 mg arm vs. 3.7 months on the fulvestrant arm (HR 0.58 in 75 mg vs. fulvestrant, HR 0.67 in 150 mg vs. fulvestrant). In the 37% of patients with tumors with an *ESR1* mutation, median PFS was 6.3 months on the 75 mg arm and 9.2 months on the 150 mg arm vs. 2.2 months on the fulvestrant arm (HR 0.33 in 75 mg vs. fulvestrant, HR 0.55 in 150 mg vs. fulvestrant) (Oliveira, 2022).

3 Regulatory Background

3.1. US Regulatory Actions and Marketing History

The Applicant's Position:

Elacestrant is not currently registered (or approved) in the US or in any other part of the world.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Radius Health (Radius) developed elacestrant and was the sponsor of the clinical trials, conducted under IND 124748. In July 2020, global development and commercialization rights were licensed to the Menarini Group (Menarini), however, Radius remained the owner of IND 124748. Radius completed the development of elacestrant and prepared the NDA application which was submitted by Stemline Therapeutics Inc (Stemline), a wholly owned subsidiary of Menarini.

Elacestrant was developed under IND 124748 for the treatment of (b) (4) and human epidermal factor 2 negative (HER2-) metastatic breast cancer since 2014. Key US pre-submission regulatory activities are outlined in Table 2.

Table 2: Summary of Pre-Submission Regulatory Activities

Regulatory Activity	Date	Summary
Type B (EOP1) Meeting	26Jun2017	The Agency provided feedback on the design and statistical analysis plan for a proposed Phase 2 single arm trial for registration.
Fast Track Designation	17Oct2017	Fast track designation was granted for (b) (4) men and postmenopausal women with (b) (4) estrogen receptor positive/human epidermal growth factor receptor 2 negative (ER+/HER2-) breast cancer who have received at least 1 prior line of endocrine therapy, (b) (4)
Type B (EOP1) CMC Meeting	29Nov2017	The Agency provided feedback on starting materials, API and drug product specifications, stability program and batch sizes for registration and validation.

Regulatory Activity	Date	Summary
Type B Meeting Phase 2 Guidance	15Feb2018	The Agency provided feedback on the proposed pivotal study protocol, statistical analysis plan, reproductive and developmental toxicology studies needed to support registration, proposed size of the safety database for registration, and proposal to request a waiver of pediatric studies in support of potential registration.
Type B (EOP2) Meeting	15Jun2018	The Agency provided feedback on a proposed pivotal trial design including the target patient population, comparators, primary endpoint, secondary endpoints, and planned statistical analyses to determine if this trial may support registration and approval in the proposed target population.
Type C Clinical Pharmacology and CMC Meeting	19Jun2018	The Agency provided feedback on a new tablet formulation and BE study design to show equivalence along with obtaining concurrence on ECG monitoring plan and proposed clinical pharmacology study program.
Initial Pediatric Study Plan (iPSP) Agreement	18Dec2018	FDA agreed with the iPSP and granted a full waiver of pediatric studies due to criteria meeting FDA requirements for automatic full waivers based on metastatic breast cancer and *ESR1* mutation.
Written Response: Type C Clinical Pharmacology and CMC Meeting	17Jun2019	The Agency provided feedback on study in hepatically impaired patients and not needing to conduct a study in renally impaired patients. Feedback was also provided on demonstration of bioequivalence in vitro and in vivo studies.
Written Response: Type C CMC Meeting	12Aug2020	The Agency provided feedback on API registration starting materials and specifications, drug product formulation change, and dissolution specifications.
Email Communication	20Apr2021	The provided feedback on the proposed statistical analysis plan study RAD1901-308.
Written Response: Type C Content & Format Meeting	20Jul2021	The Agency provided feedback on the proposed content and format of datasets for an NDA for elacestrant based on data from the RAD1901-308 study as well as supportive studies RAD1901-005 and RAD1901-106.
Type B Pre-NDA CMC Meeting	12Aug2021	The Agency provided feedback on starting materials, specifications of drug product and API, impact of salt policy, environmental assessment, dissolution specifications and shelf-life of intended commercial drug product.

Regulatory Activity	Date	Summary
Written Responses: Type C Toxicology	13Aug2021	The Agency provided feedback on the toxicology program to support submission of a marketing application for elacestrant.
Type B Pre-NDA Clinical and Regulatory Meeting	02Feb2022	The Agency provided feedback on the planned NDA submission for elacestrant, including the indication, safety update, device application, PREA requirements, assessment aid, and other submission elements of the NDA.
NDA Submission	17Jun2022	NDA 217639 was submitted.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of pre-submission of regulatory milestones with the following comments and clarifications.

On June 15, 2018, at the Type B (EOP) meeting, the FDA recommended that the Applicant enroll male patients to RAD1901-308 and the Applicant agreed to do so. The Applicant stated that they would test PFS in patients with tumors with *ESR1* mutations and in all patients. FDA found this proposal acceptable and recommended requesting a meeting with CDRH regarding a potential complementary or companion diagnostic. FDA also cautioned that to support an approval, elacestrant would have to demonstrate a PFS improvement which was statistically significant and clinically meaningful and that the PFS improvement should be supported by no trend towards detriment in OS.

On February 2, 2022, at the Type B (pre-NDA) meeting to review topline results from RAD1901-308, the FDA cautioned the Applicant that the PFS improvement was modest in the ITT population and that the benefit-risk assessment for elacestrant in the *ESR1*-mut and *ESR1*-mut-nd subpopulations would be a review issue. The Applicant stated that if the final event-driven OS analysis took place during the review cycle, the results would be provided to the FDA.

On June 21, 2022, the device Sponsor, Guardant Health, submitted a PMA supplement for a complementary or companion diagnostic device for elacestrant to CDRH.

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

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 1 consulted OSI to perform an audit of the Applicant as well as of the overall trial conduct. FDA selected three sites (Site 116: Dr. Patrick Dillon, Site 108: Dr. Alberto Montero, and Site 175: Dr. Hung Khong) for clinical inspection based on enrolling a larger number of patients and having longer PFS favoring the elacestrant arm relative to other sites. The key contract research organization (CRO – Parexel International Corporation) associated with the trial was also selected for clinical inspection as elacestrant is an NME and the Sponsor changed from Radius Health to Stemline Therapeutics shortly prior to NDA submission. Based on these inspections, FDA found no significant regulatory violations, the trial conduct for RAD1901-308 appears acceptable, and the submitted data from the three sites appear reliable.

Clinical inspection summaries are included here. For full details, please refer to the OSI consult note.

Site 116: Dr. Patrick Dillon

Dr. Dillon was inspected on October 11-14, 2022, as a surveillance and data audit for Study RAD1901-308. This was the first FDA inspection of the investigator.

The site enrolled 6 subjects into the study, with 5 subjects randomized to the elacestrant arm and 1 to the SOC arm. All the subjects received study treatment following randomization. As of the data cutoff date, one subject [# (b) (6) in the elacestrant arm who started treatment on (b) (6) was transferred to another study site [Site 175] on (b) (6) secondary to relocation and the rest of subjects were discontinued from study treatment due to disease progression. No subjects were found to have been discontinued from study treatment due to adverse event(s) or withdrawal.

Source records for all the 6 subjects were reviewed during the inspection and source data were compared with the Applicant's submitted data for the site. The reviewed subject records included but were not limited to the informed consents, eligibility checklists, screening-enrollment log, randomization allocation, study treatment administered, tumor assessments, adverse events (AE)/serious adverse events (SAE), laboratory results, and protocol deviations. Regulatory documentation and oversight of the study at the site were also examined, including the institutional review board (IRB) approvals of the study protocol/amendments and informed consent forms and related correspondences, delegation of authority log, site's training records (i.e., Good Clinical Practice (GCP) training and study specific training provided by the CRO Parexel), signed Form FDA 1572s, financial disclosures, study monitoring, study drug

accountability records, and access to and data entry into the electronic case report form (eCRF) system [i.e., Medidata Rave] used for this study.

The inspection found no significant regulatory deficiencies at the site. All the subjects met the eligibility criteria and the submitted clinical data were verifiable with source records reviewed. All the AEs, SAEs and protocol deviations were reported to the Sponsor.

At the conclusion of this inspection, no Form FDA 483, Inspectional Observations, was issued to Dr. Dillon.

Site 108: Dr. Alberto Montero

Dr. Montero was inspected from 09/26/2022 through 10/03/2022 as a data audit for Study RAD1901-308. For the investigator, this was the first FDA inspection. Note that the inspection was initially issued for Dr. Paula Silverman based on the Applicant's submitted data. At the time of preannouncement for the inspection, it was found that Dr. Silverman retired in July 2020 and that Dr. Montero has since served as the Principal Investigator for continuation of this study at the site.

The site enrolled 9 subjects for the study, with 5 subjects randomized to the elacestrant arm and 4 to the SOC arm. Following randomization, all the enrolled subjects received study treatment as assigned. As of data cutoff, one subject [# (b) (6) in the elacestrant arm remained on study treatment and the rest of subjects in both arms were discontinued from study treatment due to disease progression or adverse events. At the time of this inspection, Subject # (b) (6) was found to have discontinued study treatment since (b) (6) for disease progression, about (b) (6) months after the data cutoff of 09/06/2021. This study was ongoing at the site for survival follow-up but was closed to enrollment.

The inspection involved a comprehensive review of source records for the 9 subjects, eligibility determination, informed consents, scans and radiology reports, AEs, laboratory reports, and data contained in the eCRFs. Source records and data were compared to the data listings submitted by the Applicant for the site. In addition, the inspection examined regulatory documentation and the study administration and related oversight (i.e., IRB's approvals and continuing reviews) at the site as well as financial disclosures, study monitoring records, and sponsor correspondences.

The inspection identified no regulatory issues with the study conducted by the current and previous investigators at this site. The Applicant's submitted data for the site were verifiable with source records reviewed at the site. There were no unreported AEs identified.

No Form FDA 483 was issued to Dr. Montero at the conclusion of this inspection.

Site 175: Dr. Hung Khong

Dr. Khong was inspected on September 19-23, 2022, as a surveillance and data audit for Study RAD1901-308. This was the initial FDA inspection of the investigator.

The site enrolled 7 subjects into the study, with 2 subjects randomized to the elacestrant arm and 5 to the SOC arm. Following randomization, one subject [# (b) (6) in the SOC arm did not receive study treatment as assigned due to consent withdrawal and the rest of subjects received at least one dose of study treatment. In addition, this site accepted the subject [# (b) (6) transferred from Site 116 during the study. As of the data cut off, all the subjects enrolled at the site in both arms were discontinued from study treatment due to disease progression. At the time of this inspection, the subject transferred from Site 116 remained on study treatment, with the most recent study visit on (b) (6)

Source records for all the enrolled subjects were reviewed and compared with the submitted data listings. Records reviewed included the informed consents, inclusion/exclusion criteria, screening and enrollment log, randomization, study treatment administration and discontinuation, scans performed per protocol, adverse events, serious adverse events, concomitant medications, test article accountability, and protocol deviations. The inspection reviewed the activities and records related to the authority and administration of the study, including the IRB approvals and documentation, Form FDA 1572s, financial disclosures, site training activities and implementation of study procedures, source data collection and monitoring activities, adherence to and documentation of protocol-required visits, and sponsor monitoring activities.

The inspection found no significant regulatory violations at the site. The subjects' eligibility and source data were found to have been properly documented in source records reviewed and were verifiable for the submitted data listings. There was no evidence of underreporting of adverse events.

At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Khong.

Parexel International Corporation

The CRO was inspected on November 01-09, 2022, to review its conduct and management of Study RAD1901-308. For this CRO, the most recent inspection was conducted in August 2019 and the final compliance classification was No Action Indicated (NAI).

The inspection reviewed the CRO's history, organizational chart, operating procedures, and service agreements, with an inspection focus on activities associated with the conduct of Study RAD1901-308. The activities included selection of monitors and related training for the study, selection and monitoring of clinical investigators, management and monitoring of study sites including remote monitoring due to the COVID-19 pandemic, data collection and use of independent data monitoring committee (IDMC) and related IDMC charter, safety reporting and oversight, quality assurance procedures, and oversight of the outsourced services (i.e., electronic data capture (EDC) system and data management).

The inspection identified no objectionable compliance issues in the CRO's conduct and management of Study RAD1901-308. No clinical investigator sites were found to have been terminated or placed on hold due to non-compliance during the study. For the above three investigator sites, IRB approvals were verified prior to screening and enrollment of subjects, consistent with the CRO's specified requirements. The CRO has continued its agreed responsibilities from the initiation of this study through the change of sponsorship from the initial sponsor Radius Health to the current sponsor Stemline Therapeutics in June 2022.

Of note, one subject [# (b) (6) who was randomized to the SOC arm of the study was found not included initially in the NDA submission. This subject transferred study participation from Site 141 in New Jersey to Site 129 in Los Angeles, which occurred 5 weeks after randomization. About one month after the transfer, the subject died from breast cancer. The missed reporting of this subject was noted in June 2022 because of a discrepancy identified between the randomized subject count of 478 provided by Parexel and the reported data of 477 subjects in the interim analysis. The root cause for this discrepancy was analyzed and identified as "inadequate process information or documentation" due to the inadvertent transfer of the subject's data into a site within the EDC which was used to store duplicate files and other items such as erroneous entries of subject identification numbers. The corrective and preventive actions implemented for this issue were: 1) to have requested the CRO for responsible for randomization to reinstate the subject at the original Site 141; 2) to have notified the review division and resubmitted datasets and related reports and analyses; 3) to have evaluated the training material and update to reflect the best practices on Subject Data Transfers for new hires; 4) to have retrained Data Management group on the revised process to be defined in Data Management Plan.

OSI Reviewer's Comments: The missed inclusion of the above subject [# (b) (6) was reported to the Agency in August 2022, with submission of the corrected datasets and analyses in September 2022. No additional subjects who were randomized in the study were not included in the analyses. This issue appears to be isolated. The CRO's corrective and preventive actions as listed above are timely, reasonable, and acceptable.

4.2. Product Quality

The FDA Product Quality review team recommended approval for elacestrant. The review team assessed the drug substance, the drug product, quality labeling, manufacturing, biopharmaceutics, and microbiology for elacestrant and concluded that the Applicant provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed product. The review team also concluded that all associated manufacturing, testing, and packaging facilities were acceptable. There were no product quality PMRs or PMCs issued. For details, please refer to the Product Quality review.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

CDRH received a supplemental PMA Application (sPMA P200010/S010) from Guardant Health, Inc. for the Guardant360 CDx assay. CDRH considers this sPMA approvable as a companion diagnostic device for elacestrant.

The Guardant360 CDx assay is a qualitative next generation sequencing (NGS)-based *in vitro* diagnostic device which uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants and insertions/deletions in 55 genes, copy number amplifications in 2 genes, and fusions in 4 genes. The assay uses circulating cell-free DNA from plasma of peripheral whole blood. This assay is approved as a companion diagnostic for 4 other drugs: osimertinib, amivantamab-vmjw, fam-trastuzumab deruxtecan-nxki, and sotorasib, all for the treatment of NSCLC.

The clinical validity of the Guardant360 CDx assay as a companion diagnostic device for elacestrant is supported by plasma samples and clinical outcome data from RAD1901-308. Plasma samples for all patients enrolled to RAD1901-308 were tested using the Guardant360 CDx. There were 228 patients with an *ESR1* mutation detected, 249 patients without an *ESR1* mutation detected, and 1 patient whose sample had a QC failure with the bioinformatics software.

The CDRH review team concluded that the results submitted supported the clinical validity of the Guardant360 CDx assay as a companion diagnostic device to aid in the selection of patients with breast cancer with a detectable *ESR1* mutation in plasma for treatment with elacestrant. In addition, CDRH concluded that the analytical validation data for the limit of detection, sample stability, accuracy, and precision were acceptable. For details, please refer to the CDRH review.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Elacestrant (ORSERDU) belongs to the pharmacological class of estrogen receptor antagonist. Elacestrant is administered as a continuous daily oral tablet at the recommended dose of 345 mg/day (equivalent to 400 mg elacestrant dihydrochloride) and is proposed for the treatment of postmenopausal women and adult men, with estrogen receptor-positive (ER+) human epidermal growth factor receptor 2-negative (HER2-), *ESR1*-mutated advanced or metastatic breast cancer with disease progression following endocrine therapy. The nonclinical development program for elacestrant was sponsored by Radius Health, Inc and consisted of studies in mice, rats, ferrets, and monkeys to evaluate the pharmacology (primary, secondary, safety), metabolism, general and developmental toxicology, and genotoxicity. During the nonclinical development, elacestrant was referred to as RAD-1901/RAD1901.

Estrogen receptors (ERs) consist of nuclear ERs, extra-nuclear ERs, and G protein-coupled ERs. Estrogen receptor α (ERα) and estrogen receptor β (ERβ), are located in the nucleus and are encoded by the *ESR1* and *ESR2* genes, respectively. ERα is expressed in breast, prostate, uterus, liver, and bone tissues. Mutations in the *ESR1* gene, such as Y537S and D538G, contribute to ER+HER2- breast cancer resistance to endocrine therapy.

In primary pharmacology studies, elacestrant bound ERα at an IC_{50} of 48 nM and with 18-fold lower affinity to ERβ (IC_{50}= 870 nM) in an estrogen receptor competitor assay. Elacestrant led to a decrease in the basal proliferation of an ER+/PR+/HER2- breast cancer cell line at ≥10 nM, and to a dose-dependent decrease in estradiol induced cell proliferation (mean IC_{50}s ≤27 nM) and downregulation of ERα expression. In the clinical trial, all patients had received prior treatment with a CDK4/6 inhibitor plus endocrine therapy; in vitro, elacestrant was active in both *ESR1* WT and mutated (D538G and Y537S) breast cancer cell lines with comparable activity between CDK4/6 inhibitor sensitive and resistant derivatives of the cell lines. Western blot analysis of ERα and the ERα-inducible enzyme GREB showed a decrease of the proteins when *ESR1* WT and mutated CDK4/6 inhibitor sensitive and resistant cell lines were incubated with elacestrant. In in vivo ER+/PR+/HER2- xenograft and ER+ patient derived xenograft (PDX) breast cancer models, elacestrant led to ≥96% tumor growth inhibition (TGI) at ≥30 mg/kg/day. Additionally, elacestrant led to ≥72% TGI at ≥10 mg/kg/day in an *ESR1* Y537S mutated model and ≥52% TGI at ≥30 mg/kg/day in a PDX model of human ER+ breast cancer considered to have acquired resistance to palbociclib and fulvestrant combination therapy.

In secondary pharmacology studies, elacestrant was shown to inhibit human cannabinoid CB1 and have binding affinity for human adrenergic receptor a 2a (ADRA2A); however, elacestrant lacked functional (agonist or antagonist) activity across various cell-based assays above clinically relevant concentrations. The Applicant evaluated secondary effects of elacestrant on uterus tissues, luteinizing hormone (LH) release, and bone loss. In juvenile mice and rats, estradiol increased uterine weight and endometrial thickness while elacestrant led to a decrease suggesting a minimal risk for elacestrant induced hyperplasia. In ovariectomized rats,

elacestrant decreased serum LH concentration and bone mineral density (BMD) loss suggesting elacestrant may have estrogen-like activity over LH levels and provide protection against menopause related bone loss.

The Applicant conducted stand-alone GLP-compliant safety pharmacology studies with elacestrant including an in vitro hERG assay and in vivo central nervous, cardiovascular, and respiratory system assessments. Although per ICH S9 guidance stand-alone safety pharmacology studies are not warranted to support a marketing application for oncology, the studies were conducted as elacestrant was initially investigated for the treatment of menopause-related vasomotor symptoms. Consequently, the studies were conducted using female animals only. Elacestrant blocked the hERG channel up to approximately 87% at 1 µM (IC_{50}= 0.41 µM) and led to a complete block of the cardiac action potential of rabbit Purkinje fibers at 10 µM. In vivo, following a single oral dose of 100 mg/kg or human equivalent dose (HED) of 1200 mg/m^2 (C_{max}: 219 ng/mL [0.47 µM]) led to an increase in blood pressure (<10% to control) and heart rate (<25% to control) up to 4 hours post dose but did not lead to QTc prolongation in cynomolgus monkeys. Adverse cardiovascular effects were not observed in patients with ER+HER2- advanced or metastatic breast cancer who received elacestrant at the recommended dose. A single oral dose of elacestrant (≤100 mg/kg) in cynomolgus monkeys did not have adverse effects on central nervous and respiratory systems.

The Applicant conducted GLP-compliant studies assessing the effect of elacestrant on bleeding time and wound healing and non-GLP compliant studies evaluating gastrointestinal effects in ferrets. Despite an increase in prothrombin time in rat toxicology studies and the 4-week monkey toxicology study, daily oral administration of elacestrant at ≤50 mg/kg (300 mg/m^2 HED) to rats led to a non-significant increase in mean clotting time and no effects on wound healing. Administration of elacestrant to male ferrets up to 100 mg/kg (700 mg/m^2 HED) via daily oral gavage for 7 days led to dose-dependent adverse gastrointestinal effects such as low food consumption, body weight loss, emesis, and abnormal feces at mean maximum plasma concentrations (C_{max}) ≥4.6 times the human C_{max} at the recommended dose. Adverse gastrointestinal effects were among the most common in patients administered elacestrant at the recommended dose.

In vitro, elacestrant demonstrated high plasma protein binding (≥98%) in rat, monkey, and human plasma. Following a single oral administration of elacestrant, exposures (C_{max} and area under the curve [AUC_{0-t}]) increased greater than dose proportionally, and the bioavailability was dose-dependent ranging from approximately 14% to 22% in rats and 7% to 18% in monkeys for the dose range of 1 to 10 mg/kg. In repeat dose toxicology studies up to 26 weeks in rats and 39 weeks in monkeys, exposures (C_{max} and AUC_{0-24}) generally increased greater than dose proportionally with higher exposures (1.5 to 2.4-fold) observed in females rats compared to male rats and no observed sex differences in monkeys. Accumulation ratios up to 3-fold were noted in rats and <2-fold in monkeys, suggesting accumulation in rats but no to minimal in monkeys following repeated administration of elacestrant. The time to reach maximum

concentration (T_{max}) was in the range of 2 to 12 hours in rats and 2 to 9 hours in monkeys, and the terminal half-life was in the range of 3.5 to 12 hours in rats and 8 to 11 hours in monkeys. Animal to human exposure margins were calculated using the mean steady state clinical C_{max} (119 ng/mL) and AUC_{tau} (2440 ng.h/mL).

In vitro, approximately 50% of elacestrant was metabolized by human hepatocytes mainly through N-dealkylation and glucuronidation with no human specific metabolites detected. Following a single oral administration of elacestrant in rats, radiolabeled elacestrant was detected in the majority of tissues, including ocular melanin containing tissues (eye uveal tract of Long Evans rats), but not in the brain, eye lens, spinal cord, and testes, with maximum exposures observed in tissues within 4 to 8 hours post-dose. Excretion was mainly via feces, bile, and to a lesser extent in urine with the majority of administered elacestrant excreted within 48 hours post-dose.

Repeat dose toxicology studies were conducted with elacestrant in rats and monkeys for up to 26 and 39 weeks, respectively, administered via daily oral gavage up to 50 mg/kg/day or 300 mg/m^2 HED (4.1 times the human AUC at the recommended dose) in rats and up to 30 mg/kg/day or 360 mg/m^2 HED (1.3 times the human AUC at the recommended dose) in monkeys. In 4-week studies, elacestrant was administered via daily oral gavage up to 120 mg/kg/day or 720 mg/m^2 HED (6.7 times the human AUC at the recommended dose) in rats and up to 100 mg/kg/day or 1200 mg/m^2 HED (3.3 times the human AUC at the recommended dose) in monkeys. Early mortalities occurred at ≥100 mg/kg/day (4.3 times the human AUC at the recommended dose) in rats (4- and 13-week studies) with signs of abnormal respiration and at ≥50 mg/kg/day (2.1 times the human AUC at the recommended dose) in monkeys (4-week study) with observations of body weight loss, decreased food consumption, excessive salivation, vomitus, and diarrhea, leading to moribund conditions.

In surviving rats, abnormal respiration was observed at ≥50 mg/kg/day (2 times the human AUC at the recommended dose) in ≤13-week studies and abnormal feces at ≥20 mg/kg/day (0.7 times the human AUC at the recommended dose) with microscopic correlates of inflammation and foamy macrophage infiltration in the gastrointestinal tract at 100 mg/kg/day (4.3 times the human AUC at the recommended dose). Clear oral discharge and/or salivation were noted in rats (≥50 mg/kg/day) and monkeys (30 mg/kg/day), while decreased mean body weight and mean body weight gain was generally limited to male rats (≥10 mg/kg/day) with corresponding decrease in food consumption. Vomiting, diarrhea, and decreased appetite were common adverse events in postmenopausal women and men with ER+HER2- advanced or metastatic breast cancer receiving elacestrant.

Reversible hematological changes across the rat studies were generally comparable and were limited to doses ≥50 mg/kg/day in monkeys. Changes included increase in red blood cell parameters in rats (decrease in monkeys), increase in prothrombin time and white blood cell

parameters (generally neutrophils and monocytes), and decrease in reticulocytes. Reversible clinical chemistry changes in both rats and monkeys included increased liver enzymes (ALT and/or AST), decrease in total protein, albumin, and cholesterol. Additional changes in rats generally included decreases in glucose and albumin/globulin ratio. An increase in cholesterol and triglyceride levels was observed in 30% and 27% of patients, respectively. The label includes hypercholesterolemia and hypertriglyceridemia under Warnings and Precautions.

Histopathology changes in rats and monkeys, other than those of the male and female reproductive organs (discussed below under fertility studies), were generally observations of increase in macrophage and/or neutrophilic infiltrates in mesenteric lymph node, lung, small and large intestines and mammary gland atrophy or hypertrophy/hyperplasia. Additionally in the 26-week rat study, minimal alteration (females) and increase (males) in trabecular bone in femur, slight increase in granulocytes in glandular stomach and increased vacuolation in non-glandular stomach were observed.

In genetic toxicology studies, elacestrant was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay or, clastogenic in either in vitro chromosome aberration assays or an in vivo rat bone marrow micronucleus assay. Carcinogenicity studies were not conducted with elacestrant in accordance with ICH S9 guidance; however, of note, in the rat 26-week repeat dose toxicology study B-granulosa cell tumor was observed at ≥25 mg/kg/day (2.6 times the human AUC at the recommended dose) in approximately 40 to 50% of female rats and B-luteoma at 50 mg/kg/day (5.6 times the human AUC at the recommended dose) in 10% of female rats. Additionally, elacestrant did not demonstrate phototoxicity up to 31.6 µg/mL in an in vitro GLP-compliant study.

Dedicated fertility, early embryonic development, pre- and postnatal development studies were not conducted with elacestrant in accordance with ICH S9 guidance and the intended indication for the treatment of patients with advanced cancer. The Applicant assessed the effects of elacestrant on reproductive organs in the rat and monkey as part of the GLP-compliant repeat-dose toxicology studies and provided results from a GLP-compliant embryofetal development (EFD) study in rats. Toxicities to female reproductive organs from the 26-week (rat) and 39-week (monkey) general toxicology studies included vaginal, cervical, and uterine atrophy, increased vaginal epithelium mucification (rat), ovarian follicular cysts, increased ovarian stroma (monkey), and granulosa cell hyperplasia (rat) in the ovaries at ≥10 mg/kg/day (≥0.3 times the human AUC at the recommended dose). Toxicities to male rat reproductive organs included decreased cellularity of Leydig cells and degeneration/atrophy of the seminiferous epithelium in the testis at 50 mg/kg/day (2.6 times the human AUC at the recommended dose).

Elacestrant was embryo lethal and teratogenic when administered to pregnant rats at ≤30 mg/kg via daily oral gavage during the period of organogenesis on gestational days 6 through 17 followed by cesarean section on gestational day 21. Elacestrant-related maternal toxicity

(reduced body weight gain, low food consumption, red vulvar discharge) and embryo-fetal mortality (increased resorptions, post-implantation loss, and reduced number of live fetuses) were noted at ≥3 mg/kg/day (approximately 0.1 times the human AUC at the recommended dose). Additional fetal adverse effects included reduced weight and external malformations of the limbs (hyperflexion, malrotation) and head (domed, misshaped, flattened) with corresponding skeletal malformations of the skull at doses ≥10 mg/kg/day (approximately 0.5 times the human AUC at the recommended dose). The label advises females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of elacestrant based on the recommendations for duration of contraception for nongenotoxic pharmaceuticals that cause teratogenicity or embryo-fetal lethality from the FDA guidance, "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations". The guidance recommends a contraception period of 5 half-lives (elacestrant half-life = 38.6 hours after repeated dosing) for small molecules. Additionally, the label advises lactating women not to breastfeed during treatment and for 1 week (b) (4)) after the last dose due to the potential for severe adverse reactions in a breastfed child.

Recommendation:
The nonclinical data submitted to this NDA are adequate to support approval of ORSERDU for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no other referenced NDAs, BLAs, or DMFs applicable to the nonclinical pharmacology/toxicology of elacestrant.

In order to maintain consistency with the submitted modules and reports, doses of nonclinical pharmacology/toxicology studies are expressed as elacestrant dihydrochloride salt.

5.3. Pharmacology

Primary pharmacology

In summary, elacestrant binds with high affinity (IC50 48 nM) and selectivity to the ERα (Study RAD-001). In the presence of 17β-estradiol (E2, 0.01 and 0.1 nM), elacestrant shows concentration-dependent antagonism (IC_{50} 4.2 and 27 nM) of E2-mediated stimulation of ER-positive MCF7 breast cancer cell proliferation (Study RAD-002) through down-regulation and degradation of the ER (Study STC-RAD-02). Antiproliferative activity has been also demonstrated in tumor cells resistant to t CDK4/6 inhibitors (Study 18RAD2023) and harboring *ESR1* mutations (Study 17RAD2022). In a mouse xenograft model, treatment with elacestrant inhibited the estrogen-dependent growth of MCF7 breast cancer tumors when administered either alone or in combination with a cyclin-dependent kinase (CDK4/6) inhibitor or a mammalian target of rapamycin (mTOR) inhibitor (Study 15RAD219). In addition, in tumor models xenografted from patient samples (PDX), who had been exposed to multiple prior

endocrine therapies (including PDX models insensitive to fulvestrant and models harboring *ESR1* mutations), elacestrant was found to have potent antitumor activity (Study 16RAD240).

The FDA's Assessment:

FDA agrees with the Applicant's position. The data in combination with CDK4/6 and mTOR inhibitors were not reviewed since the proposed indication is for elacestrant monotherapy.

Data (presented by the FDA):

#RAD-001 – Elacestrant bound ERα with an IC_{50} of 48 nM, while the (b) (4) (a drug substance impurity), (b) (4), bound ERα with an IC_{50} of (b) (4) nM assessed via an estrogen receptor competitor assay. Elacestrant bound ERβ with 18-fold lower affinity (IC_{50} = 870 nM) compared to ERα.

#RAD-002 – Elacestrant led to reduced basal cell proliferation of ER+/PR+/HER2- MCF7 breast cancer cells at ≥10 nM. In the presence of estradiol, 0.01 or 0.1 nM, elacestrant led to a dose-dependent decrease in estradiol induced cell proliferation with mean IC_{50}s of 4.2 nM and 27 nM, respectively. The (b) (4) had an approximately (b) (4) anti-proliferative and approximately (b) (4) antagonist activity compared to elacestrant, corresponding to the lower binding affinity to ERα.

#STC-RAD-02 – Elacestrant led to a dose-dependent downregulation of ERα after 48 hours of incubation (IC_{50} range of 0.6 nM to 76 nM) in ER+/PR+/HER2- MCF7 and T47D breast cancer cell lines, respectively, assessed via ERα ELISA in cell lysates.

#16RAD203/16RAD209/16RAD210 – Elacestrant led to a dose-dependent decrease in ERα protein levels in ER+/PR+/HER2- breast cancer cell lines MCF7, T47D, and HCC1428 at 8-, 24-, and 48-hours of drug exposure assessed via western blot. Additionally, the Applicant provided reference to the literature showing that ERα protein levels remained comparable to vehicle control when MCF7 cells were pretreated with the proteasome inhibitor MG132, suggesting ERα degradation through a proteasomal pathway (Wardell et al. 2015).

#17RAD2022 – Elacestrant led to dose-dependent inhibition of breast cancer cell proliferation in the *ESR1* WT HCC1428 long term estrogen deprived (LTED) breast cancer cell line and *ESR1* mutated MCF7 *ESR1* Y537S and MCF7 *ESR1* D538G breast cancer cell lines with comparable IC_{50}s between CDK4/6 inhibitor (palbociclib, abemaciclib, ribociclib) sensitive and resistant derivatives of the cell lines. The IC_{50}s ranged from 0.13 to 0.25 nM for HCC1428-LTED, from 3 to 25 nM for MCF7 *ESR1* Y537S, and from 14 to 118 nM for MCF7 *ESR1* D538G cell lines. Western blot analysis of ERα, the ERα-inducible enzyme GREB, transcription factor E2F1 and regulator of cell cycle progression CyclinD1 protein levels generally decreased in the presence of elacestrant in *ESR1* WT and mutated CDK4/6 inhibitor sensitive and resistant cell lines.

#18RAD2023 – Elacestrant led to a dose-dependent inhibition of cell proliferation of the ER+/PR+/HER2- breast cancer cell lines HCC1428-LTED and palbociclib resistant HCC1428-LTED, demonstrating comparable activity in the IC_{50} in the range of 0.17 to 4.6 nM (mean 1.77 nM) and 0.5 to 3.7 nM (mean 1.69 nM), respectively.

#15RAD219 – Administration of elacestrant to 17β-estradiol pellet implanted and ER+/PR+/HER2- MCF7 breast cancer tumor bearing female mice at 30 or 60 mg/kg dosed daily

via oral gavage for 28 days led to 96% and 103% tumor growth inhibition (TGI) at 30 and 60 mg/kg, respectively, compared to control. Elacestrant plasma concentration was highest at the 2-hour post last dose timepoint and was 147 ng/mL and 360 ng/mL at the 30 and 60 mg/kg dose, respectively.

#16RAD240 – The anti-tumor activity of elacestrant was assessed in the ST941/HI patient derived xenograft (PDX) model representing ER+ hormone independent breast cancer with an *ESR1* Y537S mutation. Daily administration of elacestrant led to 72%, 84%, and 93% tumor growth inhibition (TGI) at 10, 30, and 60 mg/kg, respectively, compared to the control on Day 26, while weekly subcutaneous administration of fulvestrant at 3 mg/kg (4 total doses) lacked anti-tumor response with a mean tumor volume comparable to control. Body weight loss of 10% to 30% compared to pre-test weights was observed in 6/8 animals given 60 mg/kg elacestrant generally during the first two weeks of dosing. Two animals that lost 22% and 25% body weight were found dead on Day 14 and 20, respectively; the other surviving animals recovered their body weights.

#18RAD202 – The ST3932 PDX model represents a human ER+ breast cancer from a patient previously treated with a combination of fulvestrant and palbociclib and showed 7.5-month response; the patient is considered to have an acquired resistant to the combination. Daily oral administration of elacestrant at 30 or 60 mg/kg for 60 days led to 62% and 52% TGI compared to control on Day 35. The response to 50 mg/kg daily palbociclib and 3 mg weekly fulvestrant monotherapies were 38% and 52% TGI, respectively.

Secondary Pharmacology

The Applicant's Position:

Binding selectivity of elacestrant at 1 µM was assessed in a screen against a broad panel of 166 molecular targets which demonstrated > 50% inhibition of binding for 5 of them, but without apparent functional effects (Studies 1035439, 1035745, 09RAD043, and 10RAD005).

Secondary pharmacodynamic effects were studied on uterine tissues in immature rats and mice, luteinizing hormone (LH) release in ovariectomized (OVX) rats, and bone loss in OVX rats. Elacestrant did not stimulate endometrial proliferation, or increase uterine weight, and it was a potent antagonist of E2-mediated proliferation (Studies 14RAD020, 14RAD022, and RAD-003).

Elacestrant demonstrated a weak estrogen-like agonist activity by decreasing serum LH in OVX rats (40% inhibition at 10 mg/kg ip, as compared with 85% by E2) compared with vehicle (Study RAD-008).

Elacestrant prevented bone loss in OVX rats at oral dose levels as low as 0.1 mg/kg and preserved bone microarchitecture at 1 mg/kg (Study RAD-004), with protection against bone loss achieved at least in part by a reduction in bone resorption (Study RAD-006).

The FDA's Assessment:

FDA agrees with the Applicant's position.

Data (presented by the FDA):

#1035439/1035745 – Elacestrant (1 µM) induced >50% inhibition of human cannabinoid CB_1 (99%, IC_{50}=0.08 µM), ERβ (98%), growth hormone secretagogue (51%, IC_{50}=1.3 µM), motilin

(71%, IC_{50}=0.26 µM), and somatostatin sst1 (52%, IC_{50}=0.8 µM) among 166 molecular targets including ion channels, enzymes and receptors.

#09RAD-043 – Elacestrant did not demonstrate functional (agonist or antagonist) activity through the cannabinoid receptor 1 (CNR1) in either a G-protein mediated cell-based assay, an arrestin mediated cell-based assay, or a cAMP assay compared to reference compounds.

#10RAD005 – The Applicant referred to a study that demonstrated elacestrant having binding affinity (IC50) of 167 nM to the adrenergic receptor a 2a (ADRA2A). In this follow-up study, elacestrant did not demonstrate functional (agonist or antagonist) activity through ADRA2A across three assays including GTPγS binding assay, cAMP assay, and a reporter assay.

#14RAD020 – Elacestrant led to a non-dose dependent and statistically significant decrease in uterus weight (up to 78%) and endometrial epithelium thickness (up to 30%) at ≥0.1 mg/kg/day compared to control when administered to juvenile CD1 mice (n=6/group) via daily oral gavage up to 100 mg/kg/day between 18 to 20 days old (sacrificed at 21 days old).

#14RAD022 – Elacestrant led to a generally non-dose dependent decrease in uterus weight (48%) and endometrial epithelium thickness (56%) at ≥0.1 mg/kg/day compared to control when administered to juvenile Sprague Dawley rats (n=6/group) via daily oral gavage up to 100 mg/kg/day between 21 to 23 days old (sacrificed at 24 days old). Statistical significance for uterine weight decrease was reached at ≥30 mg/kg/day and for endometrial epithelium thickness at ≥0.1 mg/kg/day compared to control.

#RAD-003 – Elacestrant did not elicit statistically significant changes in uterine weight, endometrial epithelial thickness or uterine C-3 complement gene expression up to 100 mg/kg/day compared to control when administered to Sprague Dawley rat pups (19 days old) for 3 consecutive days via subcutaneous injection or oral gavage. However, co-administration of elacestrant up to 10 mg/kg/day and estradiol (0.01 mg/kg/day) led to a dose-dependent inhibition of estradiol mediated increase in uterine weight and C-3 complement gene expression, reaching statistical significance at ≥0.1 mg/kg/day (uterine weight) and ≥1 mg/kg/day (gene expression). The (b) (4) did not inhibit the estradiol induced uterine weight.

#RAD-008 – Elacestrant led to an approximately 32% and 40% decrease in serum luteinizing hormone (LH) concentration (ng/mL) compared to vehicle control when administered to ovariectomized Wistar rats once daily for 3 consecutive days via intraperitoneal injection at 1 and 10 mg/kg/day, respectively. In comparison, the administration of estradiol (0.01 mg/kg/day) to ovariectomized rats led to an 85% decrease in serum LH concentration compared to vehicle control.

#RAD-004 – Elacestrant led to a statistically significant decrease in femur and lumbar spine bone mineral density (BMD) loss at ≥0.1 mg/kg/day when administered once daily via oral gavage to ovariectomized Sprague Dawley rats for 4 weeks compared to vehicle control treated rats. Additionally, elacestrant (1 mg/kg/day) led to a statistically significant increase (up to 29%) in bone volume density, trabecular number, connectivity density, apparent bone density and decrease (-29%) in trabecular spacing compared to vehicle control treated ovariectomized rats.

#RAD-006 – Compared to sham, ovariectomized Fischer rats had a statistically significant increase (103%) in urine deoxypyridinoline (a marker of bone resorption). Elacestrant, when

administered to ovariectomized rats at 10 mg/kg/day via daily (5 days/week) oral gavage for 8 weeks, demonstrated comparable urine deoxypyridinoline levels to sham.

Safety Pharmacology

The Applicant's Position

Stand-alone safety pharmacology studies to support clinical studies in patients with advanced/metastatic cancer are not required. However, dedicated Good Laboratory Practice (GLP)-compliant safety pharmacology studies to assess the cardiac safety, respiratory effects, and neurological effects of elacestrant were performed early in development to support the treatment of menopause-related vasomotor symptoms with elacestrant. Accordingly, the in vivo safety pharmacology studies were conducted in female animals only, but no appreciable sex-specific differences of vital organ functions were observed in repeat-dose toxicity studies. Additional GLP-compliant safety pharmacology studies investigated the effects of elacestrant on bleeding time, wound healing and on gastrointestinal tolerability. Elacestrant inhibited hERG in vitro (IC_{50} of 0.41 µM) (Study 7801-126) but it did not modify action potentials parameters in rabbit Purkinje fibers up to 1 µM (study 7801-131). In vivo, elacestrant transiently increased blood pressure and heart rate but it did not prolong QT/QTc interval in cynomolgus monkeys up to 100 mg/kg p.o. (Study 7801-118). Elacestrant did not change respiratory parameters (Study 7801-119) and no central nervous system (CNS) effects were observed (Study 7801-120) in rats up to oral doses of 100 mg/kg. Elacestrant (20 and 50 mg/kg) slightly increased bleeding time (< 2-fold as compared with vehicle, versus 3.3- to 4.6-fold of warfarin) (Study 14RAD009) but the same doses did not affect the wound healing (Study 14RAD030). Gastrointestinal tolerance was studied in ferrets; elacestrant (30 and 100 mg/kg) induced emesis, but at 30 mg/kg, the frequency of these events decreased after repeated administrations (Studies 15RAD250, 16RAD223, and 16RAD231). In these in vivo safety pharmacology studies elacestrant exhibited no major adverse effects on the cardiovascular system, respiratory system, CNS or wound healing, and the gastrointestinal tolerability improved following repeated doses.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The cardiovascular safety studies were initially reviewed by the FDA under an IND with the Division of Bone, Reproductive, and Urologic Drugs.

Data (presented by the FDA):

Cardiovascular system

#7801-126 – Elacestrant led to a mean hERG current inhibition of 5.0%, 32.6%, 72.4%, and 86.8% at 0.1, 0.3, 0.6, and 1.0 µM, respectively with an IC_{50} of 0.41 µM. The hERG inhibition at ≥0.3 µM concentrations were statistically significant compared to vehicle control.

#7801-131 – In cardiac Purkinje fibers isolated from New Zealand White rabbits, elacestrant led to dose-dependent alterations in action potential duration between 0.1 and 1 µM, although not statistically significant from vehicle control, and were depolarized and rendered unable to generate an action potential at 10 µM, possibly indicating block of sodium and/or calcium channels.

#7801-118 – In female cynomolgus monkeys administered a single dose of elacestrant at 0, 25, 50, or 100 mg/kg via oral gavage, a statistically significant increase in diastolic, systolic, and mean arterial pressures by 11%, 6%, and 8%, respectively, at 1-hour post dose were observed in animals given 100 mg/kg. Additionally at 100 mg/kg (mean C_{max}= 219 ng/mL [477 nM]), statistically significant increase in heart rate was noted by 10%, 14%, and 22% compared to control at 1, 2, and 4 hours post dose, respectively, returning to control levels by 8 hours post dose. ECG parameters were unremarkable, although a dose-related trend for increased heart rate, decreased QT and RR intervals (no change in QTc) were noted.

Central nervous system

#7801-120 – In female Sprague Dawley rats administered a single dose of elacestrant at 0, 25, 50, or 100 mg/kg via oral gavage, there were no changes compared to control using a modified Irwin battery of neurological assessments, including cage side, hand-held, open field, and elicited response observations at pre-dose, 2-, 4-, 6-, 8-, and 24-hours post dose.

Respiratory system

#7801-119 – In female Sprague Dawley rats administered a single dose of elacestrant at 0, 25, 50, or 100 mg/kg via oral gavage, there were no changes compared to control in respiratory parameters including respiratory rate, tidal volume, and minute volume assessed at pre-dose, 1-, 2-, 3-, 4-, 5-, 6-, and 24-hours post dose using the head-out plethysmography method.

Bleeding time and wound healing

#14RAD009 – In a cutaneous bleeding time assessment study, Sprague Dawley rats administered elacestrant at 20 or 50 mg/kg via daily oral gavage for 7 days had an increase, although not statistically significant compared to control, in the mean clotting time (minutes) by 10% (males) and 94% (females) given 20 mg/kg and by 80% (males) and 50% (females) given 50 mg/kg. In comparison, the positive control warfarin led to a mean clotting time increase by 360% (males) and 226% (females) compared to control.

#14RAD030 – In a wound healing study, Sprague Dawley rats administered elacestrant at 0.25, 20, or 50 mg/kg via daily oral gavage for 7 days following the creation of 2 linear incisions of 2 cm (one on each side of the back of each animal) had increased incidence and grade of erythema (up to grade 3 [moderate to severe]) and edema (up to grade 2 [slight]), although a dose-relationship was not apparent, compared to control when observed up to 21-days post last dose. Female rats given 50 mg/kg were also observed with eschar or curst-like formation (up to grade 3 [covering 25% to 50% of the test site]). Overall, administration of elacestrant did not lead to differences in wound healing compared to control.

Gastrointestinal effects

#15RAD250 – Administration of elacestrant, formulated in (b) (4), to male ferrets (n=6/group) at 0, 10, 30, or 100 mg/kg via daily oral gavage for 7 days led to low food consumption in 1/6, 2/6, and 6/6 animals at 10, 30, and 100 mg/kg/day, respectively, discolored, non-formed and/or mucoid feces and body weight loss (up to 22%) compared to pre-test in 6/6 animals given 100 mg/kg/day. Emesis was observed in all animals given ≥30 mg/kg/day on Day 1, with higher number of incidences observed at 100 mg/kg/day. The number of animals and frequency of emesis decreased with time in animals given 30 mg/kg/day, while all animals given 100 mg/kg/day experienced emesis throughout dosing. The

mean plasma concentration was 557 ng/mL and 973 ng/mL at 4 to 8 hours post dose at 30 and 100 mg/kg on Day 7.

#16RAD231 – Administration of elacestrant to male ferrets (n=6/group) at 0, 30, or 60 mg/kg via either (b) (4) film or (b) (4) coated tablets for 7 days generally led to low food consumption in 30% to 60% of the animals given ≥30 mg/kg/day (b) (4) film tablets and 60 mg/kg/day (b) (4) coated tablets without any adverse effects on body weight. Emesis was noted in 80% to 100% of the animals at ≥30 mg/kg/day (b) (4) film tablets on all observational days (1, 2, 3, 7) without a clear dose relationship, while a lower incidence of emesis occurred in animals given the (b) (4) coated tablets namely on Day 3.

5.4. ADME/PK

The Applicant's Position:

Absorption
After single-dose oral administration of elacestrant, the mean time to reach maximum concentration (T_{max}) ranged from 1.75 to 24 hours in rats and from 1 to 8 hours in monkeys. The oral bioavailability of elacestrant at doses ranging from 1 to 10 mg/kg was dose-dependent in rats and monkeys, ranging from 14.0% to 22.3% in rats and from 7.6% to 18.1% in monkeys.
Distribution
Elacestrant was highly bound to the proteins in rat, monkey, and human plasma (approximately 99% binding). The percent unbound values were similar across the species and did not show the concentration dependence over the tested concentration range. After oral administration of radiolabeled elacestrant in in a tissue distribution study in nonpigmented Sprague Dawley and partially pigmented Long Evans rats. In a tissue distribution study, elacestrant-derived radioactivity was readily distributed to most tissues, with the highest exposures of radioactivity (excluding the gastrointestinal tract and contents) in the exorbital lacrimal gland, adrenal gland, liver, spleen, and intraorbital lacrimal gland for nonpigmented Sprague Dawley rats and in the uveal tract, eye, pituitary gland, liver, and Harderian gland for partially pigmented Long Evans rats. Poor distribution to the brain was noted. T_{max} was reached by 2 to 4 hours postdose in blood and plasma and by 4 to 8 hours postdose in the majority of tissues. Mean blood:plasma radioactivity concentration ratios ranged from 0.899 to 1.55.
Metabolism
Elacestrant metabolism was assessed in an in vitro study using rat, monkey, and human hepatocytes, and additional metabolite profiling and identification were assessed in rat plasma, urine, and feces collected from an in vivo absorption, distribution, metabolism, and excretion (ADME) study following a single oral dose of ^{14}C-elacestrant. Elacestrant was extensively metabolized in rats, both in vitro in hepatocytes (< 25% parent remaining) and in vivo (yielding 53 metabolites), and in vitro in monkey hepatocytes (< 33% parent remaining). Less extensive metabolism was observed in human hepatocytes (approximately 40% to 50% parent remaining). No human-specific metabolites were detected in hepatocyte incubations. In vitro, *N*-dealkylation and glucuronidation were common metabolic pathways in all species. In vivo in rats, metabolism occurred primarily by oxidative *N*-dealkylation.
Excretion
In rats, the predominant route of excretion was biliary-fecal. Following oral administration of ^{14}C-elacestrant, radioactivity was excreted as elacestrant parent form in feces from both intact and bile duct-cannulated rats, as metabolites in feces and urine (to a lesser extent) from intact rats, and predominantly as conjugated metabolites in bile from bile duct-cannulated rats. No urinary or biliary excretion of elacestrant parent form was observed. Radioactivity was excreted quickly, with most of the administered dose recovered within 48 hours postdose. Minor sex-dependent differences in excretion of radioactivity were observed.
Summary PK parameters from pharmacokinetic studies

Single-dose PK and toxokinetics of elacestrant were investigated following intravenous (IV) bolus, oral, or subcutaneous administration to rats and following IV, oral, or nasogastric intubation administration to monkeys; doses ranged from 1 to 900 mg/kg in rats and from 0.85 mg/kg to 200 mg/animal in monkeys. Clearance of elacestrant following a single IV dose of 1 mg/kg was approximately 2.12 ± 0.168 L/h/kg in female rats and 1.53 ± 0.431 L/h/kg in female cynomolgus monkeys, representing approximately 64% and 59% of liver blood flow in rats (3.31 L/h/kg) and monkeys (2.61 L/h/kg), respectively (Davies and Morris, 1993). The volume of distribution in female rats and cynomolgus monkeys was 19.1 ± 2.39 L/kg and 23.8 ± 5.36 L/kg, respectively. Repeat-dose oral toxokinetics (TK) of elacestrant was evaluated in rats and monkeys at doses ranging from 3 to 300 mg/kg/day. Increases in maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) were dose proportional or slightly greater than dose proportional up to doses of 100 mg/kg/day but were generally less than dose proportional at doses higher than 100 mg/kg/day. Female exposures were higher than in males for the 13- and 26-week rat studies, but in other studies no marked (> 2-fold) sex differences were observed in rats or monkeys. Accumulation ratios ranged from 0.722 to 3.47 in the 13- and 26-week repeat-dose studies in rats but no accumulation or slight accumulation (< 2-fold) was observed in rats and monkeys following repeated administration in other studies.
Integrative summary table of C_{max} and AUC parameters across toxicology studies (general, reproductive, and carcinogenicity, if conducted).
A summary of C_{max} and AUC parameters can be found in Table 3 and Table 4 of Module 2.6.4.
Tabulation of any exposure margins used in proposed labeling.
Exposure margins will be calculated by FDA. (As per comments to the AAid)

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. See the clinical pharmacology Section 6 for information regarding human data and drug interaction studies.

Data (presented by the FDA):

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Collection of Samples for Determination of the Bioavailability of RAD-1901 After Single Oral and Intravenous Doses to Female Rats
(Study# 7801-122)</td><td>Rat
Following a single oral administration of elacestrant:
• C_{max} and AUC_{0-t} generally increased greater than dose proportionally
• T_{max} was reached at 4 hours post dose and the half-life was approximately 6 hours
• Bioavailability was dose dependent and ranged from 14 to 22.3%

Mean PK parameters of elacestrant in female rats
<table>
<tr><th>Dose* (mg/kg)</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>AUC_{0-t} (ng.h/mL)</th><th>$T_{1/2}$ (hr)</th><th>Bioavailability (%)</th></tr>
<tr><td>0.87</td><td>5.81</td><td>4</td><td>40</td><td>6.10</td><td>14</td></tr>
<tr><td>2.60</td><td>17.1</td><td>4</td><td>204</td><td>5.79</td><td>17.8</td></tr>
<tr><td>9.85</td><td>80.5</td><td>4</td><td>948</td><td>6.43</td><td>22.3</td></tr>
</table>
*Intended doses were 1, 3, and 10 mg/kg</td></tr>
<tr><td>Collection of Samples for Determination of the Bioavailability of RAD-1901 After Single Oral and Intravenous Doses to Female Monkeys
(Study# 7801-121)</td><td>Monkey
Following a single oral administration of elacestrant:
• C_{max} and AUC_{0-t} increased greater than dose proportionally
• T_{max} ranged from 1 to 4 hours post dose, and the half-life ranged from approximately 9 to 11 hours
• Bioavailability was dose dependent and ranged from 7.6 to 18.1%

Mean PK parameters of elacestrant in female monkeys
<table>
<tr><th>Dose* (mg/kg)</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>AUC_{0-t} (ng.h/mL)</th><th>$T_{1/2}$ (hr)</th><th>Bioavailability (%)</th></tr>
<tr><td>0.96</td><td>3.85</td><td>4</td><td>35.2</td><td>11.1</td><td>7.6</td></tr>
<tr><td>3.06</td><td>25.5</td><td>1</td><td>226</td><td>9.74</td><td>12.8</td></tr>
<tr><td>10.6</td><td>87.2</td><td>2</td><td>1052</td><td>10.3</td><td>18.1</td></tr>
</table>
*Intended doses were 1, 3, and 10 mg/kg</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>In Vitro Binding of RAD-1901 to Rat, Monkey, and Human Plasma Proteins
(Study# 7801-132)</td><td>The protein binding of elacestrant in rat (n=3 females), monkey (n=3 females), and human (n=3 females) pooled plasma was determined by equilibrium dialysis for 1 hour at concentrations of 20, 50, 100, 1,000, and 10000 ng/mL.
• Plasma protein binding was not dose or species dependent at the tested concentrations.
• RAD-1901 was 100% protein bound to plasma proteins from rat, monkey, and human plasma at ≥20 ng/mL.</td></tr>
<tr><td>Determination of In Vitro Protein Binding of Elacestrant (RAD1901) in Sprague Dawley Rat, Cynomolgus Monkey, and Human Plasma Using Ultracentrifugation</td><td>The protein binding of RAD-1901 in rat, monkey, and human pooled plasma (n=3/sex/species) was determined by ultracentrifugation for 6 hours, 37°C, at concentrations of 0.2, 2, and 20 µM. Samples were analyzed using LC-MS/MS.
• RAD-1901 bound ≥98% to the proteins in rat, monkey, and human plasma at ≥0.2 µM.</td></tr>
</table>

(Study# 21RAD233)	
Pharmacokinetics, Distribution, Metabolism, and Excretion of ^{14}C-RAD1901 Following Oral Administration to Rats (Study# 19RAD219)	**Rat** Tissue distribution of ^{14}C-RAD1901 was assessed in rats (Sprague Dawley [SD] and Long Evans [LE]) after a single 30 mg/kg oral dose. Tissue distribution was assessed by Quantitative Whole-Body Autoradiography (QWBA). • ^{14}C-RAD-1901-derived radioactivity in male SD and LE rats was quantifiable in the majority of tissues examined, except in the brain, eye lens, spinal cord, and testes (SD rats) where exposures were below the limit of quantitation at all timepoints. • The highest distribution (≥20000 ng/g) of RAD-1901, excluding bile and urine, was observed in the adrenal gland, eye uveal tract (LE rats), liver, lungs, pituitary gland (SD rats), spleen, and thyroid. • The T_{max} was generally observed between 4 and 8 hours post dose.
Metabolism	
In Vitro Biotransformation of ^{14}C-RAD1901 by Rat, Monkey, and Human Hepatocytes (Study# 7801-106)	Primary rat, monkey, and human hepatocytes were incubated with 1 or 10 µM ^{14}C-RAD-1901 for 0, 30, 60, and 120 minutes. Supernatants were analyzed for RAD-1901 by high-performance liquid chromatography with radiochemical detection and its metabolites by liquid chromatography/mass spectrometry (LC/MS). • No human specific metabolites were detected; all human metabolites were observed in monkey hepatocytes. • The remaining parent RAD-1901 (10 µM) was approximately 24% in rat, 33% in monkey, and 53% in human hepatocytes. • N-Dealkylation and glucuronidation were common metabolic pathways in all species.
Pharmacokinetics, Distribution, Metabolism, and Excretion of ^{14}C-RAD1901 Following Oral Administration to Rats (Study# 19RAD219)	**Rat** Metabolites of RAD-1901 were assessed in rats (SD) after a single 30 mg/kg oral dose. • There was an apparent sex difference in the percent of RAD1901 and exposure to its major metabolites. RAD1901 exposure was 21.3% and 53.4% of total plasma radioactivity in male and female rats, respectively. • N-Dealkylated and cleavage metabolite EAEBA (M1) and its acyl-glucuronide conjugate M16 were the most abundant metabolites in plasma. • Plasma exposures for EAEBA (M1) accounted for 28.1% and 8.85% of total plasma radioactivity exposure in male and female rats, respectively. • Plasma exposures of EAEBA glucuronide (M16) accounted for 7.3% and 3.53% of total plasma radioactivity exposure in male and female rats, respectively.
Excretion	
Pharmacokinetics, Distribution, Metabolism, and Excretion of ^{14}C-RAD1901 Following Oral Administration to Rats (Study# 19RAD219)	**Rat** Excretion of ^{14}C-RAD1901 was assessed in rats (SD and LE) after a single 30 mg/kg oral dose. Urine, bile, and feces were analyzed by HPLC, with radiochemical and high-resolution mass spectrometry (HRMS) to quantitate and identify RAD-1901 and metabolites. • Excretion was mainly via feces (≥83%) in intact rats and in feces and bile (>40%) in bile duct-canulated rats, and to a lesser extent in urine (≤10%). • The majority of the administered dose was excreted within 48-hours post dose.
TK data from general toxicology studies 26-Week Toxicity and Toxicokinetics Oral Gavage	**Rat** Dosing schedule: once daily

Study with RAD1901 in Rats with a 4-Week Recovery Phase (Study # 15RAD215)

Drug/Exposure Relationship: C_{max} and AUC_{0-24} generally increased greater than dose proportionally with 1.5 to 2.4-fold higher exposures in females compared to males upon repeated dosing
Accumulation: 1.3 to 2.4x (Day 88 vs. Day 1) and 1.5 to 3.1x (Day 178 vs. Day 1); accumulation ratios higher in females correlating to the higher exposures observed in females
$T_{1/2}$ and/or T_{max}: 5.75 to 12 hours ($T_{1/2}$; Day 1), and 2 to 6 hours (T_{max}) independent of dose

Mean plasma TK parameters of elacestrant in rat (26-week dosing)

Study Day	Dose (mg/kg)	Sex	C_{max} (ng/mL)	C_{max} Ratio	AUC_{0-24} (ng.h/mL)	AUC_{0-24} Ratio
Day 1	10	M	46.8	1.0	546	1.0
		F	54.8	1.0	782	1.0
	25	M	184	3.9	2180	4
		F	163	3	2100	2.7
	50	M	447	10	4370	8
		F	505	9.2	5700	7.3
Day 88	10	M	115	1.0	942	1.0
		F	173	1.0	1500	1.0
	25	M	266	2.3	2840	3
		F	399	2.3	4970	3.3
	50	M	323	2.8	5570	5.9
		F	653	3.8	11500	7.7
Day 178	10	M	125	1.0	1180	1.0
		F	190	1.0	1890	1.0
	25	M	275	2.2	3800	3.2
		F	415	2.2	6460	3.4
	50	M	414	3.3	6470	5.5
		F	982	5.2	13600	7.2

13-Week Oral Gavage Toxicity and Toxicokinetic Study with RAD-1901 in Rats with a 4-Week Recovery Phase (Study# 7801-130)

Rat
Dosing schedule: once daily
Drug/Exposure Relationship: C_{max} increased dose proportionally and AUC_{0-24} greater than dose proportionally with approximately 2-fold higher exposures in females compared to males
Accumulation: 1.2 to 1.7x (Day 90 vs. Day 1)
$T_{1/2}$ and/or T_{max}: 3.5 to 6 hours ($T_{1/2}$; Day 1), and 2 to 12 hours (T_{max}) independent of dose

Mean plasma TK parameters of elacestrant in rat (13-week dosing)

Study Day	Dose (mg/kg)	Sex	C_{max} (ng/mL)	C_{max} Ratio	AUC_{0-24} (ng.h/mL)	AUC_{0-24} Ratio
Day 1	20	M	85.3	1.0	788	1.0
		F	114	1.0	1270	1.0
	50	M	215	2.5	2558	3.2
		F	277	2.4	4379	3.4
	100	M	523	6.1	6888	8.7
		F	588	5.2	9889	7.8
Day 90	20	M	78.5	1.0	1099	1.0
		F	157	1.0	2176	1.0
	50	M	217	2.8	3259	3
		F	411	2.6	6592	3
	100	M	435	5.5	7934	7.2
		F	852	5.4	13231	6

39-Week Toxicity and Toxicokinetic Oral Gavage Study with RAD1901 in Cynomolgus Monkeys with a 4-Week Recovery Phase (Study#15RAD216)

Monkey
Dosing schedule: once daily
Drug/Exposure Relationship: C_{max} and AUC_{0-24} generally increased greater than dose proportionally, with no apparent gender differences
Accumulation: ≤1.7x (Day 89 vs. Day 1) and ≤1.3x (Day 270 vs. Day 1)
$T_{1/2}$ and/or T_{max}: 8 to 11 hours ($T_{1/2}$; Day 1), approximately 3 to 6 hours (T_{max})

Mean plasma TK parameters of elacestrant in monkey (39-week dosing)

Study Day	Dose (mg/kg)	Sex	C_{max} (ng/mL)	C_{max} Ratio	AUC_{0-24} (ng.h/mL)	AUC_{0-24} Ratio
Day 1	10	M	38.4	1.0	518	1.0
		F	40.6	1.0	527	1.0
	20	M	118	3.1	1650	3.2
		F	97	2.4	1270	2.4
	30	M	228	5.9	3120	6
		F	214	5.3	3080	5.8
Day 89	10	M	47.1	1.0	731	1.0
		F	69.7	1.0	886	1.0
	20	M	134	2.8	1920	2.6
		F	101	1.5	1480	1.7
	30	M	245	5.2	3780	5.2
		F	257	3.7	4110	4.6
Day 270	10	M	44.6	1.0	645	1.0
		F	49	1.0	700	1.0
	20	M	111	2.5	1910	3
		F	105	2.1	1640	2.3
	30	M	152	3.4	2840	4.4
		F	211	4.3	3520	5

13-week Nasogastric Intubation Toxicity and Toxicokinetic Study in Monkeys with a 4-week Recovery Phase (Study#7801-134)

Monkey
Dosing schedule: once daily
Drug/Exposure Relationship: C_{max} and AUC_{0-24} generally increased dose proportionally, with no apparent gender differences
Accumulation: ≤1.3x (Day 90 vs. Day 1)
$T_{1/2}$ and/or T_{max}: 8 to 11 hours ($T_{1/2}$; Day 1), approximately 2 to 8 hours (T_{max})

Mean plasma TK parameters of elacestrant in monkey (13-week dosing)

Study Day	Dose (mg/kg)	Sex	C_{max} (ng/mL)	C_{max} Ratio	AUC_{0-24} (ng.h/mL)	AUC_{0-24} Ratio
Day 1	10	M	80.5	1.0	823	1.0
		F	52.6	1.0	671	1.0
	20	M	162	2	1956	2.4
		F	111	2.1	1582	2.4
	30	M	296	3.7	3838	4.7
		F	168	3.2	2562	3.8
Day 90	10	M	61.9	1.0	775	1.0
		F	79.1	1.0	914	1.0
	20	M	131	2.1	1882	2.4
		F	135	1.7	2099	2.3
	30	M	253	4	4124	5.3
		F	239	3	3250	3.6

TK data from reproductive toxicology studies
An Oral Gavage Embryo-Fetal Developmental

Rat
Dosing schedule: once daily
Drug/Exposure Relationship: C_{max} and AUC_{0-24} generally increased greater than dose proportionally

<table>
<tr>
<td>Toxicity and Toxicokinetic Study of RAD1901 (Elacestrant) in Crl:CD (SD) Rats (Study#19RAD230)</td>
<td>Accumulation: Minimal, 1.5 to 2x (GD 17 vs.GD 6)
$T_{1/2}$ and/or $T_{max:}$ 4 to 8 hours (T_{max})

Mean TK parameters of elacestrant in maternal rat plasma
<table>
<tr><th>Study Day</th><th>Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>T_{max} (h)</th><th>AUC_{0-24} (ng.h/mL)</th><th>$T_{1/2}$ (h)</th></tr>
<tr><td rowspan="3">GD 6</td><td>3</td><td>9.67</td><td>8</td><td>121</td><td>NR</td></tr>
<tr><td>10</td><td>40.2</td><td>8</td><td>600</td><td>NR</td></tr>
<tr><td>30</td><td>181</td><td>8</td><td>2750</td><td>NR</td></tr>
<tr><td rowspan="3">GD 17</td><td>3</td><td>13.2</td><td>4</td><td>188</td><td>NR</td></tr>
<tr><td>10</td><td>76.3</td><td>4</td><td>1220</td><td>8.72</td></tr>
<tr><td>30</td><td>299</td><td>8</td><td>5110</td><td>NR</td></tr>
</table>
GD: gestational day; NR: not reported due to inability to calculate the elimination phase

Note: On GD 6 and 17, the 0.3 mg/kg/day group received approximately 54% to 79% of the intended dose and the concentrations were generally below the lower limit of quantitation (<5.00 ng/mL); therefore, the group was excluded from the TK analysis. No assessments were made in amniotic fluid or fetal serum.</td>
</tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position

Integration of multiple toxicology studies demonstrates that elacestrant was generally well tolerated at doses and exposure levels that exceeded the anticipated therapeutic levels in humans.

Single-Dose Toxicity Studies

Single-dose oral toxicity studies have been conducted in Sprague-Dawley female rats at doses up to 1200 mg/kg and in female cynomolgus monkeys at doses up to 500 mg/kg.
In 2 single-dose studies in female rats, the oral maximum tolerated dose (MTD) was 900 mg/kg (GLP Study 7801-113; 7801-111). There were elacestrant-related clinical observations at > 900 mg/kg, body weight decreases at > 600 mg/kg, clinical pathology changes at > 100 mg/kg, thus the NOAEL was set at 100 mg/kg.
In the single escalating-dose monkey study, the oral MTD was > 500 mg/kg (GLP Study 7801-112). No adverse finding was recorded following a single IV dose (MTD at 0.85 mg/kg) in monkeys (GLP Study 7801-136).

Repeat-Dose Toxicity Studies

Elacestrant has been dosed up to 26 weeks in rats (GLP studies 7801-114, 16RAD206, 7801-130, and 15RAD215) and up to 39 weeks in monkeys (GLP studies 7801-115, 7801-134, and 15RAD216) in repeat-dose toxicity studies. Initial studies were performed in female animals only, but a 28-day rat study and all longer-duration toxicity studies in rats and monkeys included both sexes of animals to reflect clinical use that will include both men and women.

Overall, the most relevant toxicological effects were adverse macroscopic and microscopic findings (atrophy of uterus, vagina and cervix and ovary cysts) in female reproductive organs at

all drug doses in both rats and monkeys that were consistent with the exaggerated pharmacology of elacestrant. Regarding the atrophy of the uterus, vagina, and cervix observed in both rats and monkeys, this finding has been considered adverse due to the important physiological consequences, but the relevance for the target patient population of elacestrant (i.e., postmenopausal women) is minimal because these women have already lost reproductive function. Likewise, the relevance of rodent granulosa benign ovary cell tumors observed in the 26-week rat study at doses ≥ 25 mg/kg (2-fold the human exposure based on the AUC) is questionable because this effect is due by the endocrine perturbation caused by the interruption of the feedback in the hypothalamic pituitary-ovarian axis in reproductively active animals. Therefore, this potential concern associated with chronic treatment using elacestrant is not applicable to the target patient population.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The single dose toxicity studies were not reviewed since the Applicant provided repeat dose toxicology studies in rats and monkeys of up to 26 and 39 weeks, respectively.

Data (presented by the FDA):

Study/ID: 26-Week Toxicity and Toxicokinetics Oral Gavage Study with RAD-1901 in Rats with a 4-Week Recovery Phase/15RAD215

- The major clinical sign was clear oral discharge at 50 mg/kg that correlated with excessive salivation at ≥25 mg/kg during the central nervous system assessment.
- Hematology changes included increased RBC parameters, prothrombin time, neutrophils, decreased platelets and reticulocytes. Clinical chemistry changes included increased ALP, phosphorous, potassium, chloride, decreased glucose, total protein, albumin, A/G ratio, cholesterol, triglycerides, calcium. Changes were reversible.
- Major target organs included the femur, lung, mesenteric lymph node, and female reproductive organs at ≥10 mg/kg, mammary gland and stomach at ≥25 mg/kg, and testis at 50 mg/kg. Findings were generally reversible or showed recovery trends, except in the femur.

GLP compliance: Yes; except characterization and stability of the test article

Methods:

Dose:	0, 10, 25, or 50 mg/kg
Frequency of dosing:	Once daily for 182 days
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	Main: 10/sex/group Recovery: 5/sex (control and high dose groups)
Age:	6 to 7 weeks
Satellite groups/unique design:	TK: 3/sex (control) or 9/sex/treatment group

Deviation from study protocol affecting interpretation of results:	No

Observations and Results: Changes from control

Parameters	Major findings
Mortality	There were no RAD-1901 related early deaths. Early deaths (moribundity or found dead) occurred in one control male, one male given 10 mg/kg, two females given 10 mg/kg (one main and one TK animal), and one male given 25 mg/kg (TK animal) between Days 88 and 182. The unscheduled deaths were unlikely to be test article related due to death in the control group, death following blood collection attributed to the procedure, or death of unknown cause due to lack of similar histopathology findings in surviving animals at higher doses.
Clinical Signs	Oral discharge in 2/15 males and 1/15 females given 50 mg/kg on one to four occasions during dosing; the observations correlated to excessive salivation noted during the neurotoxicity assessment. Whole body twitching was noted in 1/5 males and irregular breathing in 1/5 females given 50 mg/kg during recovery; there were no clinical or histopathology correlates.
Body Weights	Males - Decreased mean body weight (up to -23%) and mean body weight gain (up to -34%) at ≥10 mg/kg compared to control beginning Day 29 of dosing. The decrease in mean body weight gain correlated to decreased mean food consumption (up to -23%) compared to control beginning week 3 of dosing. Findings were reversible. Females - Transient decrease in mean body weight (up to -19%) and mean body weight gain (up to -43%) at 10 mg/kg compared to control. The decrease in mean body weight gain correlated to transient decrease in mean food consumption (up to -17%) compared to control. Findings were reversible.
Ophthalmoscopy	Timepoint: Pre-test and Week 26 of dosing (recovery observations were not conducted due to lack of findings at the end of the dosing phase) Unremarkable
Neurological Assessment (Functional Observational Battery)	Timepoint: Week 25 of dosing and Day 25 of recovery

Functional observational battery

Dose mg/kg	0		10		25		50	
Sex	M	F	M	F	M	F	M	F
No. Animals T	14	15	10	9	10	10	15	15
R	5	5	0	0	0	0	5	5
Impaired righting reflex							1	
Excessive salivation					5	1	3	1
Audible respiration								1/1R
Hunched posture					1	1		1
	Percent Deviation from Control							
Forelimb grip strength average			-13		-13		-7/**-20R**	
Hindlimb grip strength average			-17		-6		-11/**-24R**	
Foot splay average							-17/-21R	

T: treatment; R: recovery; Blank: no related findings; **value: p≤0.05**

The decreased grip strength was attributed to the decreased body weights. Per the Applicant, the microscopic observation of increased trabecular bone noted in males may have also contributed to the decreased grip strength in these animals.

Hematology | Timepoint: Days 88 and 183 of dosing and end of recovery

Hematology, percent deviation from control

Dose (mg/kg)		10		25		50	
Sex		M	F	M	F	M	F
No. Animals T		10*	10*	10	10	15	15
R		0	0	0	0	5	5
	Day 88		**11**		**11**		**9**
Red blood cells	Day 183		**10**		**8**		**10**
	Day 88		**9**		**8**		**4**
Hemoglobin	Day 183		**10**		**7**		**6**
	Day 88		**11**		**10**		**7**
Hematocrit	Day 183		**12**		**9**		**7**
	Day 88	**-15**		**-22**		**-25**	-13
Reticulocytes	Day 183	-15		**-20**		**-25**	-13
	Day 88	**-5**		**-5**		**-4**	**-2**
MCV	Day 183						**-3**
	Day 88	**-4**		**-4**		**-4**	**-4**
MCH	Day 183						**-4**
	Day 88						**-2**
MCHC	Day 183		**-2**		**-2**		**-2**
Platelets	Day 88		**-21**	-6	**-28**	-5	**-15**
	Day 88				26		**78**
Neutrophils	Day 183						**109**
	Day 88	**-33**		**-33**		**-27**	
	Day 183	**-41**		**-41**		**-29**	
Eosinophils	Recovery	-		-		**-67**	
	Day 88	**13**	**3**	**11**	**8**	**7**	**8**
PT	Day 183	**11**	**11**	**9**	**18**	**7**	**21**

T: treatment; R: recovery; Blank: unremarkable; "-"not applicable; "value" not significant;
"value" p≤0.05; *N=9 on Day 183 due to early death

Clinical Chemistry | Timepoint: Days 88 and 183 of dosing and end of recovery

Clinical chemistry, percent deviation from control

Dose (mg/kg)		10		25		50	
Sex		M	F	M	F	M	F
No. Animals T		10*	10*	10	10	15	15
R		0	0	0	0	5	5
	Day 88		**108**	**22**	**116**	**18**	**119**
ALP	Day 183		**178**		**174**		**183**
	Day 88						-9
Glucose	Day 183				**-15**		**-13**
	Day 88		**-13**		**-12**		**-16**
Total Protein	Day 183		**-16**		**-15**	**-6**	**-18**
	Day 88		**-21**		**-20**	**-5**	**-25**
	Day 183		**-26**		**-26**	-5	**-29**
Albumin	Recovery	-	**-**	**-**	**-**		**-11**
	Day 88		**-24**		**-24**		**-24**
	Day 183		**-30**		**-35**		**-35**
Albumin/globulin	Recovery	-	**-**	**-**	**-**		**-20**
	Day 88	**-71**	**-30**	**-71**	**-54**	**-61**	**-55**
Cholesterol	Day 183	**-68**	**-42**	**-72**	**-51**	**-62**	**-53**
	Day 88		-39	-15	-38	-26	-23
	Day 183		-22	-7	-18	-29	-18
Triglycerides	Recovery					-19	-41
	Day 88					-13	
Urea nitrogen	Day 183					**-23**	
Creatinine	Day 183	**-17**		**-17**		**-17**	
	Day 88	**-3**	**-7**	**-3**	**-7**	-3	**-5**
	Day 183		**-8**		**-8**		**-7**
Calcium	Recovery	-	**-**	**-**	**-**		**-3**
	Day 88		7		7		12
Phosphorous	Day 183		**16**		**16**		**17**
	Day 88						9
Potassium	Day 183				**10**		**14**
Sodium	Day 183		**2**		**2**		**1**
Chloride	Day 183		**2**		**2**		**3**

T: treatment; R: recovery; Blank: unremarkable; "-"not applicable; "value" not significant;
"value" p≤0.05; *N=9 on Day 183 due to early death

Urinalysis

Timepoint: Days 88 and 183 of dosing and end of recovery
Unremarkable

Gross Pathology

Gross pathology findings

Dose mg/kg	0		10		25		50	
Sex	M	F	M	F	M	F	M	F
No. Animals T	9	10	9	9	10	10	10	10
R	5	5	0	0	0	0	5	5
D	1	0	1	1	0	0	0	0
Ovary								
-cyst	-		-	1	-	4	-	5/1R
-enlarged	-		-	1	-		-	1
Uterus								
-small	-		-	1	-		-	2

T: treatment; R: recovery; D: early death; Blank: no related findings; "-": not applicable

Organ Weights

Organ weight changes, percent deviation from control

Dose (mg/kg)		10		25		50	
Sex		M	F	M	F	M	F
No. Animals T		9	9	10	10	10	10
R		0	0	0	0	5	5
Terminal Body Weight		**-19**	-8	**-22**	-3	**-24/-16R**	3
Kidney*	*Abs.*	**49**		**27**		12	
	TBWT	**84**		**64**		**48**	
	Br.WT	**51**		**32**		15	
Pituitary gland*	*Abs.*	**-22**	**-39**	-17	**-49**	**-31/-18R**	**-46**
	TBWT		**-32**		**-47**		**-47**
	Br.WT	**-21**	**-39**	-15	**-50**	**-29/**-11R	**-46**
Salivary gland*	*Abs.*	-13		**-19**		**-19/-27R**	
	TBWT					-13R	
	Br.WT	-11		**-16**		**-17/-21R**	
Ovary	*Abs.*	-	**56**	-	**60**	-	**187/81R**
	TBWT	-	**68**	-	**64**	-	**180/81R**
	Br.WT	-	**54**	-	**54**	-	**187/80R**
Uterus	*Abs.*	-	**-67**	-	**-70**	-	**-69/-40R**
	TBWT	-	**-63**	-	**-69**	-	**-69/-40R**
	Br.WT	-	**-67**	-	**-71**	-	**-68/-40R**

Abs.=absolute; Adj. TBWT=adjusted to terminal body weight; Adj. Br. WT = adjusted to brain weight; T: treatment; R: recovery; Blank: unremarkable; "-"not applicable; "value" not significant; **"value" p≤0.05**; *no microscopic correlates

Histopathology
Adequate battery: Yes
Peer Review: Yes

Microscopic findings are summarized in the table below.

Microscopic findings

Dose mg/kg	0		10		25		50	
Sex	M	F	M	F	M	F	M	F
No. Animals T	9	10	9	9	10	10	10	10
R	5	5	0	0	0	0	5	5
D	1	0	1	1	0	0	0	0
Femur								
Trabecular bone, alteration								
Minimal				2		7		
Slight		1R		3		3		9/5R
Trabecular bone, increased								
Minimal	1		3		5		5/3R	
Kidney								
Tubule mineralization								
Minimal		2/3R	5/1D	9	6	7	6/3R	7/5R
Slight		1/1R	3		2		3/2R	
Moderate			1					
Lung								
Fibrosis, interstitium								
Minimal								1
Pigment								
Minimal								1
Infiltrate, macrophages, alveolus								
Minimal	1		4	1	2	2	1	3
Slight				1		1		1
Moderate				1				
Stomach, glandular								
Granulocytes, increased								
Minimal	1	1			4	3	6	3
Slight							1	1
Stomach, non-glandular								
Vacuolation, increased								
Minimal	1	1/1R			5	4	5	3
Slight					1		4	3
Mesenteric lymph node								
Macrophage aggregates								
Minimal	5/1D	6/1R	1	1/1D		1		
Slight	3/3R	3/3R	5	4	5	5	1R	4
Moderate	2R		2	4	5	4	2/4R	4/2R
Marked							8	2/3R
Mammary gland								
Hyperplasia/hypertrophy, alveolar								
Minimal	-		-		-	4	-	3
Slight	-		-		-	1	-	5
Moderate	-		-		-		-	1
Spinal cord								
Hemorrhage								
Slight							1	
Cervix								
Atrophy								
Minimal	-		-	2	-	2	-	
Slight	-		-	5/1D	-	5	-	5
Moderate	-		-		-	2	-	5
Mucification, increased, epithelium								
Minimal	-		-	2	-		-	
Slight	-		-	3/1D	-	6	-	3
Moderate	-		-	2	-	2	-	7

Ovary							
Cyst, follicle							
Minimal	-	5/1R	-		-		-	3/1R
Slight	-		-	2	-	1	-	2R
Moderate	-		-	3	-	4	-	3/1R
Marked	-		-	2	-		-	2
Corpora lutea, decreased							
Slight	-	1R	-	1	-		-	3
Moderate	-	1	-	4/1D	-	4	-	1
Marked	-	4/2R	-	2	-	6	-	6/1R
Hyperplasia, granulosa cell							
Minimal	-		-	1	-		-	1
Slight	-		-	1	-		-	2
Moderate	-		-		-		-	1
Marked	-		-	1D	-	1	-	1
B-granulosa cell tumor	-		-		-	5	-	5/1R
B-luteoma	-		-		-		-	1
Uterus							
Atrophy							
Slight	-		-		-		-	3R
Moderate	-		-	4	-	2	-	1/2R
Marked	-		-	5/1D	-	8	-	9
Vagina							
Atrophy							
Minimal	-		-	2	-	2	-	
Slight	-		-	5/1D	-	5	-	5
Moderate	-		-		-	2	-	5
Mucification, increased, epithelium							
Minimal	-		-	4	-	1	-	
Slight	-		-	2/1D	-	4	-	3
Moderate	-		-	1	-	2	-	7
Testis							
Cellularity, decreased, interstitial Leydig cells							
Minimal		-		-		-	7	-
Degeneration/Atrophy, seminiferous epithelium							
Minimal		-		-		-	2/1R	-
Hemorrhage							
Marked		-		-		-	1R	-

T: treatment; R: recovery; D: early death; Blank: unremarkable; "-" not applicable
Note: Only early death observations that were also noted in surviving animals is included in the table.

Study/ID: 39-Week Toxicity and Toxicokinetic Oral Gavage Study with RAD1901 in Cynomolgus Monkeys with a 4-Week Recovery Phase/15RAD216

- Clinical observations of excessive salivation at 30 mg/kg.
- Reversible clinical chemistry changes of increased liver enzymes (ALT/AST) at ≥20 mg/kg.
- Target organs included the small and large intestine, mesenteric lymph node, and pituitary gland with general findings of increased macrophage and/or neutrophilic infiltrates, and female reproductive organs with findings of atrophy, ovarian follicular cysts and increased ovarian stroma.

GLP compliance: Yes; except characterization and stability of test article

Methods

Dose:	0, 10, 20, or 30 mg/kg
Frequency of dosing:	Once daily for 273 days
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	Main: 4/sex/group Recovery: 2/sex (control and high dose groups)
Age:	31 to 36 months old
Satellite groups/ unique design:	Not applicable
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: Changes from control

Parameters	Major findings
Mortality	All animals survived to their scheduled necropsy.
Clinical Signs	Excessive salivation was observed in animals given 30 mg/kg between Days 103 and 143 at one timepoint in 1/6 males and one to four times in 3/6 females. Low food consumption was observed across all groups, including control, affecting similar number of animals; however, in females given ≥20 mg/kg low food consumption was observed more frequently (14 to 47 times during dosing) compared to males (≤8 times during dosing).
Body Weights	Unremarkable
Ophthalmoscopy	Timepoint: Pre-test and Day 268 of dosing (recovery observations were not conducted due to lack of findings at the end of the dosing phase) Unremarkable
ECG	Timepoint: Pre-test, Days 4 and 271 of dosing, and Day 25 of recovery at 4 to 6 hours post-dose Unremarkable
Neurological Assessment (Functional Observational Battery)	Timepoint: Days 176 and 269 of dosing Unremarkable
Hematology	Timepoint: pre-test, Days 88 and 274 of dosing, and Day 29 of recovery Unremarkable
Clinical Chemistry	Timepoint: pre-test, Days 88 and 274 of dosing, and Day 29 of recovery

Clinical chemistry, percent deviation from control

Dose (mg/kg)		10		20		30	
Sex		M	F	M	F	M	F
No. Animals T		4	4	4	4	6	6
R		0	0	0	0	2	2
AST	Day 88				**46**	55	**71**
	Day 274				58	24	81
ALT	Day 88			51	29	**97**	**134**
	Day 274			60	48	**72**	**141**

T: treatment; R: recovery; Blank: unremarkable; "value" not significant**; "value" p≤0.05**

Urinalysis

Timepoint: pre-test, Days 88 and 274 of dosing, and Day 29 of recovery

Generally unremarkable. Decreased pH was observed on Day 274 in males given 30 mg/kg (pH 6) compared to control (pH 7.4) and baseline (pH 7.8).

Gross Pathology

Gross pathology findings

Dose mg/kg	0		10		20		30	
Sex	M	F	M	F	M	F	M	F
No. Animals T	4	4	4	4	4	4	4	4
R	2	2	0	0	0	0	2	2
Colon								
-discolored							1	
Mesenteric lymph node								
-discolored					1	1	1	2
Ovary								
-cyst	-		-	1	-	1	-	1
-discolored	-		-		-	1	-	
-large	-		-		-	2	-	1

T: treatment; R: recovery; Blank: no related findings; "-": not applicable

Organ Weights

Organ weights, percent deviation from control

Dose (mg/kg)		10		20		30	
Sex		M	F	M	F	M	F
No. Animals T		4	4	4	4	4	4
R		0	0	0	0	2	2
Pituitary gland	*Abs.*	10		12		27	
	TBWT					20	
	Br.WT	11		15		28	
Ovary	*Abs.*	-	**464**	-	**464**	-	**1163/77R**
	TBWT	-	**359**	-	**456**	-	**1180/85R**
	Br.WT	-	**440**	-	**475**	-	**1118/77R**
Uterus	*Abs.*	-	**-63**	-	-45	-	-52/-23R
	TBWT	-	**-66**	-	-46	-	-52/-20R
	Br.WT	-	**-64**	-	-45	-	-53/-25R

Abs.=absolute; Adj. TBWT=adjusted to terminal body weight; Adj. Br. WT = adjusted to brain weight; T: treatment; R: recovery; Blank: unremarkable; "-"not applicable; "value" not significant**; "value" p≤0.05**

Histopathology
Adequate battery: Yes
Peer Review: Yes

Microscopic findings

Dose mg/kg	0		10		20		30	
Sex	M	F	M	F	M	F	M	F
No. Animals T	4	4	4	4	4	4	4	4
R	2	2	0	0	0	0	2	2
Adrenal cortex								
Extramedullary hematopoiesis								
Minimal						1		
Hyperplasia								
Minimal							1	
Hypertrophy								
Minimal								1
Duodenum								
Erosion								
Minimal							1	
Infiltrate, macrophage, vacuolated								
Minimal						2	2	3
Infiltrate, neutrophils								
Minimal							1/1R	
Hemorrhage								
Minimal							1R	
Pigment								
Minimal	1						3	3
Ileum								
Infiltrate, macrophage, vacuolated								
Minimal	1				1	2	2	4
Slight							1	
Jejunum								
Infiltrate, macrophage, vacuolated								
Minimal					2	2	3	2
Slight							1	2
Infiltrate, neutrophils								
Minimal							1	
Colon								
Hemorrhage								
Minimal							2	
Infiltrate, neutrophils								
Minimal							1	1
Mesenteric lymph node								
Infiltrate, macrophages, pigmented								
Minimal					3	1	1	2
Slight					1	2	3/1R	1/1R
Moderate								1/1R
Pituitary gland								
Basophilic pituicytes, increased								
Minimal	1				1			
Slight					3			
Mammary gland								
Atrophy								
Minimal	-	1	-	2	-	1	-	2/1R
Slight	-		-	2	-	3	-	2/1R
Mandibular salivary gland								
Atrophy								
Minimal							1	
Cervix								
Atrophy								
Slight	-		-	2	-	1	-	
Moderate	-		-	1	-	2	-	3
Marked	-		-	1	-	1	-	1
Lumen, exudate								
Minimal	-		-	1	-	3	-	2/2R
Slight	-		-		-		-	1
Ovary								
Cyst, follicle								

Present	-	-	4	-	4	-	4
Stroma, increased							
Minimal	-	-	1	-	1	-	1
Slight	-	-	1	-	2	-	1R
Moderate	-	-		-	1	-	
Marked	-	-		-		-	1
Severe	-	-		-		-	1/1R
Uterus							
Atrophy							
Slight	-	-	4	-	2	-	1
Moderate	-	-		-	2	-	3
Vagina							
Atrophy							
Slight	-	-	1	-		-	
Marked	-	-	1	-	1	-	
Severe	-	-	2	-	3	-	4

T: treatment; R: recovery; Blank: unremarkable; "-" not applicable

General toxicology; additional studies

GLP-compliant 4- and 13-week daily oral repeat dose toxicology studies were conducted in rats and monkeys (only female monkeys in the 4-week study). The 13-week studies in rats and monkeys were initially reviewed by the FDA under IND 124748. The main findings are summarized below and generally reflect those observed in the GLP-compliant 26-week (rat) and 39-week (monkey) studies.

Study/ID: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with RAD-1901 in Rats with a 4-Week Recovery Phase/7801-130 (GLP)

Dosing: Sprague Dawley rats (main: n=10/sex/group; recovery: n=5/sex control and high dose) were administered RAD-1901 (lot# 01RAD07-05-38, 98.6% purity) once daily via oral gavage at 0, 20, 50, or 100 mg/kg for 13 weeks followed by a 4-week recovery period for control and high dose groups.

Results: The following were noted:

- Early deaths occurred in one female and one male given 100 mg/kg on Day 69 and 87, respectively; additionally, early deaths occurred among the toxicokinetic group in three males and one female given 100 mg/kg on Days 23, 35, and 83. The cause of death was not specified in the report, but animals were generally moribund with hunched posture, abnormal breathing, and rough/discolored haircoat.
- Clinical signs in early death and surviving animals included abnormal feces at all doses, abnormal respiration (audible, labored, or irregular) and rough/discolored hair coat at ≥50 mg/kg, and clear oral discharge at 100 mg/kg.
- In males at all doses, reversible mean body weight and body weight gain were up to -23% and up to -40% lower compared to control, respectively. In females at the low dose, non-statistically significant mean body weight and body weight gain was up to -14% and up to -30% lower compared to control, respectively. Decreased food consumption reflected the decreased body weight changes.
- Reversible hematology changes included ≤10% non-dose dependent increase in red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and approximately 14% increase in

prothrombin time in females; at the high dose in both sexes, <200% increase in white blood cells (neutrophils, monocytes), and ≤20% increase in platelets.
- Clinical chemistry changes generally at all doses included <-50% decrease in glucose, cholesterol, total protein, albumin, albumin/globulin ratio, calcium, and increased ALP and ALT (males). At the high dose, increased AST, phosphate (females) and potassium (females), and decreased urine pH (males). Changes generally demonstrated partial or full recovery.
- The major target organs were the mesenteric lymph node, spleen, lung, small and large intestine, and female reproductive organs. Findings were generally in animals given the high dose, except in female reproductive organs that were affected at all doses.
    - Mesenteric lymph node: up to moderate histiocytic and foamy macrophage infiltrates
    - Spleen: up to slight foamy macrophage infiltrates in marginal zone of splenic follicle
    - Lung: alveolar histiocytosis
    - Small intestine (duodenum, ileum, jejunum): up to slight chronic active inflammation/necrosis and up to moderate foamy macrophage infiltrates in the lamina propria
    - Colon: foamy macrophage infiltrate
    - Ovary: observed macroscopically as large with correlative increase in organ weight and microscopic observations of cystic follicles
    - Uterus: observed macroscopically as small with correlative decrease in organ weight and microscopic observations of up to moderate atrophy
    - Cervix and vagina: up to moderate atrophy
    - Findings were either fully reversible or showed a recovery trend.

Study/ID: RAD1901: 4-Week Oral Gavage Toxicity and Toxicokinetic Study in Rats/ 16RAD206 (GLP)

Dosing: Sprague Dawley rats (n=10/sex/group) were administered RAD-1901 (lot# 16-01601-01, 97.5% purity) once daily via oral gavage at 0, 20, 50, or 120 mg/kg for 28 days without a recovery period.

Results: The following were noted:
- Early deaths occurred at 120 mg/kg; two females were found moribund with abnormal breathing on Day 15 and 18, and one male was found dead on Day 25. The cause of death was undetermined; histopathology findings reflected those observed in surviving animals.
- In males at all doses, mean body weight and body weight gain were up to -23% and up to -45% lower compared to control, respectively, with statistically significant differences observed by Day 15 of dosing. In females at 120 mg/kg, statistically significant lower mean body weight and body weight gain of up to -10% and up to -43% compared to control, respectively, was observed during the second and third week of dosing. Decreased food consumption, up to -28% (males) and up to -24% (females) compared to control, reflected the decreased body weight changes.
- Hematology changes at 120 mg/kg/day included ≤8% increase in red blood cell parameters (erythrocytes, hemoglobin, hematocrit), up to 9% non-dose dependent increase in prothrombin time, and ≤65% increase in white blood cells including neutrophils, monocytes,

and lymphocytes with the largest increase (up to +300% compared to control) in neutrophils.

- Clinical chemistry changes were generally noted in females at all doses and at the high dose in males including decrease in total protein (up to -17%), albumin and A/G ratio (up to -31%), cholesterol (up to -58%), calcium (up to -5%), urea nitrogen (-13% in high dose females), increase in ALP (up to 63%), AST (up to 48%) and ALT (up to 45%) in females.
- The major target organs were the mesenteric lymph node, spleen, liver, lung, small intestine, and female reproductive organs. Findings were generally in males given the high dose and females given the mid and high dose, except in female reproductive organs that were affected at all doses.
    - Mesenteric lymph node: up to moderate vacuolated sinus macrophages
    - Spleen: up to slight vacuolated histiocytes (HD females)
    - Liver: up to slight vacuolation in epithelial cells of bile duct
    - Lung: up to slight alveolus vacuolated macrophage infiltrates
    - Small intestine (duodenum, ileum, jejunum): up to slightly increased vacuolated macrophages in the villus
    - Ovary: observed macroscopically as cysts present with correlative increase in organ weight and microscopic observations of up to marked cystic follicles
    - Uterus: decreased organ weight and microscopic observations of up to moderate atrophy

Study/ID: 13-Week Nasogastric Intubation Toxicity and Toxicokinetics Study with RAD-1901 in Cynomolgus Monkeys with a 4-Week Recovery Period/7801-134 (GLP)

Dosing: Cynomolgus monkeys (main: n=3/sex/group; recovery: n=2/sex control and high dose) were administered RAD-1901 (lot# 01RAD07-05-38, 98.6% purity) once daily via nasogastric intubation at 0, 10, 20, or 30 mg/kg for 13 weeks followed by a 4-week recovery period for control and high dose groups.

Results: The following were noted:

- There were no early mortalities, or elacestrant-related clinical observations, body weight, ophthalmoscopy, or ECG changes.
- Non-statistically significant dose dependent decrease in white blood cells up to -20%.
- Non-statistically significant dose dependent increase in ALT, and decrease in total protein, GGT, and globulin in males.
- The major target organs were the salivary and mammary glands, and female reproductive organs observed at all doses.
    - Salivary gland: slight atrophy in acinar cells (observed in one high dose male)
    - Mammary gland: mild to slight hypertrophy or hyperplasia (increased numbers of mammary ducts)
    - Ovary: observed macroscopically as large with correlative increase in organ weight and microscopic observations of cystic follicles
    - Uterus: decreased organ weight with microscopic correlates of mild to slight endometrial atrophy
    - Cervix and vagina: minimal to moderate atrophy

- Findings were either fully reversible or showed a recovery trend.

Study/ID: 28-Day Gavage Toxicity and Toxicokinetic Study with RAD-1901 in Cynomolgus Monkeys with a 2-Week Recovery Phase/7801-115 (GLP)

Dosing: Female cynomolgus monkeys (main: n=3/group; recovery: n=2 control and high dose) were administered RAD-1901 (lot# 01RAD07-03-38, 97.2% purity) once daily via oral gavage at 0, 20 or 50 mg/kg for 29 days and 100 mg/kg for 15 days followed by a 2- or 4-week recovery period for control and high dose groups, respectively.
Results: The following were noted:

- Early death due to moribundity in three females given 100 mg/kg on Day 13 or 15. Additionally, one female given 50 mg/kg was sacrificed on Day 27 due to moribundity. Clinical signs leading to moribundity, also generally noted in surviving animals at ≥20 mg/kg, included body weight loss, decreased food consumption, excessive salivation, vomitus, and/or liquid/non-formed feces. Microscopic findings in early decedent(s) included multi-organ (kidney, liver, gallbladder, large intestine, cervix) vasculitis and/or perivasculitis in one animal dosed at 100 mg/kg and atrophy in the thymus.
- No changes in body weight in surviving animals, ophthalmoscopy, or ECG parameters.
- Hematology changes generally at ≥50 mg/kg included decrease in RBC parameters (erythrocytes, hemoglobin, hematocrit) and reticulocytes, increase in white blood cells (neutrophils, monocytes, basophils) and PT.
- Clinical chemistry changes at ≥50 mg/kg included decrease in total protein, albumin, cholesterol, bilirubin, ALP, GGT, phosphate, and increase in ALT.
- The major target organ was the ovary (≤50 mg/kg) and lungs (≥20 mg/kg).
    - Ovary: Increase in organ weight (non-statistically significant) with microscopic correlates of follicular cysts
    - Uterus: Decrease in organ weight (non-statistically significant) with no microscopic correlates
    - Lung: macrophage/lymphocyte infiltrates

5.5.2. Genetic Toxicology

The Applicant's Position:

Elacestrant was not mutagenic in bacterial reverse mutation (Ames) assays and did not induce chromosomal aberrations in human lymphocytes (GLP Studies 7801-100, 15RAD251, 15RAD252, and 7801-101). Elacestrant was not aneugenic or clastogenic in an in vivo rat bone marrow micronucleus assay (GLP Study 7801-102).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Data (presented by the FDA):

The genetic toxicology studies were initially reviewed by the FDA under IND 124748 and are summarized below.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study/ID: Salmonella-Escherichia coli/Mammalian-microsome reverse mutation assay with a conformation assay/7801-100

Key Study Findings:

- RAD-1901 was negative in all tester strains in the presence and absence of S9 activation.

GLP compliance: Yes (OECD)

Test system: RAD-1901 (lot# 01RAD07-02-38, 97.8% purity) was evaluated up to 5000 µg/plate with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2uvrA strains in the absence and presence of S9.

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study/ID: RAD-1901 2HCl: in vitro human lymphocyte chromosome aberration assay/ 15RAD252

Key Study Findings:

RAD-1901 was positive for the induction of numerical aberrations, increase in cells with polyploidy, in the presence of S9 activation for 3-hour treatment at 39 to 43.2 µg/mL (inducing 24% and 54% cytotoxicity, respectively) with one lot of RAD-1901 and at 40.2 µg/mL (inducing 57% cytotoxicity) with another lot of RAD-1901. GLP compliance: Yes

Test system: Human primary peripheral blood lymphocytes were treated with RAD-1901 (lot# 02RAD08A-01-50, 99.1% purity; and lot# 16-01601-01, 99.3% purity) up to 84 µg/mL in the presence and absence of S9 activation for 3-hours.

Study is valid: Yes

Note: The increase in cells with polyploidy occurred at concentrations resulting in higher cytotoxicity and was outside the historical control range for the vehicle control (0-1%) at up to 4.3% suggesting elacestrant may have aneugenic potential. However, there was a very narrow window of mitotic inhibition (MI), making it difficult to accurately select a concentration to achieve 50% MI, such that comparable concentrations resulted in different MI. In addition, elacestrant was negative in this study without metabolic activation after 3-hour and 24-hour treatment and negative in another in vitro human lymphocyte chromosome aberration assay at concentrations resulting in >50% cytotoxicity and in an in vivo rat bone marrow micronucleus assay. The Applicant cited reference to the literature demonstrating a correlation between high frequency polyploidy and an increase of mitotic index reduction in this test system, suggesting polyploidy may not be a reliable indicator of aneugenicity in this assay system. The positive result is, therefore, likely a false positive.

Study/ID: Chromosomal aberrations in cultured human peripheral blood lymphocytes/7801-101

Key Study Findings:

- RAD-1901 was negative for inducing chromosomal aberration at doses up to 40 µg/mL.

GLP compliance: Yes (OECD)

Test system: Human peripheral blood lymphocytes were treated with RAD-1901 (lot# 01RAD07-02-38, 97.8% purity) up to 40 µg/mL in the presence and absence of S9 activation for 3-hours and 22-hours, respectively.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study/ID: In vivo rat bone marrow micronucleus assay/7801-102

Key Study Findings:

- Oral doses of RAD-1901 up to 900 mg/kg/day did not induce statistically significant increases in micronucleated polychromatic erythrocytes in the bone marrow of female rats.

GLP compliance: Yes (OECD)

Test system: Female Sprague Dawley rats (n=5/group) were administered two doses of RAD-1901 (lot# 01RAD07-02-38, 97.8% purity) approximately 24 hours apart at 0, 50, 300, or 900 mg/kg; bone marrow micronuclei were assessed.

Study is valid: Yes

5.6. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies have not been conducted with elacestrant, in accordance with ICH S9 Guidance for Nonclinical Evaluation for Anticancer Pharmaceuticals (2009). However, granulosa ovary cell benign tumors were present in female rats following 26-week treatment with elacestrant at doses ≥ 25 mg/kg/day (GLP Study 15RAD215).

The FDA's Assessment:

The FDA agrees with the Applicant's Position.

5.6.1. Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility studies were not conducted. Adverse effects of elacestrant on both male and female fertility can be anticipated based on its mechanism of action. Decreased cellularity of Leydig cells was noted in male rats at the highest dose of elacestrant (50 mg/kg/day) in the 26-week repeat-dose study, and this result was in line with the impaired male (and female) fertility described in ERα knockout mice.

In an embryo/fetal development study of pregnant rats administered oral elacestrant during the period of organogenesis (Gestation Days 6 to 17), there were elacestrant-related dose-responsive effects on fetal development at 3-, 10-, and 30-mg/kg/day dose levels, which were considered adverse at 10 and 30 mg/kg only (GLP Study 19RAD230). Adverse effects included increased resorptions, increased post-implantation loss, reduced number of live fetuses, and fetal abnormalities, including external variations and malformations and malformations of the skull. The maternal NOAEL was set at the nominal dose level of 0.3 mg/kg/dose (the lowest dose tested) and was determined based on red vulvar discharge, increases in resorptions and postimplantation loss, and fewer live fetuses at higher doses. The fetal NOAEL was 3 mg/kg/day.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. In the embryo-fetal development study, elacestrant related embryo-fetal mortalities were observed at ≥3 mg/kg/day and teratogenicity at ≥10 mg/kg/day.

Data (presented by the FDA):
The Applicant assessed the effects of elacestrant on reproductive organs as part of the GLP-compliant repeat-dose toxicology studies up to 26 weeks in rats and up to 39 weeks in monkeys (see Section 5.5.1 for FDA assessment). Fertility and early embryonic development and pre- and post-natal studies were not needed to support the proposed advanced cancer population in accordance with ICH S9 guidance.

Embryo-Fetal Development

Study/ID: An Oral Gavage Embryo-Fetal Developmental Toxicity and Toxicokinetic Study of RAD1901 (Elacestrant) in Crl:CD (SD) Rats/19RAD230

- Adverse elacestrant related maternal toxicities and embryo-fetal mortalities were observed at ≥3 mg/kg/day.
- Fetal external and skeletal malformations were observed at ≥10 mg/kg/day.

GLP compliance: Yes

Methods

Dose:	0, 0.3, 3, 10, or 30 mg/kg
Frequency of dosing:	Daily (Gestation Days [GD] 6 through 17)
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	10 pre-mated females/group
Satellite groups:	TK: 3 pre-mated females (control group) 9 pre-mated females/treatment group
Study design:	Cesarean section performed on GD 21: gross observations, uterine contents and weights, live/dead fetuses, early/late resorptions, abnormalities, number of corpora lutea. Fetal examinations included: sex, body weights, external abnormalities, visceral and skeletal examinations.
Deviation from study protocol affecting interpretation of results:	No; the low dose group received lower than intended doses. This did not impact the study negatively as higher doses allowed for appropriate toxicity assessments.

Observations and Results

Parameters	Major findings
Mortality	All animals survived to their scheduled necropsy.
Clinical Signs	

Clinical observations

Dose mg/kg	0 (n=10)	0.3* (n=10)	3 (n=10)	10 (n=10)	30 (n=10)
Vulva – discharge, red			5	6	7
Excretion – discolored bedding, red			2	5	7
Fur					
-uro-genital area, brown				1	1
-uro-genital area, red				3	2
Thin appearance					1

*actual dose: 0.16 (GD 6) to 0.24 (GD 17) mg/kg/day

Red vulval discharge was noted on GD 15 or 16; 1/5 (3 mg/kg), 3/6 (10 mg/kg) and 6/7 (30 mg/kg) females were examined by the veterinarian and were noted as bright, alert, with normal urine color, no active bleeding, and overall normal appearance.

Body Weights

Decreased mean maternal body weight gain was observed at ≥3 mg/kg (up to -12%) with statistical significance generally reached at ≥10 mg/kg (up to -22%) compared to control. Mean maternal body weight gain based on the corrected weight (terminal body weight – gravid uterine weight) decreased by -55%, -54%, -51% at 3, 10, and 30 mg/kg, respectively, compared to control during GD 4 to 21.

Statistically significant decrease in mean maternal food consumption was observed at ≥3 mg/kg throughout the study (GD 6 to 21) with decreases up to -33% compared to control; the mean maternal food consumption decreased by -21%, -18%, -22% at 3, 10, and 30 mg/kg, respectively, compared to control during GD 6 to 21.

Mean male/female fetal weight was approximately -12%/-12%, -15%/-8%, and -21%/-13% at 3, 10, and 30 mg/kg, respectively, compared to control. The mean fetal weight decrease reached statistical significance compared to control at ≥3 mg/kg/day; fetal weights were outside the conducting laboratory's historical control values at ≥10 mg/kg/day.

Necropsy findings
Cesarean Section Data

Cesarian section data

Dose mg/kg	0 (n=10)	0.3* (n=10)	3 (n=10)	10 (n=10)	30 (n=10)
Gravid uterine weights (g) (mean)	87.87	95.92	93.07	**57.7**[#]	**54.8**[#]
Females mated (n)	10	10	10	10	10
Pregnancy rate (%)	90	100	100	100	100
Delivered early (n)	0	0	0	0	0
Dams with total litter loss (n)	0	0	1	3	2
Dams with viable fetuses (n)	9	10	9	7	8
Corpora lutea (mean)	13.7	13.9	14.6	12.8	13.5
Implantation sites (mean)	12.2	12.3	13.5	11.6	11.4
Preimplantation loss (mean%)	10.57	10.26	6.68	8.75	13.82
Post implantation loss (mean%)	9.98[#]	3.33	27.96[#]	**62.86**[#]	**66.53**[#]
Resorptions:					
Early n(%)	7 (6.4)	3 (2.4)	21[#] (15.4)	**52**[#] **(44.8)**	**34**[#] **(29.6)**
Late n(%)	0 (0)	1 (0.8)	**14**[#] **(10.3)**	**21**[#] **(18.1)**	**45**[#] **(39.1)**
Total n(%)	7 (6.4)	4 (3.2)	35 (25.7)	73 (62.9)	79 (68.7)
Dead fetuses n(%)	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.9)
Live fetuses n(%)	103 (93.6)	119 (96.8)	100[#] (73.5)	**43**[#] **(37)**	**35**[#] **(30.4)**

value: p≤0.05 compared to control *actual dose: 0.16 (GD 6) to 0.24 (GD 17) mg/kg/day
#outside the conducting laboratory's historical control values

Maternal macroscopic observations included abnormal tan/brown uterine fluid in 3/10 and 1/10 dams given 10 and 30 mg/kg, respectively; abnormal black/red semisolid content in the stomach in 1/10 and 3/10 dams given 10 and 30 mg/kg, respectively; abnormal black contents in the intestine (1/10 dams at 10 mg/kg), discolored white gelatinous pancreas (1/10 dams at 10 mg/kg), and abnormal brown gelatinous contents in the vagina (1/10 dams at 30 mg/kg).

Necropsy findings
Offspring

Fetal necropsy findings

Dose mg/kg	0	0.3*	3	10	30
Litters evaluated	9	10	9	7	8
Fetal External Findings					
Fetuses evaluated (live)	103	119	100	43	35
Variations [n (%fetal)]					
Edema	0 (0)	1 (0.8)	12 (12)	**12 (28)**	**6 (17)**
Malformations [n (%fetal)]					
Head					
-domed	0 (0)	0 (0)	0 (0)	2 (4.7)	5 (14)
-flattened	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.7)
-misshapen	0 (0)	0 (0)	0 (0)	3 (7)	**4 (11)**
-micrognathia	0 (0)	0 (0)	0 (0)	**6 (14)**	2 (5.7)
Limbs					
-hyperflexion	0 (0)	0 (0)	0 (0)	1 (2.3)	3 (8.6)
-malrotation	0 (0)	0 (0)	5 (5)	**13 (30)**	**6 (17)**
Mouth					
-macroglossia	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.8)
-palate, high arched	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.8)
-tongue, protruding	0 (0)	0 (0)	0 (0)	2 (4.7)	2 (5.7)
Ear, pinna malpositioned	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.8)
Eye, bulge, malpositioned	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.8)
General					
-anasarca (edema)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.8)
-anogenital region, distended	0 (0)	0 (0)	0 (0)	1 (2.3)	2 (5.7)
-pelvic region, narrow	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.8)
Fetal Skeletal Findings					
Fetuses evaluated (live)	52	59	50	22	19
Malformations [n (%fetal)]					
Skull#					
-misshapen interparietal	0 (0)	0 (0)	0 (0)	0 (0)	2 (10.5)
-misshapen orbital socket	0 (0)	0 (0)	0 (0)	2 (9.1)	6 (31.6)
-short maxilla	0 (0)	0 (0)	0 (0)	0 (0)	3 (15.8)
-small nasal	0 (0)	0 (0)	0 (0)	2 (9.1)	2 (10.5)
-small premaxilla	0 (0)	0 (0)	0 (0)	2 (9.1)	2 (10.5)

value: p≤0.05 compared to control *actual dose: 0.16 (GD 6) to 0.24 (GD 17) mg/kg/day
#generally associated with fetuses that had external malformations of the head

Adverse elacestrant related maternal and embryo-fetal toxicities were observed at ≥3 mg/kg and fetal malformation at ≥10 mg/kg. The C_{max} and AUC_{0-24} for elacestrant in pregnant females given 3 mg/kg was 13.2 ng/mL and 188 ng*hr/mL, respectively, on gestational day 17, which is approximately 27% and 36% higher, respectively, compared to the exposure seen on gestational day 6. The mean steady state clinical C_{max} and AUC_{0-24} for elacestrant at the recommended dose was 119 ng/mL and 2440 ng*hr/mL, respectively; therefore, embryo-fetal toxicity was seen at approximately 0.1 times the human AUC at the recommended dose.

5.6.2. Local Tolerance

Local tolerance was evaluated following the IV (0.2 mg in 1 mL) and perivenous (0.04 mg in 0.2 mL) administration of elacestrant in the left ear of rabbits (GLP Study 7801-135). Elacestrant was well tolerated following either route of administration.

5.6.3. Other Toxicology Studies

The Applicant's Position:

Impurities

The spectrum of impurities present in lots of elacestrant to be used for clinical studies and subsequently the commercial product has improved with process changes in drug substance production. There are no mutagenic impurities in the current drug substance based on the in silico predictions with Derek Nexus and Leadscope software methods (Studies 20RAD232, 185100B, and 8379173). Two (b) (4) (b) (4) were considered to be potentially mutagenic (Class 3 compound) based on structural alerts. These 2 (b) (4) (b) (4) and are not present in the current batches of drug substance.

Additionally, impurities present in clinical lots of elacestrant exceeding qualification threshold levels, per ICH Q3A (for non-oncology indications), are either considered qualified in repeat-dose toxicology studies or associated with no additional risks beyond the active pharmaceutical ingredient, which is currently indicated for advanced/metastatic breast cancer.

Overall, the risk associated with impurities in the current elacestrant drug substance are considered acceptable.

Phototoxicity

The potential phototoxicity of elacestrant was assessed in BALB/c 3T3 mouse fibroblasts in GLP Study 16RAD249. Elacestrant did not demonstrate phototoxic potential.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The local tolerance (intravenous/perivenous) study (#7801-135) in male New Zealand rabbits was not reviewed as the route of administration of elacestrant is oral.

Data (presented by the FDA):

The FDA's Computational Toxicology Consultation Services within the Center for Drug Evaluation and Research (CDER) predicted that there are no mutagenic impurities in the current drug substance using (Q)SAR methods.

The nonclinical studies qualified the impurities. The qualifications were based on a 50 mg/kg dose in rats, which did not lead to severe toxicities.

Impurity acceptance criteria in the Drug Substance (DS)

Impurity Name	Acceptance criteria (%)	Qualified levels reported by Applicant	FDA Assessment
(b) (4)	NMT (b) (4)	(b) (4)	Concur with Applicant

(b) (4)		(b) (4)		(b) (4)	
	NMT				Concur with Applicant
	NMT				Concur with Applicant
	NMT				Concur with Applicant
	NMT				Concur with Applicant
	NMT				Concur with Applicant
	NM				Concur with Applicant

(b) (4)

#16RAD249 – The phototoxicity potential of elacestrant was assessed using BALB/c 3T3 mouse fibroblasts with and without ultraviolet radiation (UVR); promethazine was used as the positive control. Cells were incubated with elacestrant, or the positive control for 90 minutes followed by exposure to UVA (5 J/cm^2) and UVB (21 mJ/cm^2). Elacestrant did not have phototoxic potential under the conditions tested.

X	X
Primary Reviewer	Supervisor
Nikolett Biel	Tiffany Ricks

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Elacestrant is an oral estrogen receptor antagonist indicated for treatment of postmenopausal women or adult men, with ER-positive, HER2-negative, *ESR1*-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

The Applicant proposed dosage of elacestrant is 345 mg taken orally, once daily, (b) (4) (b) (4) The primary evidence of efficacy and safety was obtained from a randomized Phase 3 Study RAD1901-308 (EMERALD), in which patients were randomized (1:1) to receive elacestrant at dose of 345 mg QD administered with food in the treatment arm (n=239) or investigator's choice in the control arm (n=239). The study was conducted in patients with or without *ESR1* mutations, and the primary endpoint was progression free survival. In patients with *ESR1*-mut, the elacestrant arm (n=115) achieved a clinically meaningful and statistically significant improvement in PFS compared to the control arm (n=113); the hazard ratio for PFS was 0.55 (95% CI: 0.39, 0.77). Additionally, the median PFS was 3.8 months (95%CI: 2.17, 7.26) in the elacestrant arm compared to 1.9 months (95% CI: 1.87, 2.14) in the investigator's choice arm.

The clinical pharmacology key review questions focused on the dosage recommendations for patients with hepatic impairment, dosage recommendations for patients receiving strong and moderate CYP3A4 inhibitors or inducers with elacestrant (a substrate of CYP3A4), the adequacy of data to support elacestrant administration without food, and heterogeneity of response to elacestrant across *ESR1* mutations.

The recommended daily dose was selected based on PK and safety information obtained from the dose escalation study RAD1901-005. In study RAD1901-005, the maximum tolerated dose was determined to be 345 mg QD. Exposure-response analysis at a dosage ranging from 173 mg QD and 518 mg QD was considered limited and did not identify a relationship between elacestrant exposure and efficacy endpoints (PFS and clinical benefit rate) or safety endpoints. In clinical studies conducted in metastatic breast cancer (mBC) patients, elacestrant was administered with food to minimize the incidence of gastrointestinal adverse reaction, and data obtained from healthy volunteers suggested improved gastrointestinal tolerability when elacestrant was administered with food.

No dosage modifications are recommended based on age, sex, body weight, renal impairment, or mild hepatic impairment. Based on clinical data and PBPK analysis, patients with moderate hepatic impairment should receive a reduced dose of 258 mg QD. However, the effect of severe hepatic impairment on elacestrant is unknown.

Based on clinical studies and PBPK modeling, the coadministration of elacestrant with moderate or strong inhibitors or inducers of CYP3A4 should be avoided.

6.1.1. Recommendations

The Clinical Pharmacology review team has reviewed the information contained in NDA 217639 and recommends approval. The key review issues with specific recommendations and/or comments are summarized in Table 3 below.

Table 3. Summary of key review issues and recommendations for NDA 217639

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of efficacy and safety is provided by a randomized Phase 3 Study RAD1901-308 (EMERALD).
General dosing instructions	The proposed elacestrant dosage is 345 mg orally once daily with food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Avoid use in patients with severe hepatic impairment. Reduce the dosage for patients with moderate hepatic impairment to 258 mg once daily. No dosage adjustment is recommended for patients with mild hepatic impairment. • No dose adjustment is recommended for patients with renal impairments. • No dose adjustment is required based on age, sex, body weight.
Drug Interactions	• Avoid concomitant use with strong or moderate CYP3A inhibitors. • Avoid concomitant use of strong or moderate CYP3A inducers. • Reduce the dosage of P-gp substrates per their Prescribing Information when minimal concentration changes may lead to serious or life-threatening adverse reactions. • Reduce the dosage of BCRP substrates per their Prescribing Information when minimal concentration changes may lead to serious or life-threatening adverse reactions.

Labeling	Generally acceptable. The review team has specific content and formatting changes to the proposed labeling. Labeling language was reviewed, corrected, and updated according to the guidance of clinical pharmacology section of labeling for human prescription drug and biological products - content and format (published December 2016).
Bridge between the to-be-marketed and clinical trial formulations	The Applicant conducted a relative bioavailability study (Study RAD1901-116) to bridge between the to-be-marketed tablets formulation and the clinical tablets formulation used in the Phase 3 Study RAD1901-308.

6.1.2. Post Marketing Requirements and Commitments

The rationale and description of post marketing requirement (PMR) are detailed in Table 4. One PMR was issued to further characterize the pharmacokinetics and safety of elacestrant in patients with severe hepatic impairment.

Table 4. Rationale and description of post-marketing requirements for NDA 217639

Post Marketing Requirement -1	
PMR Rationale	Elacestrant is mainly eliminated via metabolism in the liver. The effect of mild or moderate hepatic impairment on the exposure of elacestrant has been characterized. A dose reduction to 258 mg once daily is recommended in patients with moderate hepatic impairment. The effect of severe hepatic impairment on the exposure of elacestrant is unknown and should be evaluated to guide recommendations for dosage modification.
PMR description	Complete a pharmacokinetic trial to determine an appropriate dose of elacestrant in patients with severe hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Elacestrant PK properties following single dose and multiple doses were assessed in healthy men, postmenopausal women, and in postmenopausal women and men with mBC. The results from in vitro human biomaterial studies, in vivo clinical pharmacology studies in healthy

subjects (mass balance, food effect and acid reducing agents drug-drug interaction (DDI), highly- protein bound drugs DDI, hepatic impairment, DDI studies with cytochrome P450 3A4 (CYP3A4) modulators, and DDI study with P-glycoprotein (P-gp)/ breast cancer resistance protein (BCRP) substrates), Phase 1 and Phase 3 studies in patients with mBC as well as population PK analysis conducted on pooled Phase 1 and Phase 3 data were integrated to describe the ADME properties of elacestrant in humans and assess intrinsic and extrinsic factors that may affect the PK of elacestrant.

In addition, the outcomes of the exposure-response analyses for safety and efficacy conducted on Phase 1 and Phase 3 studies supported the use of the recommended dose of 345 mg elacestrant, administered orally, once daily.

In addition, a physiologically based PK (PBPK) model was developed to aid in the assessment of potential DDIs and to support dose adjustments in subjects with hepatic impairment.

The potential relationship between elacestrant concentration and heart rate-corrected QT interval (QTc) was evaluated using a model-based approach.

Summary of Pharmacokinetics

An overview of the ADME properties, clinical PK, and DDI potential of elacestrant is provided below.

Absorption: Under fasting condition, the oral absorption of elacestrant was rapid (t_{max} < 4 hours), with an absolute bioavailability of approximately 10%. Elacestrant exposure was slightly higher when administered with food.

Coadministration of elacestrant with an acid-reducing agent had no effect on the elacestrant PK profile.

The 86- and 345-mg commercial tablets were shown to be bioequivalent to the 86- and 345-mg tablets used in clinical development.

Distribution: Based on the final population PK (PopPK) analysis, the apparent volume of distribution of the central compartment (Vc/F) was 422 L, suggesting wide distribution into tissues. In vitro, elacestrant was highly bound to human plasma proteins (protein binding > 99%). The unbound fractions were similar across species and independent of plasma concentration. Elacestrant protein binding was measured in subjects with different degrees of hepatic impairment and with normal hepatic function, confirming high binding to plasma proteins, with no trend with hepatic impairment.

In a human mass balance study, arithmetic mean blood/plasma concentration ratios ranged from 0.607 to 0.794, indicating little to no association of radioactivity with red blood cells.

Elacestrant was shown to penetrate the blood brain barrier (BBB) in a dose-dependent manner.

Metabolism: Elacestrant human metabolism was predominantly oxidative mediated by CYP3A4. In accordance with the in vitro data, the major metabolic pathways involve N-dealkylations, N-demethylations, and a variety of other oxidations, including hydroxylations, oxidation to carboxylic acids, and dehydrogenations. Phase II glucuronidation is substantive in plasma but not in the excreta. In human plasma only 1 major radiometabolite (41.3% of drug-related material) was identified, corresponding to the product of oxidative N-dealkylation coupled to glucuronidation. Elacestrant central apparent clearance (CL/F) also appeared to be dose

dependent, with a trend for decreasing CL/F with increasing dose after single and repeat dose administration.

Excretion: Elacestrant and its metabolites are mainly excreted in the feces (81.5%) after oral administration. Excretion in the urine is minor (7.53%), with only a small fraction of the dose being excreted as unchanged elacestrant.

Clinical Pharmacokinetics:

Elacestrant C_{max} and AUC increased with increasing oral dose in a greater than dose-proportional manner after a single dose (> 43 mg) and after repeated dosing (> 22 mg orally once daily [QD]). This may be ascribed to saturation of intestinal first-pass metabolism mediated by CYP3A4. Accumulation was observed, with an accumulation ratio (R_{ac}) of approximately 2 (for both C_{max} and AUC) after 7 days of QD oral administration. In the final PopPK analysis, elacestrant was absorbed following linear kinetics with a lag time (T_{lag}) of 0.81 hours.

Elacestrant elimination half-life ($t_{1/2}$) was approximately 30 hours independent of dose. After repeated oral administration, elacestrant $t_{1/2}$ tended to be longer (up to 47 hours).

In vitro victim DDI risk: Elacestrant is mainly metabolized by CYP3A4. Elacestrant is not a substrate of efflux transporters, renal transporters, or hepatic transporters with the exception of OATP2B1.

In vitro perpetrator DDI risk: The DDI potential of elacestrant was assessed in vitro with all common metabolic enzymes and transporters. Elacestrant does not induce or inhibit CYP450 at therapeutic concentrations. Elacestrant does not inhibit renal and hepatic transporters, however it is a relevant inhibitor of P-gp and BCRP transporters.

Summary of the Effect of Intrinsic Factors

Special Population

Hepatic impairment:

Elacestrant exposure and $t_{1/2}$ tended to increase with increasing severity of hepatic impairment. Exposure in subjects in the mild hepatic impairment group was similar to that of the normal hepatic function group. The AUCs of the moderate hepatic impairment group were considerably higher (76% to 83%) than those of the normal hepatic function group. Based on PBPK model simulations, elacestrant exposure in subjects with severe hepatic impairment would increase considerably (about 3-fold for AUC and 2-fold for C_{max}) compared to subjects with normal hepatic functions.

Demographic factors:

During the final PopPK analysis, several intrinsic factors (e.g., body weight, sex, clinical laboratory values) were investigated and statistically tested in order to characterize their effect on elacestrant PK variability across studied populations. Baseline body weight was a significant covariate on all volumes and clearances, which increased with increasing body weight; CL/F was also found to decrease with age and apparent intercompartmental clearance (Q/F) was higher for male subjects.

Health status, time-varying body weight, and clinical laboratory parameters were explored and did not reveal any trends on major PK parameters. Based on the magnitude of the covariate effects, no dose adjustment due to weight, age, or sex appeared to be necessary.

Summary of the Effect of Extrinsic Factors

Effect of food:

Administration of elacestrant with food (high-fat meal) increased systemic exposure of elacestrant compared to fasted conditions. Elacestrant AUC was increased by 22% (12% to 34%) and C_{max} by 42% (26% to 60%) when elacestrant 400-mg commercial tablet was administered in the fed state compared to administration when fasted.

Drug-drug interactions:

Coadministration of elacestrant with itraconazole (a strong CYP3A4 inhibitor) increased the elacestrant C_{max} by 4.4-fold (3.95- to 4.38-fold) and AUC by 5.3-fold (4.7- to 5.9-fold). Coadministration of elacestrant with rifampin (a strong CYP3A4 inducer) decreased the elacestrant C_{max} by 73% (69% to 77%) and AUC by 86% (84% to 88%).

Simulations using a PBPK model predicted that inhibitors of CYP3A4 increase elacestrant exposure (AUC increase ≥ 5-fold, ≥ 2-fold and < 5-fold, and < 2-fold for strong, moderate, and weak inhibitors, respectively) and moderate inducers of CYP3A4 decrease elacestrant exposure (AUC decrease ≥ 50% and < 80%).

Coadministration of elacestrant with an acid-reducing agent (omeprazole) had no significant effect on elacestrant PK.

Coadministration of elacestrant with warfarin (both very highly protein-bound drugs) showed no significant effect on either elacestrant or warfarin PK. The PD of warfarin were also unaffected by the presence of elacestrant.

Summary of Exposure-Response Analyses

Exposure-efficacy relationship:

In an initial exposure-efficacy analysis performed using data from Phase 1 studies (Studies RAD1901-005 and RAD1901-106) in the dose range 200 to 600 mg QD, no relationship was identified between various elacestrant exposure metrics (AUC, C_{max}, and C_{min}) metrics and efficacy endpoints (objective response [OR] and Clinical Benefit [CB]).

In the final E-R analysis for efficacy performed using data from the Phase 3 Study RAD1901-308, in both the nonparametric and the parametric survival analysis for PFS, elacestrant exposure (AUC_{av}) did not achieve the predefined significance level of $p < 0.001$. This indicates no difference in PFS across the observed range of elacestrant exposures.

The results of both analyses support the fact that maximum efficacy is achieved for doses ≥ 173 mg QD, in line with the high target engagement (i.e., mean percentage reduction from baseline of 18F-fluoro-17β-estradiol [FES] uptake ≥ 75%) observed in Study RAD1901-106. Despite some trends of survival associated with some covariates, no statistically significant ($p > 0.001$) differences in response to treatment were observed among subpopulations (e.g., visceral metastasis, estrogen receptor 1 [*ESR1*] gene mutational status, and prior lines of therapy).

Exposure-safety relationship:

In an initial exposure-safety analysis carried out using data from Phase 1 studies following elacestrant doses of 173, 345, and 518 mg QD, it was demonstrated that elacestrant exposures after doses higher than 345 mg QD may lead to higher probability of experiencing serious AEs (SAEs), AEs leading to study discontinuation, and AEs of Grade ≥ 3.

In the final E-R analysis for safety, performed using data from the Phase 3 Study RAD1901-308, logistic regression analyses did not indicate a higher incidence of nausea with increasing elacestrant exposure, which confirms the adequacy of the dose of 345 mg QD. In the elacestrant population concentration-QTc analysis, across the various analyses undertaken, there was no evidence of QT interval corrected with Fridericia's method (QTcF) prolongation associated with elacestrant treatment.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the clinical pharmacology of elacestrant is adequately characterized expect for the assessment elacestrant exposure in patients with severe hepatic impairment. Applicant used a PBPK model to evaluate exposure of elacestrant in patients with severe hepatic impairment. FDA concludes that the severe hepatic PBPK model, without validation by clinical PK data in participants with severe hepatic impairment, is inadequate. A PMR is issued to conduct a pharmacokinetic trial to determine an appropriate dose of elacestrant in patients with severe hepatic impairment. See Section 6.1.2 for details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The 345 mg QD dose of elacestrant used in Study 308 was selected based on nonclinical data as well as safety, efficacy, and PK data from 6 Phase 1 (including 2 in healthy postmenopausal women and 2 in postmenopausal women with mBC) and Phase 2 (in subjects with vasomotor symptoms) clinical studies of elacestrant.

In Study 005 Part A (dose escalation), subjects received elacestrant doses of 173 mg QD, 345 mg QD, and 518 mg QD. Although no dose-limiting toxicities were reported PP, the 518 mg dose was deemed not tolerable due primarily to gastrointestinal events. The incidence of nausea, vomiting, and constipation was higher in subjects who received the 518 mg dose (67% to 100%) compared to those who received the 345 mg dose (17% to 67%) at the time of the analysis. Therefore, the 345 mg dose, which was associated with fewer gastrointestinal events, was selected as the recommended Phase 2 dose (RP2D) for the subsequent clinical studies.

Expansion cohorts in Parts B, C, and D of Study 005 confirmed the acceptability of the safety profile, and antitumor activity was observed at this dose level (objective response rate [ORR] 19.4%). The dose of 345 mg was also tested in Study 106 in postmenopausal women with mBC with an acceptable safety profile. In this study, elacestrant greatly reduced FES uptake from baseline to Day 14. A higher proportion of subjects in the 345 mg dose cohort (7/8; 87.5%) obtained a greater than 75% reduction in FES uptake when compared to the 173/345 mg cohort (4/7; 57%). Furthermore, residual ER availability (>25% persistence in FES uptake) on Day 14

was observed in 3 subjects receiving 173/345 mg (3/8; 37.5%) and 1 subject receiving 345 mg (1/8; 12.5%).

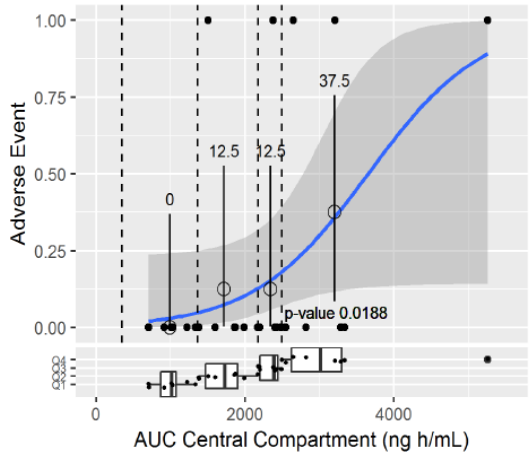
In addition, an exposure-safety analysis was conducted using results from Studies 005 and 106, which confirmed that doses higher than 345 mg may increase the probability of SAEs, AEs leading to discontinuation, and AEs of Grade 3 or higher. The results of the logistic regressions for the different exposure metrics, including estimates for intercept and slope, p-value (for slope only), log-likelihood (logLik), AIC and BIC for all the tested models, are reported in Table 5, while the plot of the logistic regression for AEs vs. AUC is presented in Figure 1. Additional details of this analysis are discussed in Section 2.3.1 of Module 2.7.2.

Table 5: Logistic regression parameters for Exposure-Safety analysis

Model	logLik	AIC	BIC	Intercept	Slope	P-value (slope)
AUC (ng*hr/mL)	-11.10779	26.21558	29.14705	-4.750264	0.001300465	0.01877934
Cavg (ng/mL)	-11.10779	26.21558	29.14705	-4.750264	0.03121117	0.01877934
Cmax (ng/mL)	-10.583	25.16601	28.09748	-5.810366	0.02904139	0.01036235
Cmin (ng/mL)	-11.58497	27.16995	30.10142	-3.908063	0.03467324	0.03258258

(Source: Applicant's slide 29 in Pop PK and E-R Analyses of RAD1901_2017)

Figure 1: Logistic regression plot for Adverse Events vs AUC



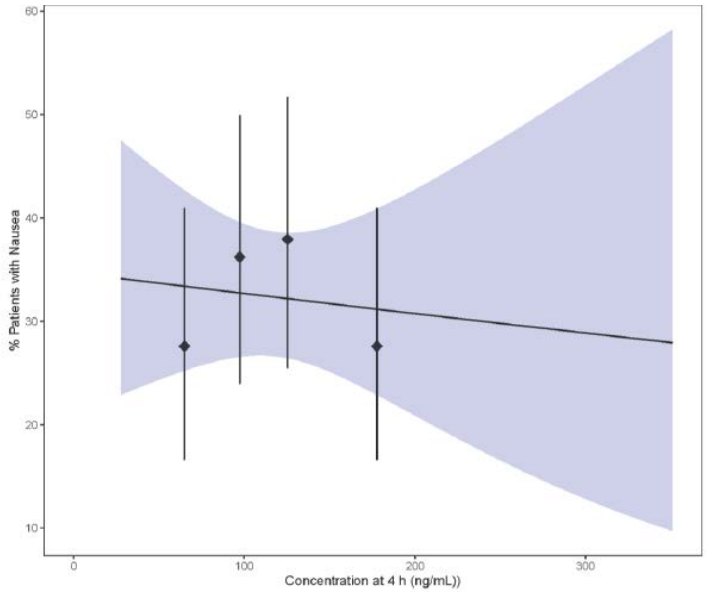
(Source: Applicant's slide 30 in Pop PK and E-R Analyses of RAD1901_2017)

Based upon the favorable safety and efficacy data observed following the administration of elacestrant 345 mg QD in both of these studies, 345 mg QD was selected as the dose for Study 308.

Dose selection was confirmed by the exposure-response analysis using data from Study 308 following the administration of 345 mg QD (Section 2.3.2 of Module 2.7.2). Indeed, the exposure-safety analysis showed no evidence that elacestrant exposure (concentration at 4

hours post-dose) increased the occurrence of nausea. Based on the logistic regression analysis, the predicted probability of nausea vs. Conc4h, is presented in Figure 2. The results of the logistic regression, including estimates, standard error, p-value, odds ratios including 95% CI and AIC, for both the model with only Conc4h as a predictor and the model including Conc4h and all covariates are presented in Table 6.

Figure 2: Percent patients with Nausea vs. Concentration at 4 h post-dose



(Source: Figure 5-10 in Applicant's Report 3882-0012)

Table 6: Odds Ratio for Nausea - Models for Concentration at 4 h post-dose and Covariates

Model	Variable	Estimate	SE	P-value	Odds Ratio	Lower 95% CI	Upper 95% CI	AIC
Nausea~Conc4h	Intercept	-0.632	0.352	0.072	0.531	0.267	1.058	295.89
	Conc4h	-0.001	0.003	0.742	0.999	0.994	1.004	
Nausea~Conc4h	Intercept	-0.841	0.648	0.194	0.431	0.121	1.536	302.97
	Conc4h	-0.001	0.003	0.627	0.993	0.999	1.004	
+ECOG	Score 1	0.146	0.295	0.622	1.157	0.649	2.063	
+VISC	Yes	-0.009	0.310	0.978	0.991	0.540	1.820	
+ESRSTATN	ESR1-mut	-0.185	0.293	0.528	0.831	0.468	1.476	
+PRFULVFL	Yes	-0.066	0.421	0.876	0.936	0.411	2.135	
+PRAIFL	Yes	-0.067	0.462	0.884	0.935	0.378	2.312	
+ETCHLINE	2 Lines	0.719	0.321	0.025	2.052	1.094	3.849	
+ETCHLINE	3 Lines	0.119	0.552	0.829	1.127	0.382	3.322	

Conc4h: Concentrations at 4h; VISC=Prior Visceral Disease; ESRSTATN= ESR1 mutational status; PRFULVFL: prior fulvestrant; PRAIFL= prior aromatase inhibitors; ETCHLINE= Lines of therapy; SE=standard error, CI=confidence interval, AIC= Akaike Information Criterion.

(Source: Table 5-14 in Applicant's Report 3882-0012)

The exposure-efficacy analysis also confirmed the adequacy of the selected dose for the entire patient population. Indeed, neither elacestrant exposure nor any of the covariates reached the predefined level of significance during non-parametric and parametric survival analysis for PFS,

indicating no differences in PFS across the observed range of elacestrant exposures, as shown in Table 7and Table 8, respectively.

Table 7: Summary of Non-Parametric Survival Analyses with Average Daily AUC

Models	Variable	Estimate	SE	P-value	Hazard Ratio	L95%	U95%
Categorical AUCav							
PFS ~AUCav	Above Median	0.337	0.170	0.047	1.401	1.005	1.953
PFS ~AUCav	1stQ-2ndQ	0.192	0.255	0.453	1.211	0.734	1.998
	2ndQ-3rdQ	0.373	0.251	0.137	1.453	0.889	2.375
	Above 3rdQ	0.506	0.247	0.041	1.658	1.022	2.692
Continuous AUCav							
PFS ~AUCav	AUCav	0.112	0.076	0.138	1.119	0.964	1.298
PFS							
~AUCav	AUCav	0.144	0.083	0.081	1.155	0.982	1.359
+ECOG	Score 1	-0.200	0.186	0.283	0.819	0.568	1.180
+VISC	Yes	0.387	0.191	0.042	1.473	1.013	2.140
+ESRSTATN	ESR1-mut	-0.308	0.174	0.076	0.735	0.523	1.033
+PRFULVFL	Yes	0.164	0.263	0.532	1.178	0.704	1.972
+PRAIFL	Yes	0.176	0.282	0.534	1.192	0.685	2.073
+ETCHLINE	2 Lines	0.213	0.196	0.278	1.237	0.842	1.817
+ETCHLINE	3 Lines	0.816	0.293	0.005	2.262	1.275	4.014

VISC=Prior Visceral Disease; ESRSTATN= ESR1 mutational status; PRFULVFL: prior fulvestrant; PRAIFL= prior aromatase inhibitors; ETCHLINE= Lines of therapy; SE=standard error, CI=confidence interval

(Source: Table 5-9 in Applicant's Report 3882-0012)

Table 8: Summary of Parametric Survival Analyses with Average Daily AUC

Models	Variable	Estimate	SE	P-value	Hazard Ratio	L95%	U95%
PFS ~AUCav	Intercept	5.575	0.188	<2e-16			
	AUCav	-0.117	0.071	0.100	1.133	0.975	1.318
PFS							
~AUCav	Intercept	5.972	0.329	<2e-16			
	AUCav	-0.145	0.073	0.047	1.181	1.001	1.392
+ECOG	Score 1	0.267	0.162	0.099	0.737	0.512	1.061
+VISC	Yes	-0.341	0.167	0.041	1.476	1.017	2.143
+ESRSTATN	ESR1-mut	0.361	0.152	0.017	0.663	0.471	0.931
+PRFULVFL	Yes	-0.106	0.232	0.649	1.128	0.672	1.895
+PRAIFL	Yes	-0.271	0.240	0.258	1.363	0.796	2.335
+ETCHLINE	2 Lines	-0.203	0.176	0.249	1.261	0.850	1.871
+ETCHLINE	3 Lines	-0.646	0.256	0.012	2.091	1.172	3.730

VISC=Prior Visceral Disease; ESRSTATN= ESR1 mutational status; PRFULVFL: prior fulvestrant; PRAIFL= prior aromatase inhibitors; ETCHLINE= Lines of therapy; SE=standard error, CI=confidence interval, AIC= Akaike Information Criterion.

(Source: Table 5-10 in Applicant's Report 3882-0012)

Additional details of this analysis are discussed in Section 2.3.2 of Module 2.7.2.

The FDA's Assessment:

FDA agrees with the Applicant's position on elacestrant dosage of 345 mg once daily. In the registrational Study RAD1901-308, the proposed dosage demonstrated a favorable benefit-risk profile compared to fulvestrant or an aromatase inhibitor in patients with *ESR1*-mutated advanced or metastatic breast cancer. Elacestrant improved PFS by 1.9 months (median of 3.8 month for elacestrant arm vs 1.9 month for fulvestrant or an aromatase inhibitor arm, with HR of 0.55) in patients with *ESR1*-mutated advanced or metastatic breast cancer with an acceptable safety profile. The proposed dosage was found to be tolerable in Study RAD1901-308. Permanent discontinuation, dosage interruptions, and dosage reduction of elacestrant due to an adverse reaction occurred in 6%, 15%, and 3% of patients, respectively. In Study RAD1901-308, there are no clear exposure-response relationships for efficacy or safety based on available data at only 345 mg once daily.

The Applicant proposed that the recommended dosage of elacestrant is 345 mg once daily (b) (4)

During the clinical development, all the clinical studies in breast cancer patients (RAD1901-308, RAD1901-005 and RAD1901-106) were conducted with food to minimize the risk of gastrointestinal adverse reactions. There are no data in patients with breast cancer regarding gastrointestinal tolerability to support administering elacestrant without food. Moreover, in the dose escalation Study RAD1901-005, 518 mg taken with food was not tolerable due primarily to gastrointestinal adverse events. The incidence of nausea, vomiting, and constipation was higher in 518 mg compared to 345 mg. In addition, administering elacestrant with food was found to improve gastrointestinal tolerability based on data from Study RAD1901-116 in healthy participants.

6.2.2.2. Therapeutic Individualization

Data:

Intrinsic Factors

Population PK analysis using pooled data from Phase 1 studies (RAD1901-004, RAD1901-109, RAD1901-110, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-005, and RAD1901-106) and Phase 3 study (RAD1901-308) identified dose, body weight, gender, and age as statistically significant covariates impacting elacestrant PK (Study 3882-0012). Boxplots of elacestrant AUCs for different age groups, gender, and quartiles of body weight are presented in Figure 3, Figure 4, Figure 5, respectively. Overall, the boxplots show an overlap of interquartile ranges and whiskers for each covariate, thus indicating that no dose adjustment is warranted based on body weight, age, and gender. Additional covariates (e.g., formulation, disease status, renal function) were not found to affect elacestrant PK.

Age

Elacestrant CL/F was found to decrease with age. The decrease in elacestrant clearance was of approximately 6% in a typical subject aged 75 years old when compared to a typical subject

aged 65 years old. This reduction in clearance with age translates in a negligible increase in elacestrant AUC at steady state (AUC_{ss}) for all age groups, as shown in Figure 3. Therefore, no dose adjustment appears to be necessary for age.

Gender

Gender was found to affect elacestrant intercompartmental clearance (Q/F). The increase in Q/F for males with respect to females (1.28-fold) translates into a slightly higher mean AUCss for females. However, as shown in Figure 4, the interquartile ranges and whiskers of the AUC_{ss} distribution overlap, thus indicating that no dose adjustment is required based on gender.

Body Weight

Body weight was found to affect all elacestrant PK parameters (i.e., CL/F, apparent volume of distribution of the central compartment [Vc/F], Q/F, and apparent volume of distribution of the peripheral compartment [Vp/F]). Nevertheless, the combined effect of body weight on elacestrant PK parameters does not translate into a significant change in AUCss in the explored range of body weight (41.3 kg to 142.6 kg) (Figure 5). Therefore, no dose adjustment is warranted based on body weight.

Hepatic Impairment

The effect of mild and moderate hepatic impairment on elacestrant PK was evaluated in a clinical study (Study RAD1901-117). The effect of hepatic impairment on elacestrant exposure and $t_{1/2}$ tended to increase with increasing severity of hepatic impairment. Significant increase in AUC_{0-t} (76%) and $AUC_{0-\infty}$ (83%) was observed in the moderate hepatic impairment group compared to the normal hepatic function group, while C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values were similar between subjects in the mild hepatic impairment group and the normal hepatic function group.

A PBPK model for elacestrant was developed based on in vitro and in vivo data (Study RADI-2B Ad Hoc; Module 2.7.2, Section 2.2.3.1.2). The changes in elacestrant exposures as a result of hepatic impairment were predicted and verified using data from Study RAD1901-117, suggesting that the PBPK model is able to well predict elacestrant PK in subjects with hepatic impairment. The model was used to predict steady-state exposures following 173, 259, and 345 mg QD in subjects with mild, moderate, and severe hepatic impairment.

A comparison between PBPK simulated steady-state $AUC_{(0-24)ss}$ following 14 days of 173, 259, and 345 mg QD in mild, moderate, and severe hepatic impairment groups and nominal steady-state $AUC_{(0-24)ss}$ for the subjects in Study RAD1901-308 is reported in Figure 6.

Based on the PBPK model-predicted elacestrant exposure, no dose adjustment is required for subjects with mild hepatic impairment, (b) (4)

Renal Impairment

The renal excretion of elacestrant is minimal, therefore no renal impairment studies have been conducted. The negligible role of renal function on elacestrant elimination was confirmed by the PopPK analysis, where creatinine clearance was found to have no effect on elacestrant clearance (Module 2.7.2, Section 3.1.5.5). Therefore, no dose adjustments are required in subjects with renal impairment.

Extrinsic Factors

Drug-drug interactions:

Coadministration of elacestrant with itraconazole (strong CYP3A4 inhibitor) increased elacestrant C_{max} by 4.4-fold and AUC by 5.3-fold (Study RAD1901-110). Coadministration of elacestrant with rifampin (strong CYP3A4 inducer) decreased elacestrant C_{max} by 73% and AUC by 86% (Study RAD1901-113).

The PBPK model predicted an increase in elacestrant AUC between ≥ 2- and < 5-fold when elacestrant is coadministered with moderate CYP3A4 inhibitors (i.e., fluconazole and erythromycin).

The PBPK model predicted a decrease in elacestrant AUC between ≥ 50% and < 80% when elacestrant is coadministered with moderate CYP3A4 inducer (i.e., efavirenz).

Overall, coadministration of elacestrant with a strong or moderate CYP3A4 inducer may decrease elacestrant activity, and coadministration of elacestrant with a strong or moderate CYP3A4 inhibitor may increase adverse reactions. Therefore, concomitant use of moderate or strong CYP3A4 inhibitors and/or inducers should be avoided. However, no dose modifications are required for mild CYP3A4 inducers and inhibitors.

Coadministration of the proton pump inhibitor omeprazole (40 mg QD) had no effect on the single oral dose PK profile of elacestrant in healthy men and postmenopausal women (Study RAD1901-115). Therefore, no dose adjustments are required when elacestrant is administered with acid-reducing agents.

Coadministration of elacestrant with warfarin (both very highly protein-bound drugs) showed no significant effect on either elacestrant or warfarin PK. The PD of warfarin were also unaffected by the presence of elacestrant (Study RAD1901-114). Therefore, no dose adjustments are required when elacestrant is administered with highly protein-bound drugs.

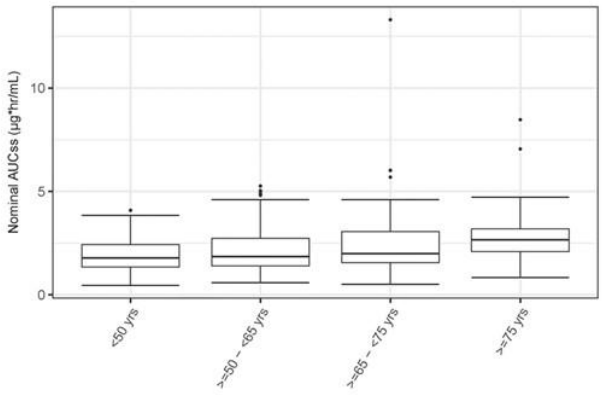
Food effect:

The presence of food (high-fat meal) increased systemic exposure of elacestrant compared to fasted conditions. Elacestrant AUC was increased by 22% and C_{max} by 42% when elacestrant 345 mg commercial tablet was administered in the fed state compared to administration when fasted. In the pivotal clinical Study RAD1901-308, elacestrant was administered with a light meal.

Model-based simulations were carried out to assess the impact of fasting on exposure and the risk of not achieving the threshold C_{min} (C_{min} > 20 ng/mL) associated with high target engagement (mean FES uptake above 75%).

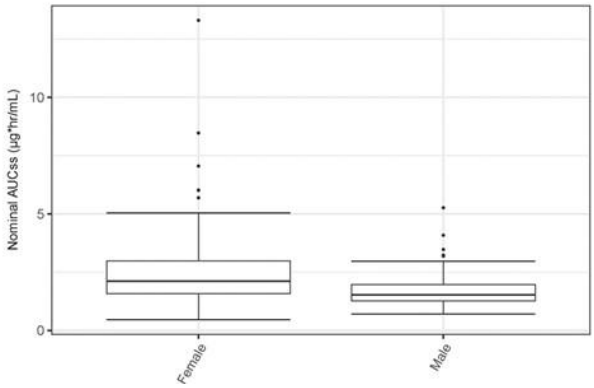
No difference was observed in terms of target exposure attainment between fed and fasted conditions at doses of 259 and 345 mg QD. Therefore, the effect of food on elacestrant exposure is not deemed clinically relevant (b) (4) Food intake was found to improve gastrointestinal tolerability in Study RAD1901-116.

Figure 3: Boxplot of Elacestrant AUCss by Age Group



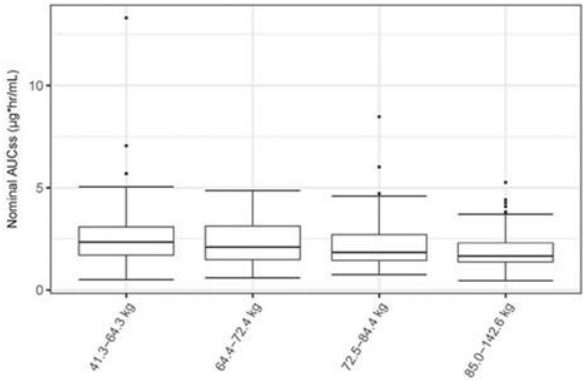
Abbreviations: AUC_{ss} = area under plasma concentration-time curve at steady state; IQR=interquartile range.
Black center line represents median. Top and base of the box represent first and third quartiles (IQR). Whiskers represent 1.5*IQR. Outliers beyond upper or lower 1.5*IQR are represented by circles.
Source: Module 2.5, Figure 1

Figure 4: Boxplot of Elacestrant AUCss by Gender



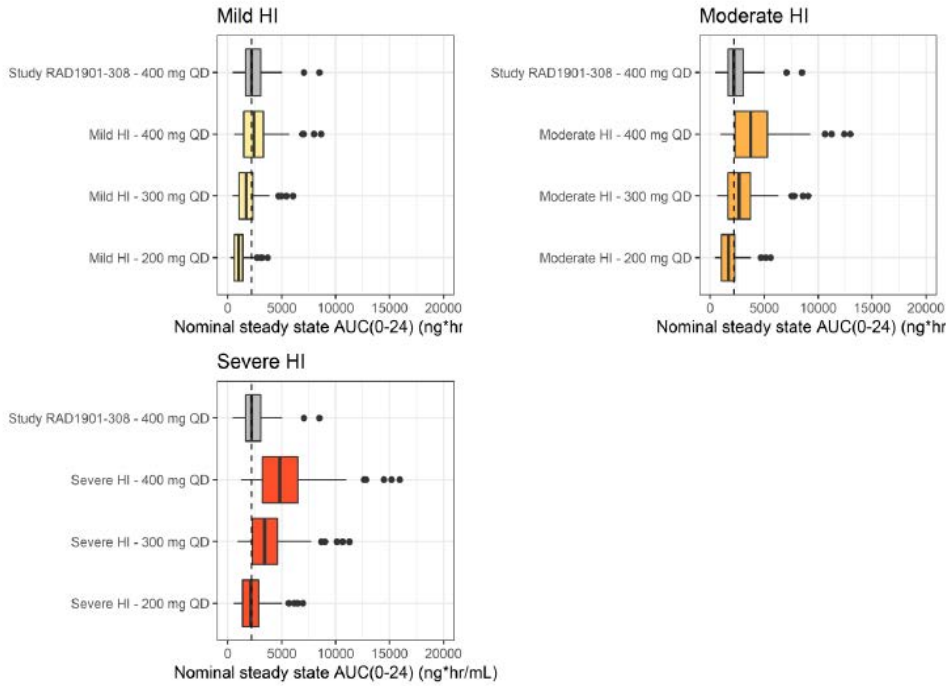
Abbreviations: AUC_{ss} = area under the plasma concentration-time curve at steady state; IQR=interquartile range.
Black center line represents median. Top and base of the box represent first and third quartiles (IQR). Whiskers represent 1.5*IQR. Outliers beyond upper or lower 1.5*IQR are represented by circles.
Source: Module 2.5, Figure 2

Figure 5: Boxplot of Elacestrant AUCss by Body Weight



Abbreviations: AUC_{ss} = area under the plasma concentration-time curve at steady state; IQR=interquartile range.
Black center line represents median. Top and base of the box represent first and third quartiles (IQR). Whiskers represent 1.5*IQR. Outliers beyond upper or lower 1.5*IQR are represented by circles.
Source: Module 2.5, Figure 3

Figure 6: Boxplot of Nominal Steady State AUC(0-24) for the Subjects in Study RAD1901-308 and PBPK Simulated Steady State AUC(0-24) Following 14 Days of 173, 259, and 345 mg QD in Mild, Moderate, and Severe Hepatic Impairment Groups



Abbreviations: $AUC_{(0-24)}$=area under the plasma concentration-time curve from time zero to 24 hours postdose; HI=hepatic impairment; PBPK = physiologically-based pharmacokinetic; QD=once daily.
Black dashed line represents median nominal steady state $AUC_{(0-24)}$ for the subjects in Study RAD1901-308.
Source: Module 2.5, Figure 4

The Applicant's Position:

No therapeutic individualization is needed for the proposed indication based on demographic factors (age, gender, body weight, etc.), in patients with renal impairment or mild hepatic impairment.

Dose reduction is necessary in patients with concomitant moderate (b) (4) hepatic impairment as outlined above and in the proposed labeling due to elacestrant metabolism by the liver.

In addition, concomitant use of elacestrant with a strong or moderate CYP3A4 inhibitors and/or inducers should be avoided. However, no dose modifications are required for mild CYP3A4 inducers or inhibitors, acid-reducing agents, or highly protein-bound drugs.

The FDA's Assessment:

FDA agrees with the proposed dosing therapeutic individualization strategies (b) (4) See the FDA's Assessment for Sections 6.3.2.3 for details.

6.2.2.3. Outstanding Issues

The Applicant's Position:

There are no known outstanding clinical pharmacology issues.

The FDA's Assessment:

There is one clinical pharmacology PMR to conduct a pharmacokinetic trial to determine an appropriate dose of elacestrant in patients with severe hepatic impairment.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 9: General Pharmacology and Pharmacokinetic Highlights

Pharmacology	
Mechanism of Action	Elacestrant is a tetrahydronaphthalene compound that is a potent, selective, and orally active estrogen receptor degrader and antagonist.
Active Moieties	Elacestrant
QT Prolongation	A concentration-QTc analysis has been conducted on pooled phase 1 and phase 3 studies. Based on the analysis, elacestrant administration is not associated with QTcF prolongation.
General Information	
Bioanalysis	Bioanalytical information are provided in Section 19.4.
Healthy Volunteers vs. Patients	Health status was explored as a potential covariate in the population PK analysis and no trend with any of the PK parameters was found, therefore no clinically relevant differences in PK are expected between the two populations.
Drug exposure at steady state following the therapeutic dosing regimen	Drug exposure at steady state following the administration of 400 mg QD was derived using the final popPK model (Report 3882-0012) for the patient population of Study RAD1901-308 (N=232): Mean Conc4hr (used as surrogate for Cmax) = 119 (CV=43.6%) ng/mL Mean AUCtau = 2440 (CV=44.3%) ng x hr/mL
Minimal effective dose or exposure	Steady state mean Cmin (20 ng/mL) associated with high target engagement (mean % reduction from baseline of FES uptake ≥ 75%) in study RAD1901-106 was used as minimal effective exposure for dose selection/confirmation. Final popPK model-based simulations showed that at the recommended dose of 400 mg QD, simulated Cmin exceeded the Minimal effective threshold for the totality of patients compared to a dose of 200 mg QD, where approximately half of the patients was below the threshold.
Maximal tolerated dose or exposure	600 mg QD was the maximum dose studied in ER+/HER2- advanced/metastatic breast cancer patients (Study RAD1901-005). Despite no DLTs were observed in the 600 mg QD dose group, a combination of upper gastro-intestinal events limited the tolerability of this dose. Based on the overall safety profile, 400 mg QD was determined as the RP2D.

Dose Proportionality	Elacestrant exposure (AUC and Cmax) increased with increasing oral dose in a greater than dose-proportional manner after a single dose (> 50 mg) and after repeated dosing (> 25 mg QD). Additional details are provided in section 19.4.2.		
Accumulation	The mean accumulation ratio at steady state is 1.95 (CV%=15) at 200 mg QD administered for 7 days in healthy post-menopausal women in Study RAD1901-001.		
Variability	%CV for Cmax (Conc4hr) steady state = 43.6% %CV AUCtau steady state = 44.3% No clinically significant differences in the PK of elacestrant were predicted based on age, gender, and body weight, therefore no dose adjustment is warranted based on these covariates. Creatinine clearance was not found to affect elacestrant PK.		
Absorption			
Oral absolute bioavailability	Absolute bioavailability was determined in Study RAD1901-001 by comparing treatment with 1 mg IV to treatment with 100 mg PO, both under fasted condition: Estimated ratio of Ln-transformed AUC0-last: 0.10 (90% CI 0.08-0.13)		
Bioequivalent (BE) or relative Bioavailability (BA) GMR (90% CI)	BE study RAD1901-116 (commercial vs. clinical tablet formulation)		
	Cmax	AUC_{last}	AUC_{INF}
	99.24 (89.48-110.06) – 400 mg 100.29 (94.04-106.95) - 100 mg	95.45 (88.34-103.14) – 400 mg 98.47 (92.73-104.57) – 100 mg	95.50 (88.53-103.01) – 400 mg 98.52 (92.81-104.58) – 100 mg
Oral T_{max}	Following oral administration, elacestrant was rapidly absorbed, reaching Tmax within 1-4 hours. Elacestrant absorption is not affected by the concomitant administration of gastric pH-altering drugs.		
Food effect for Tablets formulation XX Fasted/fed GMR (90% CI)	Food effect study RAD1901-116		
	Cmax	AUC_{last}	AUC_{INF}
	141.89 (126.02-159.75) - 400 mg	122.28 (111.84-133.68) -400 mg	121.82 (111.64-132.92) -400 mg
Substrate transporter systems [in vitro]	The volume of distribution from the final popPK analysis was 422 L for central volume (Vc/F) and 5411 L for peripheral volume (Vp/F).		
Distribution			
Volume of Distribution	The volume of distribution from the final popPK analysis was 422 L for central volume (Vc/F) and 5411 L for peripheral volume (Vp/F).		
Plasma Protein Binding	In vitro, elacestrant was highly bound to human plasma proteins (protein binding > 99%). In Study RAD1901-117 the lowest mean percent unbound was 0.601% and the highest was 4.48%; the majority of samples ranged from 1% to 2.5%. Elacestrant can be coadministered without the need for dose adjustment in subjects receiving highly protein-bound drugs.		
Blood to Plasma Ratio	In a human mass balance study RAD1901-111, arithmetic mean blood to plasma concentration ratios ranged from 0.607 to 0.794.		
Elimination			

Half-life	The half-life of elacestrant is predicted to be approximately 30 hours based on the final popPK model with the achievement of steady-state conditions after approximately 1 week.
Clearance	The mean (% CV) clearance of elacestrant is predicted to be 186 L/hr (43.5%) in the final popPK model.
Metabolism	
Primary metabolic pathway(s)	Elacestrant is primarily metabolized by CYP3A4 with a potential small contribution by CYP2A6 and CYP2C9. In vivo, elacestrant PK is impacted by the coadministration of strong and moderate CYP3A4 inhibitors and inducers. Coadministration of strong and moderate CYP3A4 inhibitors and inducers should be avoided. No dose modifications are required for mild CYP3A4 inhibitors and inducers.
Inhibitor/Inducer	Elacestrant does not induce cytochromes P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP3A in human hepatocytes. Elacestrant does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A at therapeutic plasma concentrations. Elacestrant is not a clinically relevant inhibitor of the renal transporters OAT1, OAT3, OCT2, MATE1, and MATE2-K, or the hepatic transporters OCT1, OATP1B1, and OATP1B3, but it was found to be an inhibitor of P-gp and BCRP transporters.
Excretion	
Primary excretion pathways	Oral elacestrant was primarily eliminated from humans by oxidative metabolism and by fecal excretion. Excretion of unchanged elacestrant via urine was low (≤ 0.04% of the administered dose) with low value of CLr (≤ 2.30 mL/min) after single and multiple dosing. No dose adjustment is required for subjects with mild hepatic impairment whereas elacestrant dose should be reduced (b) (4) in subjects with moderate (b) (4) hepatic impairment, (b) (4).

The Applicant's Position:

Elacestrant clinical pharmacology has been well characterized in a series of clinical studies in healthy subjects and patients with ER+/HER2- advanced or metastatic breast cancer to support the appropriateness of the proposed elacestrant dose regimen.

The FDA's Assessment:

FDA agrees that elacestrant clinical pharmacology has been generally characterized except for the patients with severe hepatic impairment (Child-Pugh C). See the FDA's Assessment for Sections 6.3.2.3 for details.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. Results from population PK and exposure-response analyses showed that the proposed dose and dose intensity of elacestrant lead to an efficacy benefit in the proposed label population. Gastrointestinal AEs can be managed through taking elacestrant doses with food. Other AEs can be managed through dose interruptions and dose reductions as outlined in the proposed labeling. Therefore, elacestrant has a positive benefit-risk ratio at the proposed daily dose regimen.

The FDA's Assessment:

FDA agrees that the clinical pharmacology program provides evidence of effectiveness for the proposed dosage of 345 mg elacestrant once daily. See Section 6.2.2.1 for additional details.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The proposed dose of 345 mg once daily is effective and generally well tolerated in the proposed patient population with no dosing difference based on demographic characteristics. No new safety signals were identified in Phase 3 clinical development with AEs being effectively managed through dose interruption or reduction, food, or standard clinical practice. Safety data were consistent across clinical trials and with the mechanism of action. AEs were transient and reversible upon elacestrant discontinuation.

The FDA's Assessment:

The Applicant proposed 345 mg once daily (b) (4) as the recommended dosage of elacestrant. FDA agrees that this dosage regimen provides a favorable benefit-risk profile. (b) (4) FDA concludes that elacestrant should be administered with food to minimize the risk of gastrointestinal adverse reactions. See the FDA's Assessment in Section 6.2.2.1 for details.

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

The Applicant's Position:

No. There are no alternative dosing regimens or management strategies required for subpopulations of patients based on intrinsic patient factors outside of those included in the proposed labeling.

Demographic factors

Based on data from the pooled data from Phase 1 studies (RAD1901-004, RAD1901-109, RAD1901-110, RAD1901-112, RAD1901-113, RAD1901-114, RAD1901-115, RAD1901-005, and RAD1901-106) and the Phase 3 (RAD1901-308) study boxplots show an overlap of interquartile ranges and whiskers for each covariate, thus indicating that no dose adjustment is warranted based on body weight, age, and gender.

Special populations

Renal impairment:

The renal excretion of elacestrant is minimal, therefore no renal impairment studies were conducted, which was agreed upon by the Agency (Food and Drug administration [FDA] Meeting Minutes, 17 June 2019). The negligible role of renal function on elacestrant elimination was confirmed by the PopPK analysis, where creatinine clearance was found to have no effect on elacestrant clearance. Therefore, no dose adjustments are required in subjects with renal impairment.

Hepatic impairment:

Based on the results of the clinical study in subjects with mild and moderate hepatic impairment and PBPK analysis, no dose adjustment is required for subjects with mild hepatic impairment, whereas elacestrant dose should be reduced from 345 to 258 mg QD in subjects with moderate hepatic impairment (b) (4)

The FDA's Assessment:

FDA agrees with the Applicant's population PK analysis, where no alternative dosing strategies are needed based on age (24 to 89 years), sex, body weight (41 to 143 kg). See the FDA's Assessment in Section 19.4.3 for details.

Renal Impairment:

No alternative dosing strategies are needed for renal impairment. Renal excretion is not a major clearance pathway for elacestrant. Following a single radiolabeled oral dose of 345 mg in Study RAD1901-111, the renal excretion of elacestrant was minimal (< 1% unchanged elacestrant recovered in urine). The renal clearance (≤ 0.14 L/hr) of elacestrant was low compared to overall clearance (CL/F approximately 186 L/hr and F approximately 10%).

Hepatic Impairment:

The effect of mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B) on the PK of elacestrant has been evaluated in Study RAD1901-117, Table 10. For participants with mild (Child-Pugh A), Cmax and $AUC_{0\text{-}inf}$ increased to approximately 1.11 and 1.28-fold, respectively. The increase in Cmax and AUC in participants with mild hepatic impairment is not clinically relevant. For participants with moderate (Child-Pugh B), Cmax and $AUC_{0\text{-}inf}$ increased to approximately 1.14 and 1.83-fold, respectively. FDA agrees with the reduction of elacestrant dosage to 258 mg QD in patients with moderate (Child-Pugh B) hepatic impairment. The reduction of elacestrant dosage to 258 mg QD from 345 mg QD is expected to decrease elacestrant AUC by approximately 50%. The dose reduction is also supported by a PBPK modeling approach in patients with moderate hepatic impairment.

The Applicant used a PBPK model to assess the effect of severe hepatic impairment on the exposure of elacestrant. FDA does not agree that the severe hepatic impairment PBPK model, without validation by clinical data in severe hepatic impairment, is adequate. Refer to the FDA's Assessment in Section 19.4.5 for details regarding PBPK model. A PMR was issued to

conduct a pharmacokinetic trial to determine an appropriate dose of elacestrant in patients with severe hepatic impairment.

Table 10. Statistical Analysis of Pharmacokinetic Parameters (Hepatic Function Assessment) for Elacestrant Following Single Oral Doses for Protocol RAD1901-117

Parameter	Hepatic Function Group	n	GLSM	Test versus Reference Ratio of GLSMs (90% CI)	P-value
$AUC_{0-\infty}$ (h*ng/mL)	Normal Hepatic Function (Reference)	10	537		
	Mild Hepatic Impairment (Test)	10	687	1.2807 (0.8513, 1.9267)	0.2956
	Normal Hepatic Function (Reference)	10	516		
	Moderate Hepatic Impairment (Test)	10	942	1.8269 (1.3253, 2.5184)	0.0074
AUC_{0-t} (h*ng/mL)	Normal Hepatic Function (Reference)	10	529		
	Mild Hepatic Impairment (Test)	10	667	1.2608 (0.8437, 1.8842)	0.3179
	Normal Hepatic Function (Reference)	10	508		
	Moderate Hepatic Impairment (Test)	10	894	1.7615 (1.2965, 2.3932)	0.0080
C_{max} (ng/mL)	Normal Hepatic Function (Reference)	10	20.3		
	Mild Hepatic Impairment (Test)	10	22.4	1.1051 (0.9502, 1.2851)	0.2560
	Normal Hepatic Function (Reference)	10	17.8		
	Moderate Hepatic Impairment (Test)	10	20.3	1.1376 (0.8893, 1.4553)	0.3622

Source: Table 4 in Preliminary Pharmacokinetic Report of Study 2020-012-00US2

ESR1 mutation and treatment effect:

About 50% of endocrine resistant breast cancer cases are associated with *ESR1* mutations located in the ligand binding domain (Brett et al., 2021, Toy et al. 2017, O'Leary 2018; Dustin 2019). Patients with *ESR1*-mutated breast cancer usually have multiple *ESR1* genomic alterations (Chandarlapaty et al.,2016) and the *ESR1* Y537S mutation has been reported as a driver of resistance to fulvestrant plus palbociclib combination therapy (O'Leary et al, 2018; Dustin et al, 2019). Because of the role of *ESR1* mutations in endocrine resistance, *ESR1* mutation status was selected as one of the stratification factors in study RAD1901-308, and the trial was powered to detect improvements in PFS in this group of patients. In study RAD1901-308, ctDNA was analyzed using the FDA-approved Guardant360 (Guardant Health) assay to detect the presence of *ESR1* mutations at enrollment and patients were considered *ESR1* mutation-positive if missense mutations were detected in the ligand binding domain. A total of 228 *ESR1* mutation-positive patients were enrolled, and 70 unique mutations were detected with 58 (83%) unique point mutations. The most common *ESR1* mutations were D538G (30%) and Y537S (19%), followed by Y537N (14%) and E380Q (7%) (Table 11). Forty patients had co-occurring mutations for D538G and Y537S (17.5%). FDA conducted exploratory analyses assessing the impact of *ESR1* mutations on elacestrant efficacy in the *ESR1* mutation-positive population of study RAD1901-308. Hazard ratios were estimated from a Cox proportional hazards model stratified by prior treatment with fulvestrant (yes vs no), and visceral metastasis (yes vs no). Patients carrying only the Y537S mutation showed the largest treatment effect

(HR=0.26, 95% CI: 0.10-0.67), while patients with neither Y537S or D538G mutations (i.e., patients with other *ESR1* ligand-binding domain mutations) showed similar treatment effect in the elacestrant arm and the SOC arm; these results suggest that the benefit of elacestrant compared to SOC treatments may differ depending on the *ESR1* mutation profile (Table 12). Although these results suggest variable responses based on *ESR1* mutations, the analysis was exploratory and data are limited, thus precluding definitive conclusions regarding efficacy for any particular subset.

Table 11. Most Frequently Observed *ESR1* Mutations in Study RAD1901-308

ESR1 Mutation	Total N	Elacestrant (N=115) (N%)*	SOC(N=113) (N%)*
D538G	137	69 (60.0%)	68 (60.2%)
Y537S	87	48 (41.7%)	39 (34.5%)
Y537N	63	33 (28.7%)	30 (26.5%)
E380Q	30	15 (13.0%)	15 (13.3%)
L536H	16	7 (6.1%)	9 (8.0%)
Y537C	14	7 (6.1%)	7 (6.2%)
L536P	9	5 (4.3%)	4 (3.5%)
S463P	7	3 (2.6%)	4 (3.5%)
L536L	7	3 (2.6%)	4 (3.5%)
L536R	7	3 (2.6%)	4 (3.5%)
V422del	6	2 (1.7%)	2 (1.8%)
H524L	4	2 (1.7%)	2 (1.8%)
Y537D	4	2 (1.7%)	2 (1.8%)

*Source: Reviewer exploratory analysis based on PF and ADSL datasets. ESR1=estrogen receptor 1; SOC = Standard of Care * Percentage of patients in study arm with the specific mutation, numbers do not equal 100% because some patients had more than one mutation. Mutations observed in more than one percent were included in the table.*

Table 12. *ESR1* Mutations and Elacestrant PFS in Patients with *ESR1* Mutated Population in Study RAD1901-308 (N=228)

ESR1 Mutation*	Elaces-trant (N)	SOC (N)	PFS Events in Elacestrant (N %)	PFS Events in SOC (%)	Median PFS months *** (95% CI) in Elacestrant	Median PFS months *** (95% CI) in SOC	HR (95%CI) ****
Y537S only	24	23	13 (54.17)	13 (56.52)	3.8 (1.9-10.8)	1.8 (1.7-3.9)	0.26 (0.10-0.67)
D538G only	45	52	24 (53.33)	40 (76.92)	5.0 (1.9-12.6)	1.9 (1.8-2.1)	0.51 (0.30-0.88)
Both*	24	16	11 (45.83)	12 (75.00)	3.7 (2.1-NE)	2.1 (1.8-3.8)	0.49 (0.19-1.21)
Neither**	22	22	14 (63.64)	13 (59.09)	3.7 (1.8-7.8)	3.7 (1.9-9.1)	1.12 (0.47-2.68)
Total	115	113	14 (60.87)	78 (69.03)	3.8 (2.2-7.3)	1.9 (1.9-2.1)	0.55 (0.39-0.77)

*Source: Reviewer exploratory analysis based on PF, ADSL, ADRS, and ADTTE datasets. ESR1=estrogen receptor 1; SOC = Standard of Care; PFS = Progression Free Survival; CI= Confidence Interval; HR = Hazard Ratio; *Both - Patients with both Y537S and D538G mutations; **Neither– Patients with neither Y537S nor D538G mutation. *** Kaplan-Meir estimate; 95% CI based on the Brookmeyer-Crowley method using a linear transformation. **** Hazard ratios were estimated from a Cox proportional hazards model stratified by prior treatment with fulvestrant (yes vs no), and visceral metastasis (yes vs no).*

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

The Applicant's Position:

Effect of Food

A slightly higher but not clinically relevant exposure was observed with high-fat compared to low-fat meals as described in Section 6.2.2.2. Therefore, elacestrant can be taken without regard to food. However, improved gastrointestinal tolerability was observed when tablets were taken with food.

Coadministration with CYP3A4 Inhibitors

Coadministration of elacestrant with itraconazole (strong CYP3A4 inhibitor) increased elacestrant C_{max} by 4.4-fold and AUC by 5.3-fold (Study RAD1901-110). The PBPK model predicted an increase in elacestrant AUC between ≥ 2- and < 5-fold when elacestrant is coadministered with moderate CYP3A4 inhibitors (i.e., fluconazole and erythromycin). Coadministration of elacestrant with a strong or moderate CYP3A4 inhibitor may increase adverse reactions and should be avoided. No dose modifications are required for mild CYP3A4 inhibitors.

Coadministration with CYP3A4 Inducers

Coadministration of elacestrant with rifampin (strong CYP3A4 inducer) decreased the elacestrant C_{max} by 73% and AUC by 86% (Study RAD1901-113). The PBPK model predicted a decrease in elacestrant AUC between ≥ 50% and < 80% when elacestrant is coadministered with moderate CYP3A4 inducer (i.e., efavirenz). Coadministration of elacestrant with a strong or moderate CYP3A4 inducers may decrease elacestrant activity and should be avoided. No dose modifications are required for mild CYP3A4 inducers.

Coadminstration with Acid-Reducing Agents

Coadministration of the proton pump inhibitor omeprazole (40 mg QD) had no effect on the single oral dose PK profile of elacestrant in healthy men and postmenopausal women (Study RAD1901-115). Therefore, no dose modifications are needed with coadministration with acid-reducing agents.

Coadministration with Highly Protein-Bound Drugs

Coadministration of elacestrant with warfarin (both very highly protein-bound drugs) showed no significant effect on either elacestrant or warfarin PK. The PD of warfarin were also unaffected by the presence of elacestrant (Study RAD1901-114). No dose modifications are necessary with coadministration of highly protein-bound drugs.

Coadministration with P-gp Substrates

Use of elacestrant with digoxin (P-gp substrate) slightly increased digoxin exposure by 27% for C_{max} and 13% for AUC. Monitor digoxin administration and reduce digoxin dose as necessary.

Coadministration with BCRP Substrates

Use of elacestrant with rosuvastatin (BCRP substrate) slightly increased rosuvastatin exposure by 45% for C_{max} and 23% for AUC. Monitor rosuvastatin administration and reduce rosuvastatin dose as necessary.

The FDA's Assessment:

(b) (4)

Although there is no clinically relevant food effect for elacestrant in terms of exposure in plasma, administering elacestrant with food improves gastrointestinal tolerability. FDA concludes that elacestrant should be administered with food to minimize the risk of gastrointestinal adverse reactions. During the clinical development, all the clinical studies in breast cancer patients (RAD1901-308, RAD1901-005 and RAD1901-106) were conducted with food to minimize the risk of gastrointestinal adverse reactions. There is no data in patients with breast cancer regarding gastrointestinal tolerability to support administering elacestrant without food.

FDA agrees with the Applicant's position on CYP3A4 inhibitor, CYP3A4 inducer, acid-reducing agents, highly protein-bound drugs, P-gp substrates, and BCRP substrates.

6.3.2.2 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The Applicant's Position:

Yes, the Applicant conducted the pivotal bioequivalence study (Study RAD1901-116) to bridge the proposed to-be-marketed formulation to the clinical formulation used in pivotal clinical trials. The pivotal BE study demonstrated that:

- Elacestrant 345 mg Commercial tablets and 345 mg Clinical tablets administered in fasting condition are bioequivalent as the 90% CIs of GMRs for peak and extent of exposures are within the 80.00% to 125.00% interval.
- Elacestrant 86 mg Commercial tablets and 86 mg Clinical tablets administered in fasting condition are bioequivalent as the 90% CIs of GMRs for peak and extent of exposures are within the 80.00% to 125.00% interval.

Moreover, median differences in Tmax between the two formulations were not statistically significant for both the tested doses.

This pivotal BE study evaluated also the effect of a high-fat meal on the Elacestrant 345 mg Commercial tablet. The results showed for the commercial tablet a mean increase in exposure of 22% on AUCs and of 42% on Cmax when administered with a high-fat meal. This food effect is similar to that observed in Study RAD1901-109 for the clinical tablets where a mean increase of 36% on AUC and of 26% on Cmax was observed when administered with a high-fat meal.

In addition, the effect of the formulation was evaluated during the PopPK model development on Ka, Tlag and F1 and resulted not statistically significant.

The FDA's Assessment:

FDA agrees with the Applicant's position.

X	X
Wentao Fu	Salaheldin Hamed
Jianghong Fan	Manuela Grimstien
Jielin Sun	Robert Schuck
Fang Li	Jingyu Yu
Primary Reviewers	Team Leaders

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Table 13: Listing of Clinical Studies

Study Number/ Study Type	Study Objective(s)	Key Design	Study Population Number of Subjects (M/F) Median Age (Min, Max)	Treatment	Study Status/Study Report
RAD-1901-001/ Phase 1	Safety, tolerability, and single- and multiple-dose PK of elacestrant; bioavailability; ascending dose; and food effect	Single-ascending- and multiple-ascending-dose PK	Postmenopausal women Healthy subjects N=80 SAD n=32 (24 elacestrant/8 placebo) (0 male/32 female) 66 (57, 75) years MAD: n=48 (38 elacestrant/10 placebo) (0 male/48 female) 62 (50, 75) years	SAD: Elacestrant or placebo Group 1: 1 and 22 mg capsule, fasted Group 2: 9 and 173 mg capsule, fasted Group 3: 50 mg capsule, fasted and fed Group 4: 86 mg capsule and 1 mg IV, fasted MAD: Elacestrant 9, 22, 43, 86, and 173 mg capsule or placebo QD for 7 days	Completed/ Final CSR
RAD1901-004/ Phase 1	MTD, safety, tolerability, PD, and PK of elacestrant and elacestrant concentrations in CSF	Multiple-dose PK	Postmenopausal women Healthy subjects N=52 (44 elacestrant/8 placebo) (0 male/52 female) Mean age: 59 to 64 (50, 75) years across groups	Elacestrant 173, 431, 647, and 863 mg capsule or placebo QD for 7 days	Completed/ Final CSR
RAD1901-109/ Phase 1	Effect of food on elacestrant PK	Single-dose food effect	Postmenopausal women and men Healthy subjects N=18 (9 male/9 female) 58 (42, 73) years	Elacestrant 345 mg tablet, single oral dose on Day 1 of each period	Completed/ Final CSR

Study Number/ Study Type	Study Objective(s)	Key Design	Study Population Number of Subjects (M/F) Median Age (Min, Max)	Treatment	Study Status/Study Report
RAD1901-110/ Phase 1	Effect of strong CYP3A4 inhibitor itraconazole on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18 (9 male/9 female) 59 (40, 70) years	Elacestrant 173 mg tablet QD for the first 7 days followed by elacestrant 173 mg tablet QD coadministered with itraconazole 200 mg capsule QD for the next 7 days	Completed/ Final CSR
RAD1901-111/ Phase 1	Absorption, metabolism, distribution, and excretion of ^{14}C-elacestrant	ADME (mass balance)	Men Healthy subjects N=7 (7 male/0 female) 40 (26, 55) years	^{14}C-elacestrant 345 mg capsule, single oral dose	Completed/ Final CSR
RAD1901-112/ Phase 1	Relative bioavailability (2 prototype tablets compared to clinical tablet) and food effect	Relative bioavailability and food effect	Postmenopausal women and men Healthy subjects N=36 (27 male/9 female) <u>Cohort 1</u>: N=18 (14 male/4 female) 49 (40, 58) years <u>Cohort 2</u>: N=18 (13 male/5 female) 53 (42, 59) years	<u>Cohort 1:</u> Single, oral doses of each of the following: Treatment A: elacestrant 345 mg, fed Treatment B: Prototype 1 345 mg, fasted Treatment C: Prototype 1 345 mg, fed <u>Cohort 2:</u> Single, oral doses of each of the following: Treatment A: elacestrant 345 mg, fed Treatment D: Prototype 2 345 mg, fasted Treatment E: Prototype 2 345 mg, fed	Completed/ Final CSR

Study Number/ Study Type	Study Objective(s)	Key Design	Study Population Number of Subjects (M/F) Median Age (Min, Max)	Treatment	Study Status/Study Report
RAD1901-113/ Phase 1	Effect of strong CYP3A4 inducer rifampin on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18 (12 male/6 female) 56 (43, 74) years	Treatment A: elacestrant 345 mg tablet, single oral dose on Day 1, Period 1 Treatment B: rifampin 600 mg QD (2×300 mg capsules) on Days 1 to 14; with single oral dose of elacestrant 345 mg tablet on Day 7, Period 2, approximately 1.5 hours after rifampin dose	Completed/ Final CSR
RAD1901-114/ Phase 1	Effect of highly protein-bound drugs warfarin and elacestrant on each other's PK	DDI	Postmenopausal women and men Healthy subjects N=18 (12 male/6 female) 54 (42, 60) years	Treatment A: elacestrant 345 mg tablet, single oral dose on Day 1 Treatment B: warfarin 25 mg (2×10 mg and 1×5 mg tablets), single oral dose on Day 1 Treatment C: elacestrant 345 mg tablet coadministered with warfarin 25 mg (2×10 mg and 1×5 mg tablets), single oral dose on Day 1	Completed/ Final CSR
RAD1901-115/ Phase 1	Effect of proton pump inhibitor omeprazole on elacestrant PK	DDI	Postmenopausal women and men Healthy subjects N=18 (13 male/5 female) 50 (40, 59) years	Treatment A: elacestrant 345 mg tablet, single oral dose on Day 1, Period 1 Treatment B1: multiple QD doses of omeprazole 40 mg capsules on Days 1 to 5 prior to elacestrant 345 mg tablet coadministration on Day 5, Period 2 Treatment B2: multiple QD doses of omeprazole 40 mg capsules on Days 5 to 12 following elacestrant tablet coadministration on Day 5, Period 2	Completed/ Final CSR

Study Number/ Study Type	Study Objective(s)	Key Design	Study Population Number of Subjects (M/F) Median Age (Min, Max)	Treatment	Study Status/Study Report
RAD1901-116/ Phase 1	BE (commercial tablets compared to clinical tablets) and food effect	BE and food effect	Postmenopausal women and men Healthy subjects N=84 <u>Cohort 1: 345 mg strength:</u> N=42 (37 male/5 female) 43 (23, 63) years <u>Cohort 2: 86 mg strength:</u> N=42 (38 male/4 female) 44 (24, 65) years	<u>Cohort 1:</u> Single, oral doses of each of the following: Treatment A: elacestrant 345 mg clinical tablet, fasted Treatment B: elacestrant 345 mg commercial tablet, fasted Treatment C: elacestrant 345 mg commercial tablet, fed <u>Cohort 2:</u> Single, oral doses of each of the following: Treatment D: elacestrant 86 mg clinical tablet, fasted Treatment E: elacestrant 86 mg commercial tablet, fasted	Completed/ Final CSR

Study Number/ Study Type	Study Objective(s)	Key Design	Study Population Number of Subjects (M/F) Median Age (Min, Max)	Treatment	Study Status/Study Report
RAD1901-117/ Phase 1	Effect of mild or moderate hepatic impairment on elacestrant PK	Nonrandomized, open-label, parallel-group, hepatic impairment	Women and men with mild and moderate hepatic impairment or healthy subjects N=36 Normal hepatic function: N=16 (11 male/5 female) 58 (51, 68) years Mild hepatic impairment: N=10 (5 male/5 female) 64 (49, 75) years Moderate hepatic impairment: N=10 (9 male/1 female) 60 (48, 71) years	Elacestrant 173 mg (2×86 mg tablets), single oral dose	Completed/ Final CSR
RAD1901-118/ Phase 1	Effect of elacestrant on the digoxin and rosuvastatin PK in healthy subjects (transporter-mediated DDI: P-gp and BCRP)	DDI	Women and men Healthy subjects <u>Cohort 1:</u> Digoxin: N=15 (12 male/3 female) 53 (26, 59) years <u>Cohort 2:</u> Rosuvastatin: N=21 (14 male/7 female) 56 (22, 72) years	<u>Cohort 1:</u> Single, oral doses of the following: Day 1: digoxin 0.5 mg (2×0.25 mg tablets) Day 9: digoxin 0.5 mg (2×0.25 mg tablets) + elacestrant 345 mg tablet <u>Cohort 2:</u> Single, oral doses of the following: Day 1: rosuvastatin 20 mg tablet Day 6: rosuvastatin 20 mg tablet + elacestrant 345 mg tablet	Completed/ Final CSR

Study Number/ Study Type	Study Objective(s)	Key Design	Study Population Number of Subjects (M/F) Median Age (Min, Max)	Treatment	Study Status/Study Report
RAD1901-005/ Phase 1	Safety, tolerability, PK, and MTD and/or RP2D of elacestrant	Open-label, multicenter, multipart dose escalation	Postmenopausal women with mBC N=57 (33 capsule/24 tablet) (0 male/57 female) 62 (43, 81) years	Part A: elacestrant 173, 345, and 518 mg capsule QD in 28-day cycles Part B: elacestrant 345 mg capsule QD in 28-day cycles Parts C and D: elacestrant 345 mg tablet QD in 28-day cycles	Completed/ Final CSR
RAD1901-106/ Phase 1b	Effect of elacestrant on ER expression and estradiol binding using FES-PET imaging	Nonrandomized, open-label, multicenter, 2-dose cohort study	Postmenopausal women with mBC N=16 (16 capsule/2 tablet) (0 male/16 female) 54 (43, 84) years	Elacestrant tablet and capsule Cohort 1: Elacestrant 345 mg QD Cohort 2: Elacestrant 173 mg QD on Days 1 to 14 and then escalated to elacestrant 345 mg QD	Completed/ Final CSR
RAD1901-308 (EMERALD)/ Phase 3	Efficacy (PFS) of elacestrant versus active comparators	Randomized, open-label, active-controlled, multicenter	Postmenopausal women and men with mBC N=478 (7 male/471 female) 63 (24, 89) years	Elacestrant 345 mg tablet QD or SOC (fulvestrant [500 mg IM], anastrozole [1 mg QD oral], letrozole [2.5 mg QD oral], or exemestane [25 mg QD oral]) in 28-day cycles	Enrollment completed/ Final interim CSR
Studies in Vasomotor Symptoms					
RAD1901-002/ Phase 2	Safety and efficacy of elacestrant on vasomotor symptoms	Double-blind, multicenter, placebo-controlled	Postmenopausal women with vasomotor symptoms N=100 (81 elacestrant/19 placebo) (0 male/100 female) 53 (44, 71) years	Elacestrant 9, 22, 43, and 86 mg capsule or placebo QD for 28 days	Completed/ Final CSR

Study Number/ Study Type	Study Objective(s)	Key Design	Study Population Number of Subjects (M/F) Median Age (Min, Max)	Treatment	Study Status/Study Report
VMRAD1901-203/ Phase 2b	Safety and efficacy of elacestrant on vasomotor symptoms	Double-blind, multicenter, placebo-controlled	Postmenopausal women with vasomotor symptoms N=138 (100 elacestrant/ 38 placebo) (0 male/138 female) 55 (41, 65) years	Elacestrant 5, 9, and 18 mg capsule or placebo QD for 12 weeks	Completed/ Final CSR

Abbreviations: ADME = absorption, distribution, metabolism, and excretion; BCRP = breast cancer resistance protein; BE = bioequivalence; CSF = cerebrospinal fluid; CSR = clinical study report; CYP3A4 = cytochrome P450 3A4; DDI = drug-drug interaction; ER = estrogen receptor; F = female; FES-PET = 16α-^{18}F-fluoro-17β-estradiol positron emission tomography; IM = intramuscular; M = male; MAD = multiple-ascending dose; max = maximum; mBC = metastatic breast cancer; min = minimum; MTD = maximum tolerated dose; PD = pharmacodynamics; PFS = progression-free survival; P-gp = P-glycoprotein; PK = pharmacokinetics; QD = once daily; RP2D = recommended Phase 2 dose; SAD = single-ascending dose.
Source: Module 5.2

The Applicant's Position:

Table 13 briefly describes the clinical studies included in NDA 217639.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the trials for elacestrant listed in Table 13. The FDA's evaluation of efficacy and safety is primarily based on results from Study RAD1901-308 (EMERALD).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position

Preliminary results from 2 Phase 1 studies conducted in postmenopausal women with pretreated ER+/HER2- mBC (Studies RAD1901-005 and RAD1901-106) demonstrated that elacestrant had manageable safety and tolerability and antitumor activity as monotherapy. Based on these results, the pivotal Phase 3 study (Study RAD1901-308) was conducted. Study RAD1901-308 was an international, multicenter, randomized, open-label, active-controlled study of elacestrant versus SOC therapy (fulvestrant or AI) in postmenopausal women and men with advanced or metastatic ER+/HER2- breast cancer. The design of this study was discussed with the FDA at the End-of-Phase 2 meeting, and the final statistical analysis plan (SAP) was reviewed by the Agency prior to locking the database.

The primary endpoints of PFS were evaluated in 2 groups of subjects: *ESR1*-mut subjects and all subjects (*ESR1*-mut + *ESR1*-mut-nd). The statistical analyses of these endpoints were performed using a truncated Hochberg procedure (Dmitrienko et al, 2011) to control the family-wise type I error rate and to allow alpha to pass along from the analyses of the primary endpoint of PFS to the analyses of the key secondary endpoint of overall survival (OS) performed with the traditional Hochberg procedure (Hochberg, 1988).

8.1.1. Study RAD1901-308

Trial Design

The Applicant's Description:

Study RAD1901-308 Main Design Overview

Study RAD1901-308 was an international, multisite, randomized, open-label, active-controlled, event-driven, Phase 3 clinical study comparing the efficacy and safety of elacestrant to the SOC options of either fulvestrant or an AI in postmenopausal women and men with ER+/HER2- mBC whose disease had relapsed or progressed on 1 or 2 prior lines of endocrine therapy for mBC. The prior lines of therapy must have included CDK4/6 inhibitor therapy in combination with fulvestrant or an AI. Subjects must have received no more than 1 line of cytotoxic chemotherapy for mBC. Endocrine monotherapy with 1 of the SOC drug options (fulvestrant, anastrozole, letrozole, or exemestane) must have been an appropriate treatment option for subjects enrolled in this study.

Subjects who met all eligibility criteria were enrolled into the active treatment phase of the study and randomized in a 1:1 ratio to either elacestrant or SOC – the specific SOC treatment was at the investigator's discretion. In the active treatment phase, subjects received study treatment and underwent efficacy (primarily tumor assessments at 8-week intervals), standard safety, and other assessments, including PROs/health-related quality of life (HRQOL), in support of the preplanned analysis endpoints. Subjects continued to receive treatment until any of the following occurred:

- Disease progression

- Clinically significant AEs (as determined by the investigator)
- Significant study noncompliance
- Subject unable to receive study treatment for > 14 consecutive days (unless approved by the Sponsor)
- Treatment discontinuation was in the best interest of the subject
- Subject refused further investigational treatment

Study subjects and investigators were not blinded to treatment assignment.

Subjects who discontinued the active treatment phase due to disease progression entered a follow-up phase, during which survival data and the start date and regimen name of the first new anticancer therapy were collected. For subjects who discontinued treatment for reasons other than disease progression, death, consent withdrawal, toxicity, or loss to follow-up and who did not begin new anticancer therapy, tumor assessments continued until disease progression or the first new anticancer therapy was initiated. At that time, subjects discontinued tumor assessments and continued to be monitored for survival data and the initiation of the first new anticancer therapy.

It was estimated that approximately 466 subjects (220 *ESR1*-mut and 246 *ESR1*-mut-nd) would have to be enrolled in the study in a 1:1 randomization.

Main Inclusion Criteria

- Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either locally advanced disease not amenable to resection or radiation therapy with curative intent or metastatic disease not amenable to curative therapy
- Appropriate candidates for endocrine monotherapy
- Response Evaluation Criteria in Solid Tumors version 1.1 measurable disease or bone-only disease with evaluable lesions
- Postmenopausal female or male ≥ 18 years of age
- Male subjects had to, even if surgically sterilized (i.e., status postvasectomy):
    - Agree, if appropriate, to practice highly effective barrier contraception
- ER+/ HER2- tumor status confirmed per local laboratory testing
    - Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry with or without progesterone receptor positivity
    - Documentation of HER2- tumor with an immunohistochemistry result of 0 or 1+ for cellular membrane protein expression or an in-situ hybridization negative result
- Must have previously received at least 1 and no more than 2 lines of endocrine therapy, either as monotherapy or as a combination therapy with another agent (e.g., phosphoinositide 3-kinase inhibitor), for mBC
- Must have progressed during or within 28 days of completion of prior treatment with a CDK4/6 inhibitor in combination with either fulvestrant or an AI (this counts as a line of prior endocrine therapy) for mBC
- Must have received no more than 1 line of cytotoxic chemotherapy in the advanced/metastatic setting

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1
- Resolution of all toxic effects of prior therapies or surgical procedures to Grade ≤ 1 (except alopecia and peripheral neuropathy)
- Adequate hematologic, renal, and hepatic function
- Ability to understand the protocol and provide informed consent

Dose and Mode of Administration

Elacestrant was administered QD on a continuous dosing schedule in 28-day cycles as a 100-mg or 400-mg white film-coated tablet. The starting dose was 345 mg QD. Dose reductions to a minimum of 173 mg were permitted.

The following SOC options were available for subjects randomized to this treatment group:

- Fulvestrant (for patients who received prior AIs in the metastatic setting): 500 mg administered IM into the buttocks as two 5 mL injections on Cycle 1 Day 1 (C1D1), C1D15, C2D1, and Day 1 of every subsequent 28-day cycle
- AIs (for patients who received prior fulvestrant in the metastatic setting)
    - Anastrozole: 1 mg QD orally on a continuous dosing schedule
    - Letrozole: 2.5 mg QD orally on a continuous dosing schedule
    - Exemestane: 25 mg QD orally on a continuous dosing schedule

The investigator was to select 1 of the available SOC options according to what was appropriate based on the individual subject's prior treatment history and the investigator's judgment.

Duration of Treatment

Subjects were to continue to receive treatment until any of the following occurred: disease progression, clinically significant AE (as determined by the investigator), significant study noncompliance, subject unable to receive study treatment for > 14 consecutive days (unless approved by the Sponsor), treatment discontinuation was in the best interest of the subject, or subject refused further investigational treatment.

Discussion of Key Study Design Elements

The study design was finalized after consultation with the US FDA who confirmed that the PFS endpoint, randomized 1:1 trial design, choice of comparator drug, and statistical analysis would be consistent with the currently recognized standards in this patient population. Study RAD1901-308 was designed in line with European Medicines Agency (EMA) and FDA guidance.

Discussion of Elacestrant Dose Selection

The 345 mg QD dose of elacestrant used in this study was selected based on nonclinical data and safety, efficacy, and PK data from 6 clinical studies of elacestrant: 2 Phase 1 in healthy postmenopausal volunteers, 2 Phase 1 in postmenopausal women with mBC, and 2 in Phase 2 in subjects with vasomotor symptoms. Phase 1 studies in subjects with ER+/HER2- mBC also demonstrated single-agent efficacy regardless of *ESR1* mutational status.

Discussion of Study Population Selection

Under the current treatment paradigm, the patient population enrolled in this study is considered to have a high unmet medical need as assessed by the clinical outcome of available SOC therapy. The study population enrolled in Study RAD1901-308 is representative of the proposed indication patient population. When the study was initiated, no randomized trial results for the treatment of subjects progressing after first- or second-line therapy including a CDK4/6 inhibitor were available. More recently, data from the VERONICA trial showed that treatment with fulvestrant as a single agent was associated with a median PFS of only 1.94 months and a limited CBR of 13.7% (Lindeman et al, 2021).

Choice of the Control Arm

The choice of SOC was based on treatment guidelines available when the trial was initiated in 2018 that recommended continued endocrine therapy in the absence of visceral crisis, or until all endocrine therapy options have been exhausted (National Comprehensive Cancer Network [NCCN] 2018). It is worth noting that current guidelines (NCCN, 2022; Moy et al, 2021; Cardoso et al, 2020; Burstein et al, 2021) still provide this same recommendation.

After failure of the combination of endocrine therapy and CDK4/6 inhibitors, there are limited therapeutic options. Current treatment guidelines recommend sequential endocrine therapy in the absence of visceral crisis or until all endocrine therapy options have been exhausted (NCCN, 2018; NCCN, 2022, Gennari et al, 2021). Endocrine therapy includes monotherapy, such as fulvestrant, if the first-line therapy was AI-based, or AIs, if the first-line therapy was fulvestrant-based (NCCN, 2022; Gennari et al, 2021). Combination therapy, e.g., everolimus and exemestane and for subjects with PIK3CA-mutant breast cancer, fulvestrant and alpelisib are associated with approximate 20%-25% discontinuation rate for AEs in clinical trials (everolimus USPI; alpelisib USPI). In summary, the choice of the control arm follows the current guidelines for the treatment of subjects with ER+/HER2- metastatic breast cancer after progression on the combination of endocrine therapy and a CDK4/6 inhibitor (19 June 2018, FDA Meeting Minutes).

In addition, the design allowed investigators to tailor the choice of comparator agent according to a subject's prior treatment history, that is, patients who received prior AI in the advanced/metastatic setting were to receive fulvestrant in control arm, and vice versa. This reflects the current treatment landscape for many ER+/HER2- subjects who wish to delay chemotherapy. Furthermore, the choice of the control arm benefited from discussion and advice received from FDA.

Selection of Stratification Factors

The 3 stratification factors used at randomization are known prognostic factors in this patient population.

Given the role of *ESR1* mutations in endocrine resistance (Chandarlapaty et al, 2016; Nardone et al, 2015; O'Leary et al, 2018; Dustin et al, 2019), *ESR1* mutation status was selected as one of

the stratification factors and the trial was powered to detect significant improvements in PFS in this group of patients.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of Study RA1901-308 with the following additions and clarifications to the information provided by the Applicant:

Eligibility criteria

- Patients must have had an ECOG performance status of 0 or 1 to be eligible for this trial. The FDA notes that this may not be entirely representative of the general population of men and women with ER-positive, HER2-negative advanced or metastatic breast cancer who are candidates for endocrine monotherapy, as patients with ECOG PS >1 may also be candidates for endocrine monotherapy.

Detection of *ESR1* mutations

- Patients were required to provide blood samples for circulating tumor DNA (ctDNA) analysis for enrollment. Samples were analyzed using the Guardant360 (Guardant Health) assay for detection of *ESR1* mutations. The designation of '*ESR1* detected' (*ESR1*-mut) was assigned if an *ESR1* mutation(s) was present. The designation of 'No *ESR1* mutation detected' (*ESR1*-mut-nd) was assigned if there was no *ESR1* mutation(s) present or if there was no detectable ctDNA present in the blood sample.
- Regardless of the results of blood-based testing for *ESR1* mutations, patients were not required to undergo tissue testing for *ESR1* mutation.
- In an IR response received by FDA on January 9, 2023, the Applicant clarified that *ESR1* mutation results were not provided to patients or investigators. Results were provided to sites semi-blinded (coded as Group A or Group B) for randomization purposes. *ESR1* results could be requested by the site when trial treatment was discontinued to help guide future treatment decisions for the patient.

Elacestrant Dosage

- In FDA's assessment, one sentence under Dose and Mode of Administration above contains an error. The Sponsor states that "Elacestrant was administered QD on a continuous dosing schedule in 28-day cycles as a **100-mg or 400-mg** white film-coated tablet." Elacestrant was actually administered QD as either a **86 mg or 345 mg** tablet.
- The other information regarding the elacestrant dosage throughout this section appears to be correct.

Control arm

- For patients assigned to receive investigator's choice SOC treatment, investigators received the general guidance that patients who had not received prior fulvestrant should receive fulvestrant. Patients who had progressed on prior fulvestrant should receive an AI.

- Although endocrine treatment as monotherapy appeared to be a reasonable treatment option at the time Study 1901-308 was designed, emerging data suggest that fulvestrant may be associated with a shortened PFS following treatment with a CDK 4/6 inhibitor. For more discussion regarding available therapies and the treatment paradigm, refer to the FDA's Assessment in Section 2.2.

Stratification factors

- The Applicant listed *ESR1* mutation status (detected or not detected) as a stratification factor. The other two stratification factors were prior treatment with fulvestrant (yes or no) and presence of visceral metastases (yes or no).

Concomitant therapy

- Patients were permitted to receive palliative radiotherapy while on trial treatment if there were no other options available for pain management. For FDA's analysis of the impact of concomitant palliative radiotherapy, refer to Efficacy Results – Primary Endpoint (Including Sensitivity Analyses).

Study Objectives

The Applicant's Description:

Primary:

- To demonstrate that elacestrant, when compared with the SOC options of either fulvestrant or an AI, is superior in prolonging PFS based on a blinded Imaging Review Committee (IRC) assessment in postmenopausal women and men with estrogen receptor positive/human epidermal growth factor receptor 2 negative (ER+/HER2-) advanced/metastatic breast cancer (mBC) either in subjects with *ESR1* mutations (*ESR1*-mut subjects) or in all subjects, which includes subjects without detectable *ESR1* mutations (*ESR1*-mut-nd)

Key Secondary:

- To compare OS between treatment groups in *ESR1*-mut subjects
- To compare OS between treatment groups in all subjects (*ESR1*-mut + *ESR1*-mut-nd)

Other Secondary:

The following secondary objectives were assessed for *ESR1*-mut-nd subjects:

- To compare PFS based on blinded IRC assessment between treatment groups
- To compare OS between treatment groups

The following secondary objectives were assessed for *ESR1*-mut subjects, *ESR1*-mut-nd subjects, and all subjects (ESR-mut + *ESR1*-mut-nd)

- To compare PFS based on local investigator assessment between treatment groups
- To compare ORR based on blinded IRC assessment between treatment groups
- To compare duration of response (DoR) based on blinded IRC assessment between treatment groups

- To compare CBR based on blinded IRC assessment between treatment groups
- To compare ORR based on local investigator assessment between treatment groups
- To compare DoR based on local investigator assessment between treatment groups
- To compare CBR based on local investigator assessment between treatment groups

The following other secondary objectives were assessed for *ESR1* mut subjects and all subjects (*ESR1*-mut + *ESR1*-mut-nd):

- To compare the safety and tolerability between treatment groups
- To assess the PK of elacestrant
- To describe the changes in PROs and HRQOL and the changes in PROs/HRQOL between treatment groups

Exploratory:

The following exploratory objectives were planned to be assessed in *ESR1*-mut subjects, *ESR1*-mut-nd subjects, and all subjects (*ESR1*-mut + *ESR1*-mut-nd):

- To determine the difference in time to chemotherapy between treatment groups
- To evaluate alterations in circulating tumor DNA relevant to ER+ breast cancer and the CDK4/6 pathway and to explore the relationship between these findings and clinical response
- To characterize alterations in tumor-specific genes, proteins, and RNAs related to oncogenic pathways and proliferation and cell cycle markers in tumor tissues and to explore the relationship between these findings and clinical response

The FDA's Assessment:

The FDA agrees with the Applicant's description of the trial objectives. Although the primary endpoint was PFS as assessed by IRC, patients continued or stopped trial treatment based on investigator assessment for progression of disease. A large number of patients were censored for PFS because the investigator determined that the patient experienced disease progression but the IRC did not determine disease progression. For the FDA's analysis of censoring on the PFS results, refer to the Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) section.

Statistical Analysis Plan and Amendments

Sample size

The sample size calculation for Study 308 assumed a median PFS of 5.3 months for the SOC treatment group and 8.7 months for the elacestrant treatment group, an increase of approximately 3.4 months among the *ESR1*-mut subjects.

The assumption of median PFS of 5.3 months for the SOC treatment group was based on available data at that time related to the efficacy of fulvestrant as a second/third line treatment. The effect of prior CDK4/6 inhibitor exposure on the activity of fulvestrant was not

known at the time this study was initiated. These recent data clearly showed that prior therapy with CDK4/6 inhibitors decreases response/PFS to subsequent single agent endocrine therapy.

Statistical Analysis

The primary endpoints of PFS were evaluated in 2 groups of subjects: *ESR1*-mut subjects and all subjects (*ESR1*-mut + *ESR1*-mut-nd). The statistical analyses of these endpoints were performed using a truncated Hochberg procedure (Dmitrienko et al, 2011) to control the family-wise type I error rate and to allow alpha to pass along from the analyses of the primary endpoint of PFS to the analyses of the key secondary endpoint of overall survival (OS) (Hochberg, 1988).

The 2 primary endpoints were evaluated using the Hochberg procedure to maintain the overall alpha level at 2-sided 5.0%, following these rules:

- The p-value for each of the 2 primary endpoints will be derived without any adjustment. These 2 p-values will be sorted in a numerical order so that 1 p-value is larger than or equal to the other
- If the larger p-value is < 0.05, statistical significance will be claimed for both endpoints
- If the larger p-value is ≥ 0.05 and the smaller p-value is < 0.025, statistical significance will be claimed only for the endpoint associated with smaller p-value
- If the larger p-value is ≥ 0.05 and the smaller p-value is ≥ 0.025, no statistical significance will be claimed

Analyses of all other efficacy endpoints were performed at the 2-sided alpha level of 5% without adjustment for p-values.

Analysis of the Primary Endpoints

For subjects without objective disease progression or death, PFS was censored on the date of the last tumor assessment, or, if no tumor assessment was performed after the baseline visit, at the date of randomization.

The analyses was performed based on the ITT population for *ESR1*-mut subjects and all subjects (*ESR1*-mut and *ESR1*-mut-nd) in the entire ITT population using Kaplan-Meier (KM) methods and displayed graphically with median event times and 95% confidence intervals (CIs).

The differences in the primary endpoints between treatment groups were analyzed using the stratified log-rank test, with the stratification factors of prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no), as the primary analyses. The unstratified logrank test was performed as a sensitivity analysis. The Cox regression model, including treatment and the stratification factors as above, was used to estimate the hazard ratio and 95% CI.

Analysis of the Key Secondary Endpoints

Key secondary efficacy endpoints include the following:

- OS in *ESR1*-mut subjects
- OS in all subjects (*ESR1*-mut and *ESR1*-mut-nd)

Analyses of OS in *ESR1*-mut subjects and in all subjects (*ESR1*-nut and *ESR1*-mut-nd) was performed using the ITT population for the *ESR1*-mut subjects and the entire ITT population, respectively.

For each of the 2 sets of study subjects, OS was planned to be analyzed at the following 2 time points:

- At the time of the final PFS analysis
- At the time of the final OS analysis (when 50% of the subjects have died)

At each time point, OS for the treatment groups is analyzed using KM methods and displayed graphically, with median event times and 95% CIs displayed. The Cox regression model that includes treatment and the stratification factors of prior treatment with fulvestrant (yes vs no) and presence of visceral metastases (yes vs no) is used to estimate the hazard ratio and 95% CI. In addition, the difference between treatment groups is analyzed using the stratified log-rank test. A 2-sided alpha level of 0.01% has been allocated at the final PFS analysis time point and a 2-sided alpha level of 4.99% will be allocated at the final OS analysis time point.

The Applicant's Description:

The SAP was finalized before database lock and unblinding and is provided in the CSR Appendix 16.1.9. Statistical analyses were carried out using SAS statistical analysis software Version 9.4 (SAS Institute, Inc., Cary, North Carolina, US).

No changes to planned analysis were made after database lock.

The following changes were made to the SAP dated 13 May 2021 version 1.1 from the previous version of the SAP (ISS SAP):

- The conventional Hochberg procedure was specified in the protocol to control the overall type I error rate for the testing of PFS in 2 populations. To ensure that OS can be tested in the event that PFS is statistically significant in only 1 of the populations, a parallel gatekeeping strategy based on the truncated Hochberg will be used to control the family-wise type I error rate at 5% (2-sided) and to determine how much alpha will pass along from the primary endpoint PFS to the key secondary endpoint OS.

The following changes were made to the SAP dated 05 March 2021 version 1.0 (ISS SAP) from RAD1901-308 Protocol version 6.0 dated 25 March 2020:

- The definitions of the analysis populations of RE and CBE were updated in Section 3.
- The protocol specified that "ORR and CBR will be summarized as a binomial response rate and compared between treatment groups using stratified Fisher's exact test." As there was no SAS procedure supporting stratified Fisher's exact test, the analysis method for ORR and CBR was updated to Cochran-Mantel-Haenszel test and exact test (Proc Logistic).
- The protocol specified that "Pharmacokinetic analyses will be performed using the PK population." One of the secondary objectives is to assess the PK of elacestrant. As there were only 2 PK time points, it was not possible to perform noncompartmental PK analyses. Instead, elacestrant plasma concentrations were summarized as described in

Section 4.9 of the SAP. (Note: A dedicated population PK modeling analysis is being conducted. The outcomes of the analysis will be reported in a separate document.)

- The exploratory biomarker analyses would not be conducted.
- Per-protocol Population was added. It was used in sensitivity analyses for PFS if primary endpoints were statistically significant.

The FDA's Assessment:

FDA has the following comments to the statistical analysis plan:

Sample Size: The study was powered to test the treatment benefit of PFS in both the *ESR1*-mut subpopulation and the ITT population. In the *ESR1*-mut subpopulation, assuming a median PFS of 5.3 months for the SOC arm and 8.7 months for the elacestrant arm, the study would require 160 PFS events to have a power of 80% to detect a HR of 0.61 at the 2-sided alpha level of 2.5%. In the ITT population, the study would require 340 PFS events to have a power of 92% to detect a HR of 0.67 at the 2-sided alpha level of 2.5%.

Earlier Analysis Time Than Planned for PFS: The primary PFS analysis was planned to be performed after the occurrence of 340 PFS events in ITT and 160 events in the *ESR1*-mut subpopulation. The actual primary PFS analysis was performed after 300 events in the ITT population and 140 events in the *ESR1*-mut subpopulation. This may lead to insufficient statistical power for the primary analysis. Choice of performing the primary analysis early was ultimately the Applicant's risk.

During the review of the application, the Applicant clarified in an information request that this decision was based on a blinded PFS event number projection which was influenced by the lower-than-expected median PFS and higher-than-expected rate of censoring. Given the decision was made based on a blinded look, the FDA does not consider this to have a major impact on the study integrity.

Late Changes to OS Testing Procedure: Among all subjects, the study was powered at 60% to detect an HR of 0.75 for OS at a 1-sided alpha level of 2.5%. Assuming a median OS of 25 months for the SOC treatment group, this HR represents a median OS of 33 months for the Elacestrant treatment group. Among *ESR1*-mut patients, the study was powered at 39% to detect a HR of 0.73 at a 1-sided alpha level of 2.5%. Assuming a median OS of 28 months for the SOC treatment group, this treatment effect represents a median OS of 38 months for the elacestrant treatment group.

During the study, the FDA reviewed the SAP in March 2021 and advised the Applicant to clarify the testing plan of OS. The Applicant clarified the testing plan in the following version of the SAP. In general, FDA discourages changes to the analysis plan when it is closed to unblind the trial for efficacy analysis. However, in Study RAD 1901-308, considering the fact that the timing of the interim and final OS analysis had already been specified since the protocol version 5.0 (dated March 2019), which was still at the very early stage of the trial (very few patients were

enrolled at that time) and the only change to the OS analysis plan was the addition of the formal test at the time of the primary PFS analysis, the FDA did not consider this to be a major statistical issue or to have a major impact on the integrity of the study.

Protocol Amendments

The Applicant's Description:

Details on Protocol amendments are provided in the CSR RAD1901-308, Section 9.8.1, and outlined in Table 14.

Table 14: All Protocol Versions

Protocol Version	Date	Notes	Number of Subjects Recruited
1.0	06 August 2018	No recruitment	0
2.0	17 August 2018	No recruitment	0
3.0	22 August 2018	No recruitment	0
4.0	22 August 2018	Third global amendment	18
4.1	19 April 2019	Local amendment for the UK	0
4.2	25 April 2019	Local amendment for France	0
4.3		Canada	0
5.0	28 March 2019	Fourth global amendment	234
5.1	28 June 2019	Local amendment for the UK	6
5.2	10 July 2019	Local amendment for France	21
5.3		Local amendment for Canada	0
5.3.1	05 September 2019	Local amendment for Canada	3
6.0	25 March 2020	Fifth global amendment	175
6.0		France	14
6.0		Canada	1
6.1	26 March 2020	Local amendment for the UK	5

Abbreviations: UK = United Kingdom.
Source: CSR RAD1901-308, Table 9

The FDA's Assessment:

FDA agrees with the Applicant's summary of protocol versions for Study RAD1901-308. In the FDA's assessment, the most notable protocol changes occurred in the fourth and fifth global amendments and are summarized below:

Version 5.0: Fourth Global Amendment

a. The Applicant changed the *ESR1*-WT population to the *ESR1*-mut-nd population. The Applicant states that the amended description is more accurate as patients with no ESR1 mutation detected in ctDNA analysis could include those with either wild-type tumor *ESR1* or those with unknown tumor *ESR1*.
b. The Applicant clarified that ER and HER2 status could be determined on any prior tumor sample (including the tumor tissue from the original diagnosis) rather than on the most recent biopsy from a metastatic or recurrent disease lesion.

c. The Applicant added an exclusion criterion for subjects with a Child-Pugh score >6. The Applicant stated that this was because fulvestrant had not been evaluated in patients with severe hepatic impairment.
d. The Applicant added an exclusion criterion for patients with a known bleeding disorder whose investigator choice of SOC would be fulvestrant, as this is labeled under Warnings and Precautions for fulvestrant.
e. The Applicant added an interim futility analysis at about 70% enrollment for review by the IDMC to avoid treating patients with a drug without a positive benefit:risk profile.

Reviewer Comment: The FDA notes that testing for ER, PR, and HER2 are typically repeated on metastatic tumor tissue at time of recurrence for patients with an initial diagnosis of early-stage breast cancer, as tumor receptor status may change between the initial diagnosis and metastatic recurrence. For patients enrolled to Study 1901-308, ER and HER2 could be determined on any prior tumor sample, including primary tumor tissue. FDA did not consider this to be a major review issue as all patients enrolled were being treated as if they had ER-positive, HER2-negative disease and had already received 1-2 prior lines of endocrine therapy.

Version 6.0: Fifth Global Amendment

a. The Applicant added details for the planned interim futility analysis including that it would include assessment of PFS along with OS, ORR, DOR, and CBR. The Applicant also provided rules regarding IDMC's recommendation for trial continuation/termination.
b. The Applicant added criteria for trial termination which included a serious safety concern, administrative decision, reduced efficacy of elacestrant compared to SOC, and IDMC recommendation.
c. The Applicant added that moderate CYP3A inducers or inhibitors should not be taken by patients receiving elacestrant. Strong CYP3A inducers and inhibitors were already prohibited medications for patients receiving elacestrant.

- ***Study Results***

Compliance with Good Clinical Practices

The Applicant's Position:

All clinical studies included in the clinical development of elacestrant were conducted in accordance with standard operating procedures of the Sponsor and/or delegated contract research organizations, which comply with the principles of Good Clinical Practice (GCP) for design, conduct, and analysis of clinical study data. All studies were conducted under the approval of local ethics committees or institutional review boards. Before participation in the clinical studies, all subjects provided informed consent for their participation. These studies were conducted in accordance with the version of the Declaration of Helsinki that applied at the time the studies were executed or with the laws and regulations of the country in which the

research was conducted, whichever afforded the greater protection to the subject. For most studies, strategy was discussed with the Agency and draft protocols were submitted prior to study conduct.

The FDA's Assessment:
The FDA agrees with the Applicant that Study RAD 1091-308 followed the principles of Good Clinical Practice.

Financial Disclosure

The Applicant's Position:

Details of financial disclosure are presented in CSR RAD1901-308 and signed FDA Forms 3454 and 3455 have been provided certifying that the financial disclosure show no compromises in the integrity of the study.

The FDA's Assessment:

The FDA reviewed Form 3454 and agrees with the Applicant's assessment that financial interests were unlikely to impact the results of Study RAD 1091-308. For more details regarding the FDA's assessment of financial disclosures, refer to Section 19.2.

Patient Disposition

Data:

All Subjects

The disposition of all randomized subjects is shown in Figure 7. Enrollment by region and country is shown in CSR RAD1901-308, Table 14.1.1.2.

Among all subjects, randomization was equal to each group (239 to elacestrant and 239 to SOC). More subjects were not treated in the SOC group (9 subjects [3.8%], all due to withdrawal of consent) compared to the elacestrant group (2 subjects [0.8%], 1 due to noncompliance and 1 due to withdrawal of consent).

Among most subjects who discontinued treatment, this was due to investigator-assessed progression per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (185 subjects [77.4%] in the elacestrant group and 178 subjects [74.8%] in the SOC group).

The reasons for treatment discontinuation are provided in Figure 7.

One subject (0.4%) in the SOC group had a treatment interruption of > 14 consecutive days, following which this subject was not approved to restart treatment.

As of the clinical cutoff date of 06 September 2021, 18 subjects (7.5%) in the elacestrant group and 6 subjects (2.5%) in the SOC group were still on treatment. Approximately half of subjects who discontinued treatment remain on study but are not receiving study treatment. Of the

subjects who discontinued the study as well as discontinuing treatment, the majority discontinued due to death (69 subjects [28.9%] in the elacestrant group and 78 subjects [32.8%] in the SOC group).

ESR1-mut Subjects

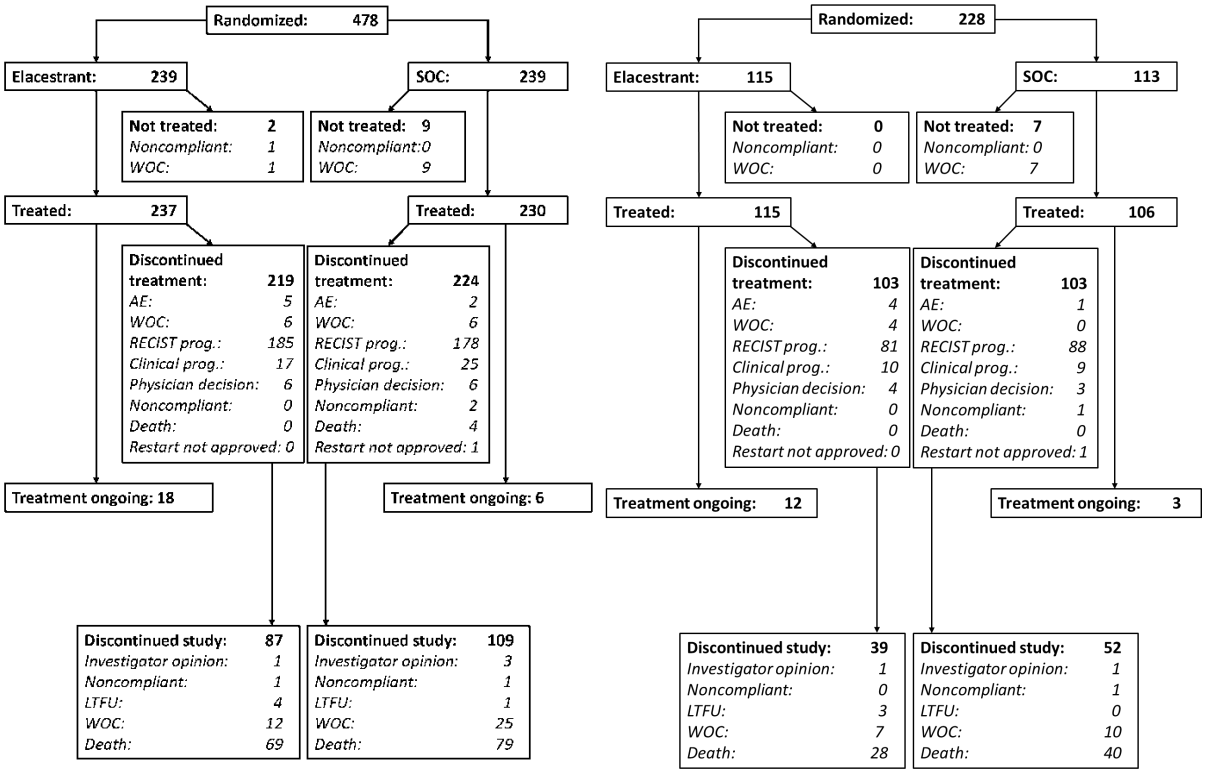
The disposition of *ESR1*-mut randomized subjects is shown Figure 7. Among *ESR1*-mut subjects, randomization was similar to each group (115 to elacestrant and 113 to SOC). Seven subjects (6.2%) withdrew from the study before being treated, all in the SOC group.

Among all *ESR1*-mut subjects, treatment discontinuation was mainly due to investigator-assessed progression per RECIST criteria (81 subjects [70.4%] in the elacestrant group and 88 subjects [77.9%] in the SOC group). There were 0 deaths on treatment for *ESR1*-mut subjects in either treatment group, and 1 subject (0.9%) in the SOC group had a treatment interruption of > 14 consecutive days, following which the subject was not approved to restart treatment.

For *ESR1*-mut subjects, as of the clinical cutoff date of 06 September 2021, 12 subjects (10.4%) in the elacestrant group and 3 subjects (2.7%) in the SOC group are still on treatment. The most common reason for treatment discontinuation was investigator-assessed progression per RECIST (81 subjects [70.4%] in the elacestrant group and 88 [77.9%] subjects in the SOC group).

Approximately half of *ESR1*-mut subjects who discontinued treatment remain on study but are not receiving study treatment. The most common reason for discontinuing the study was death in 28 (24.3%) subjects in the elacestrant group and 40 (35.4%) subjects in the SOC group.

Figure 7: Subject Disposition (All Subjects [A] and ESR1-mut [B])



Abbreviations: AE = adverse event; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; LTFU =lost to follow-up; prog. = progression; RECIST = Response Evaluation Criteria in Solid Tumors; SOC = standard of care; WOC = withdraw of consent.
Subjects who discontinued study includes the subjects who discontinued prior to starting treatment.
Source: CSR RAD1901-308, Figure 2 and Figure 3

The Applicant's Position:

The patient dispositions observed in each treatment group in Study RAD1901-308 were consistent with patients with ER+/HER2- advanced or metastatic breast cancer and the proposed indicated patient population.

The FDA's Assessment:

Information regarding enrollment by region is summarized in Table 15 (modified from the table in the CSR referenced by the Applicant). The FDA notes that Study RAD1901-308 was a multi-regional clinical trial, enrolling patients from Asia (Israel, South Korea), Australia, Europe, North America, and South America (Argentina).

Table 15: Enrollment to Study RAD1901-308 By Region

	All patients		*ESR1*-mut	
	Elacestrant (N = 239) %	SOC (N = 239) %	Elacestrant (N = 115) %	SOC (N = 113) %
Region				
Asia (Israel, South Korea)	10	11	9	14
Australia	3	2	3	1
Europe	57	51	55	44
North America	27	32	29	37
South America (Argentina)	3	4	5	4

The FDA generally agrees with the Applicant's description of disposition for patients enrolled to Study Rad1901-308. However, the FDA does not agree with the Applicant's statement that patient disposition was generally consistent with patients with ER-positive, HER2-negative advanced or metastatic breast cancer. Patient disposition is a trial characteristic and does not pertain to patients not enrolled onto a clinical trial.

In addition, the FDA expressed concern about the impact of patients withdrawing consent prior to starting trial treatment and patients stopping trial treatment due to investigator-assessed progression without IRC-assessed progression on assessment of the PFS endpoint.

The FDA also expressed concern about the impact of patients withdrawing consent on assessment of the OS endpoint. This concern was heightened by the uneven withdrawal of

consent between treatment arms observed within the *ESR1*-mut-nd subpopulation, which could result in bias in OS results.

Refer to FDA Analyses in Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) and Efficacy Results – Secondary and other relevant endpoints in 8.1.1 for more details.

Protocol Violations/Deviations

Data:

Major protocol deviations were defined as a deviation from the basic requirements of the study protocol, including main inclusion and exclusion criteria; concomitant medication restrictions; dosing (i.e., outside of ± 20% prescribed dose of study drug); or any protocol requirements that resulted in a significant added risk to the study subject, had an impact on the quality of the data collected, or had an impact on the outcome of the study. This definition was included in the latest SAP version 1.1. The final classification of the deviations into major or minor was performed after database lock. The background and strategy for this evaluation was documented in an internal report. Major protocol deviations that are shown in Table 16 were not included in the modified PP analysis. Most subjects had a minor deviation related to procedures/tests.

Table 16: Major Protocol Deviations (Intent-to-Treat Population)

	n (%)							
	All Subjects				*ESR1*-mut Subjects			
	Elacestrant		SOC		Elacestrant		SOC	
Deviation Type	N = 239		N = 239		N = 115		N = 113	
Any	6	(2.5)	11	(4.6)	1	(0.9)	8	(7.1)
Inclusion/exclusion criteria	3	(1.3)	1	(0.4)	1	(0.9)	–	–
Disallowed medications	1	(0.4)	1	(0.4)	0	–	1	(0.9)
IP admin./study treatment	2	(0.8)	9	(3.8)	0	–	7	(6.2)

Abbreviations: Admin = administration; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; IP = investigational product; n = number of subjects with the observed group characteristic; N = total number of subjects in group; SOC = standard of care.

Source: Updated Table 14.1.19.2

The Applicant's Position:

The major protocol deviations reported during the study did not impact the analyses performed or the interpretation of the results of the study.

The FDA's Assessment:

The FDA agrees with the Applicant's description of protocol deviations. There were 17 patients in the ITT population with a major protocol deviation. In an IR response received by the FDA on January 9, 2023, the Applicant further clarified the reasons for a major protocol deviation for these 17 patients which are shown in Table 17 below.

Table 17: Major Protocol Deviations, ITT Population

Unique Subject Identifier	Arm	Deviation Category	Deviation Specific Reason
(b) (6)	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	DISALLOWED MEDICATIONS	Subject had taken anastrozole prior to enrollment in this study and did not stop taking this prohibited medication after randomization to fulvestrant on (b) (6) until (b) (6)
	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	SOC	INC/EXCL CRITERIA	Eligibility criteria, Inclusion number 3 not met (Subjects must have one of the following as defined by RECIST v1.1 a. Measurable disease b. Non-measurable (evaluable) bone-only disease. Evaluable bone-only disease must include at least one lytic bone lesion or a mixed lytic-blastic bone lesion; blastic only metastases are not allowed. Subjects who have had prior radiation to bone must have at least one evaluable lesion in a non-irradiated area)

Unique Subject Identifier	Arm	Deviation Category	Deviation Specific Reason
(b) (6)	SOC	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	ELA	INC/EXCL CRITERIA	Screening hormone tests (estradiol, FSH) were not completed because no blood draw was done
	ELA	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	ELA	INC/EXCL CRITERIA	Eligibility criteria, Inclusion number 3 not met (Subjects must have one of the following as defined by RECIST v1.1 a. Measurable disease b. Non-measurable (evaluable) bone-only disease. Evaluable bone-only disease must include at least one lytic bone lesion or a mixed lytic-blastic bone lesion; blastic only metastases are not allowed. Subjects who have had prior radiation to bone must have at least one evaluable lesion in a non-irradiated area)
	ELA	IP ADMIN/STUDY TREAT	Subject randomized but not treated
	ELA	DISALLOWED MEDICATIONS	Subject continued on the trial while taking a prohibited medication , a medication known to be strong inhibitors or inducers of CYP3A
	ELA	INC/EXCL CRITERIA	Subject was enrolled in the study with a secondary malignancy, that was discovered retrospectively later on after the subject ended the trial

The FDA agrees with the Applicant's assessment that there were few major protocol deviations. The FDA assessed the impact of patients who withdrew consent (including some patients who were randomized but not treated) on overall interpretation of the trial results in Efficacy Results – Secondary and other relevant endpoints below. The FDA disagrees that patients who withdrew consent (including some patients who were randomized but not treated) had a minor impact on overall trial interpretation.

Table of Demographic Characteristics

Data:

Baseline demographic characteristics for subjects in the Intent-to-Treat (ITT) Population are shown in Table 18. Groups were balanced with respect to all baseline demographic characteristics and represented the intended subject population.

Table 18: Demographic and Baseline Characteristics (Intent-to-Treat Population)

	n (%)							
	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
Age (year)								
Median (range)	63.0	(24–89)	63.2	(32–83)	64.0	(28–89)	63.0	(32–83)
Age group, n (%)								
≥ 18 – < 50	33	(13.8)	30	(12.6)	15	(13.0)	19	(16.8)
≥ 50 – < 65	102	(42.7)	98	(41.0)	47	(40.9)	43	(38.1)
≥ 65 – < 75	64	(26.8)	65	(27.2)	36	(31.3)	34	(30.1)
≥ 75	40	(16.7)	46	(19.2)	17	(14.8)	17	(15.0)
< 65	135	(56.5)	128	(53.6)	62	(53.9)	62	(54.9)
≥ 65	104	(43.5)	111	(46.4)	53	(46.1)	51	(45.1)
Race, n (%)[a]								
n (missing)	190	(49)	195	(44)	94	(21)	92	(21)
Asian	16	(8.4)	16	(8.2)	5	(5.3)	8	(8.7)
Black or African American	5	(2.6)	8	(4.1)	4	(4.3)	4	(4.3)
White/ Caucasian	168	(88.4)	170	(87.2)	84	(89.4)	80	(87.0)
Other	1	(0.5)	1	(0.5)	1	(1.1)	–	–
Gender, n (%)								
Male	6	(2.5)	1	(0.4)	–	–	–	–
Female	233	(97.5)	238	(99.6)	115	(100.0)	113	(100.0)
Height (cm)								
n (missing)	236	(3)	237	(2)	113	(2)	112	(1)
Mean (s.d.)	162.27	(7.9)	160.97	(7.2)	161.88	(7.5)	160.65	(6.5)
Weight (kg)								
Mean (s.d.)	72.70	(16.1)	72.39	(16.4)	73.41	(17.1)	71.87	(16.5)
BMI (kg/m^2)								
n (missing)	236	(3)	237	(2)	113	(2)	112	(1)
Mean (s.d.)	27.58	(5.5)	27.92	(5.9)	28.07	(6.1)	27.88	(6.0)
ECOG performance status, n (%)								
0	143	(59.8)	135	(56.5)	67	(58.3)	62	(54.9)
1	96	(40.2)	103	(43.1)	48	(41.7)	51	(45.1)
> 1	–	–	1	(0.4)	–	–	–	–

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; n = number of subjects with the observed group characteristic; N = total number of subjects in group; s.d. = standard deviation; SOC = standard of care.

[a] Subjects could select more than one race.

Source: Updated Table 14.1.4.1

The Applicant's Position:

There are no clinically relevant differences between the treatment groups in the RAD1901-308 study.

The FDA's Assessment:

Regarding race, the FDA disagrees with the Applicant's presentation of data. The corrected frequencies for patients with missing race data as well as patients in the race categories are shown in Table 19.

Table 19: Race Information for Patients Enrolled to Study RAD1901-308

	All patients		*ESR1*-mut	
	Elacestrant (N = 239)	SOC (N = 239)	Elacestrant (N = 115)	SOC (N = 113)
Race, (%)				
Asian	16 (7%)	16 (7%)	5 (4%)	8 (7%)
Black	5 (2%)	8 (3%)	4 (3%)	4 (4%)
White	168 (70%)	170 (70%)	84 (73%)	80 (71%)
Other	1 (0.4%)	1 (0.4%)	1(1%)	0(0%)
Missing	49 (21%)	44 (18%)	21 (18%)	21 (19%)

The FDA notes that the majority of patients enrolled were White and only 3% of patients enrolled were Black. In addition, race data were missing for approximately 20% of patients enrolled. Due to the large amount of missing race data, it is not clear if the patient population enrolled to RAD1901-308 is representative of a US-based population with ER+HER2- advanced or metastatic breast cancer with respect to race.

The FDA issued a PMC for the Applicant to characterize the safety and efficacy of elacestrant in patients from racial and ethnic minority groups by conducted an integrated analysis containing data from clinical trials and other data sources. Refer to Section 13 for details.

With respect to sex, FDA notes that there were only 7 male patients enrolled and there were no male patients in the *ESR1*-mut subgroup. For further discussion regarding the assessment of efficacy in male patients, refer to Section 8.1.2.

Otherwise, the FDA agrees with the Applicant that the two arms appear balanced with respect to demographic characteristics. The FDA also notes that the demographics in the *ESR1*-mut subgroup appear similar to the ITT population, except with respect to sex as already noted.

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

Data:

Baseline disease characteristics are shown in Table 20.

Table 20: Baseline Disease Characteristics (Intent-to-Treat Population)

	n (%)							
	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
Years since initial diagnosis								
Median (range)	6.28	(0.2–32.2)	6.11	(0.5–40.1)	4.92	(0.2–28.4)	5.75	(0.9–31.0)
Stage at baseline								
IIA	1	(0.4)	1	(0.4)	1	(0.9)	–	–
IIIA	2	(0.8)	–	–	–	–	–	–
IIIC	1	(0.4)	1	(0.4)	–	–	1	(0.9)
IV	12	(5.0)	18	(7.5)	8	(7.0)	7	(6.2)
IVA	3	(1.3)	3	(1.3)	1	(0.9)	2	(1.8)
IVB	3	(1.3)	3	(1.3)	1	(0.9)	1	(0.9)
IVC	1	(0.4)	1	(0.4)	–	–	1	(0.9)
Unknown	194	(81.2)	192	(80.3)	91	(79.1)	88	(77.9)
T stage at baseline								
T1	8	(3.3)	5	(2.1)	2	(1.7)	2	(1.8)
T2	13	(5.4)	15	(6.3)	6	(5.2)	8	(7.1)
T3	6	(2.5)	4	(1.7)	3	(2.6)	–	–
T4	12	(5.0)	11	(4.6)	8	(7.0)	4	(3.5)
Unknown	54	(22.6)	54	(22.6)	24	(20.9)	25	(22.1)
N stage at baseline								
N0	14	(5.9)	12	(5.0)	8	(7.0)	3	(2.7)
N1	14	(5.9)	13	(5.4)	4	(3.5)	6	(5.3)
N2	7	(2.9)	7	(2.9)	4	(3.5)	3	(2.7)
N3	6	(2.5)	5	(2.1)	3	(2.6)	1	(0.9)
Unknown	52	(21.8)	54	(22.6)	24	(20.9)	27	(23.9)
M stage at baseline								
M0	8	(3.3)	6	(2.5)	3	(2.6)	–	–
M1	60	(25.1)	62	(25.9)	27	(23.5)	25	(22.1)
Unknown	26	(10.9)	24	(10.0)	13	(11.3)	14	(12.4)
Number of metastatic sites								
0	–	–	–	–	–	–	–	–
1	51	(21.3)	46	(19.2)	16	(13.9)	19	(16.8)
2	74	(31.0)	72	(30.1)	43	(37.4)	34	(30.1)
≥ 3	78	(32.6)	83	(34.7)	44	(38.3)	41	(36.3)
Histology								
Ductal	154	(64.4)	158	(66.1)	74	(64.3)	77	(68.1)
Lobular	36	(15.1)	32	(13.4)	17	(14.8)	12	(10.6)
Other	20	(8.4)	15	(6.3)	10	(8.7)	6	(5.3)
Unknown	26	(10.9)	32	(13.4)	13	(11.3)	17	(15.0)
Histopathology grade								
Grade 1	17	(7.1)	23	(9.6)	5	(4.3)	10	(8.8)
Grade 2	127	(53.1)	129	(54.0)	61	(53.0)	66	(58.4)
Grade 3	62	(25.9)	52	(21.8)	32	(27.8)	22	(19.5)
Estrogen receptor								

	n (%)							
	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
Positive	238	(99.6)	238	(99.6)	114	(99.1)	112	(99.1)
Progesterone receptor								
Positive	168	(70.3)	181	(75.7)	82	(71.3)	85	(75.2)

Abbreviations: *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; n = number of subjects with the observed group characteristic; N = total number of subjects in group; SOC = standard of care.
Source: Updated Table 14.1.7.1 and Table 14.1.8

The Applicant's Position:

No noteworthy differences between treatment groups were observed with respect to baseline disease characteristics.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of baseline disease characteristics shown in Table 20.

The FDA notes that the Applicant did not include any information regarding prior therapies for enrolled patients and provides that information in Table 21 (below). Targeted therapy included prior treatment with alpelisib or everolimus in combination with endocrine therapy.

Table 21: Prior Therapies for Patients Enrolled To Study RAD1901-308

	All subjects		*ESR1*-mut Subjects	
	Elacestrant (N = 239)	SOC (N = 239)	Elacestrant (N = 115)	SOC (N = 113)
Prior Treatment with Fulvestrant, n (%)				
Yes	70 (29%)	75 (31%)	27 (23%)	28 (25%)
Prior Lines of Endocrine Therapy in Metastatic Setting				
1	129 (54%)	142 (59%)	73 (63%)	69 (61%)
2	110 (46%)	97 (41%)	42 (37%)	44 (39%)
Prior Chemotherapy in Metastatic Setting				
Yes	48 (20%)	59 (25%)	26 (23%)	32 (28%)
Prior Targeted Therapy in Metastatic Setting				
Yes	10 (4%)	9 (4%)	6 (5%)	3 (3%)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

For subjects taking elacestrant or an AI, compliance was assessed using returned tablets/blister packs. Fulvestrant was administered IM at the study sites and the date and time of administration were recorded.

Median compliance was 100.0% in all treatment groups. In the elacestrant group (all subjects), the relative dose intensity was > 90% to ≤ 100% for 230 (97.0%) subjects. The 7 subjects (3.0%) with lower relative dose intensity had between > 75% and ≤ 90%.

Concomitant Medications and Procedures

Almost all subjects (456 [97.9%]) reported concomitant medication use. There were no noteworthy differences between treatment groups in the usage of any concomitant medication by name or class.

Rescue Medications

Not applicable

The Applicant's Position:

Overall, compliance to treatment in Study RAD1901-308 was high. No noteworthy differences between treatment groups were observed for the use of any concomitant medication or medication class. No rescue medications were utilized in the study.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that treatment compliance was relatively high and that there were no noteworthy differences between treatment groups.

FDA disagrees with the Applicant's assessment that there were no noteworthy differences in concomitant medications. Use of serotonin (5HT3) antagonists (e.g., ondansetron) was numerically higher in patients receiving elacestrant compared to SOC: 18% vs. 10%. For more information regarding FDA's assessment of GI toxicity, refer to Section 8.2.4.

Additionally, per the protocol, patients were permitted to receive palliative radiotherapy if there was no other option available for their pain.

In an IR response to FDA, the Applicant clarified that there were 17 patients who received palliative radiation while on trial, 12 patients on the elacestrant arm and 5 patients on the SOC arm. For FDA's assessment of the impact of palliative radiation on the PFS endpoint, refer to Efficacy Results – Primary Endpoint (Including Sensitivity Analyses) below.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Both primary endpoints of the study (PFS in all subjects and in *ESR1*-mut subjects) were met.

In all subjects, the HR for progression under elacestrant versus SOC treatment was 0.697 (95% CI: 0.552 to 0.880), stratified log-rank test p-value = 0.0018. A Kaplan-Meier plot of PFS for all subjects is shown in Figure 8. The median PFS was 2.79 months for the elacestrant group and 1.91 months for the SOC group.

In *ESR1*-mut subjects, the HR for progression under elacestrant versus SOC treatment was 0.546 (95% CI: 0.387 to 0.768), stratified log-rank test p-value = 0.0005 (Table 22). A Kaplan-Meier plot of PFS is shown in Figure 9. The median PFS was 3.78 months for the elacestrant group and 1.87 months for the SOC group.

Because the larger stratified log-rank test p-value (i.e., p = 0.0018) was < 0.0475, under the truncated Hochberg test adjusted for the interim analysis of OS, both primary objectives were met with statistical significance.

In both the all subjects and *ESR1*-mut subjects groups, elacestrant was superior to the SOC in subjects with ER+/HER2- metastatic breast cancer after 1 or 2 lines of prior endocrine therapy including a CDK4/6 inhibitor in the metastatic setting.

The numbers of subjects with any individual reason for censoring (other than absence of documented progression) were low and comparable between treatment groups.

Landmark PFS analyses were conducted at 3, 6, 12, and 18 months (Table 22). All estimates at the various timepoints favored the elacestrant arm.

- In all subjects, the 6- and 12-month PFS rates were 34.32% and 22.32%, respectively, in the elacestrant arm as compared to 20.38% and 9.42% in the SOC arm.
- In the *ESR1*-mut subjects, the 6- and 12-month PFS rates were 40.76% and 26.76%, respectively, in the elacestrant arm as compared to 19.14% and 8.19% in the SOC arm.

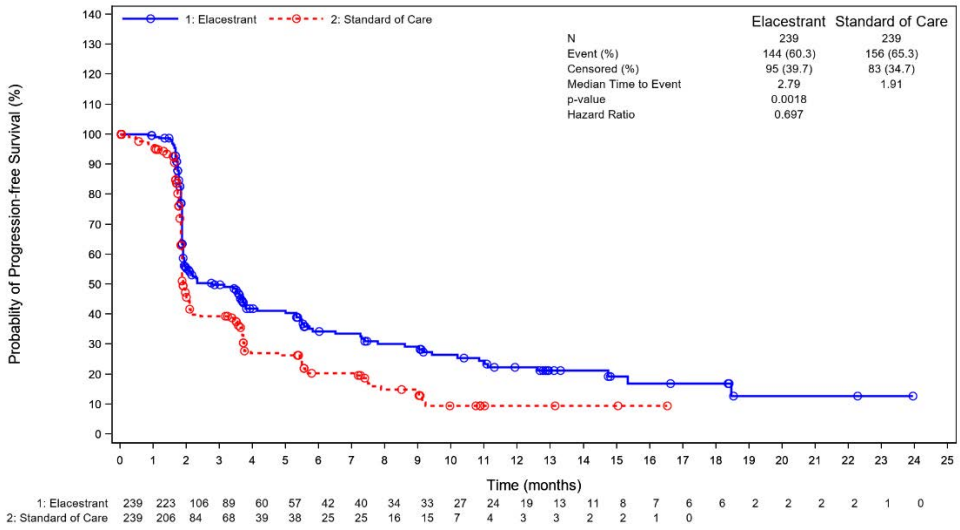
Additional landmark PFS estimates are provided in Table 22.

The PFS event sensitivity analysis is shown in CSR RAD1901-308, Table 14.2.1.2.2 (all subjects) and CSR RAD1901-308, Table 14.2.1.2.1 (*ESR1*-mut subjects). The results of the sensitivity analysis were consistent with the results of the primary analysis in both groups.

Further sensitivity analyses are shown in CSR RAD1901-308, Table 14.2.1.3.1 and CSR RAD1901-308, Table 14.2.1.3.2 (PFS backdating analysis), CSR RAD1901-308, Table 14.2.1.4.1 and CSR RAD1901-308, Table 14.2.1.4.2 (unstratified analysis). The results of these additional sensitivity analysis were also consistent with the results of the primary analysis in both groups.

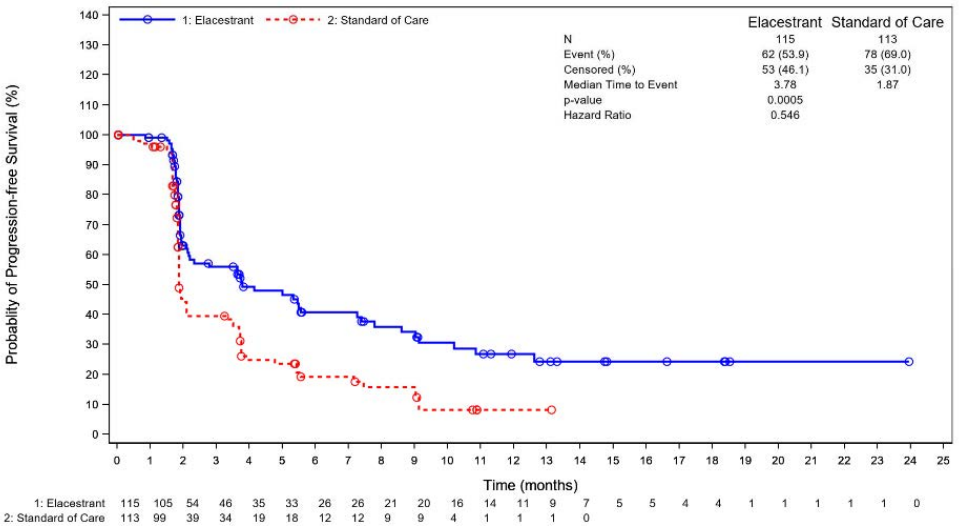
The analysis in the PP Population is shown in CSR RAD1901-308, Table 14.2.1.6.1 and CSR RAD1901-308, Table 14.2.1.6.2. This analysis was also in favor of elacestrant both in all subjects and in subjects with *ESR1*-mut.

Figure 8: Kaplan-Meier Plot for Blinded Imaging Review Committee Assessment of Progression-free Survival in All Subjects (Intent-to-Treat Population)



Abbreviations: N = total number of subjects in group.
Source: Updated Figure 14.2.1.1.2

Figure 9: Kaplan-Meier Plot for Blinded Imaging Review Committee Assessment of Progression-free Survival in ESR1-mut Subjects (Intent-to-Treat Population)



Abbreviations: *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; N = total number of subjects in group.
Source: Updated Figure 5

Table 22: Blinded Imaging Review Committee Assessment of Progression-free Survival (Intent-to-Treat Population)

	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
HR (95% CI)	0.697 (0.552–0.880)				0.546 (0.387–0.768)			
p (stratified log-rank test)	0.0018				0.0005			
Median PFS (months)	2.79		1.91		3.78		1.87	
95% CI	1.94–3.78		1.87–2.10		2.17–7.26		1.87–2.14	
Events, n (%)	144	(60.3)	156	(65.5)	62	(53.9)	78	(69.0)
Death	5	(2.1)	6	(2.5)	3	(2.6)	1	(0.9)
Progression	139	(58.2)	150	(63.0)	59	(51.3)	77	(68.1)
3-month PFS rate	49.75		39.29		55.93		39.55	
95% CI	42.85-56.65		32.28-46.31		45.80–66.05		29.44–49.65	
6-month PFS rate	34.32		20.38		40.76		19.14	
95% CI	27.16-41.47		14.09-26.67		30.10 -51.43		10.52 -27.76	
12-month PFS rate	22.32		9.42		26.76		8.19	
95% CI	15.24-29.40		4.02-14.81		16.17-17.36		1.26-15.12	
18-month PFS rate	16.82		-		24.33		-	
95% CI	9.02-24.62		-		13.68-34.98		-	

Abbreviations: CI = confidence interval; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; HR = hazard ratio; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.
Source: Updated Table 14.2.1.1.1 and Updated Table 14.2.1.1.2

The Applicant's Position:

Overall, elacestrant met the prespecified primary endpoint, PFS, in both populations (all subjects and *ESR1*-mut subjects).

The observed PFS estimates in both treatment groups were lower than the estimates used in the sample size calculation when the study was originally designed in 2018. At that time, the PFS assumptions were based on available data related to the efficacy of fulvestrant in the 2nd/3rd line (Chia et al, 2008; Baselga et al, 2017; Cristofanilli et al, 2016). None of the patients enrolled in these studies received prior CDK4/6 inhibitors. The effect of prior CDK4/6 inhibitor exposure on the activity of fulvestrant (VERONICA, median PFS: 1.94 months (Lindeman et al, 2021), SOLAR-1, median PFS: 1.8 months, (Piqray Public Assessment Report, 2020) was not known at the time this study was initiated. In addition, *ESR1* mutations have been documented as a major mechanism of resistance after prior use of the combination of CDK4/6 inhibitor and endocrine therapy (O'Leary et al, 2018; Dustin et al, 2019). This, in part, explains the lower PFS estimates observed in the trial, relative to those used when the trial was designed.

Consistent with KM plots observed in other clinical trials in pretreated patients with ER+/HER2- mBC, especially after prior use of a CDK4/6 inhibitor (e.g., Lindeman et al, 2021), there is an initial drop observed in the first 2 months of treatment, probably reflecting endocrine resistance in a subgroup of patients. Following this drop, a clear separation of the curves demonstrated longer time to progression or death in the elacestrant group that was maintained over time.

The median PFS values were, understandably, heavily impacted by this steep drop in the KM plots in the first 2 months after randomization, and, therefore, it is paramount to look at all PFS estimates that are prespecified in the protocol and reflected in the KM curves, including the hazard ratio and the landmark analysis.

The HRs reflect a 30% relative reduction in progression or death in all subjects and a 45% relative reduction in *ESR1*-mut subjects.

In addition, the prespecified landmark analyses at 6, 12, and 18 months demonstrated substantial improvements in PFS in favor of elacestrant at these later timepoint.

- In all subjects, the PFS rates were 34.32% (~1 in 3 patients is alive and progression free at 6 months) versus 20.38% (~1 in 5) at 6 months, 22.32% (~1 in 5) versus 9.42% (~1 in 10) at 12 months, and 16.82% (~1 in 6) versus "data not available" (~0) at 18 months in the elacestrant and SOC groups, respectively.
- In *ESR1*-mut subjects, the PFS rates were 40.76% (~2 in 5) versus 19.14% (~1 in 5) at 6 months, 26.76% (~1 in 4) versus 8.19% (~1 in 12) at 12 months, and 24.33% (~1 in 4) versus "data not available" (~0) at 18 months in the elacestrant and SOC groups, respectively.

These differences are considered clinically relevant in a patient population with limited treatment options prior to resorting to chemotherapy.

The FDA's Assessment:

PFS was statistically significant for both the ITT and *ESR1*-mut subpopulation; however, the treatment effect in the ITT population was driven by the *ESR1*-mut subpopulation. FDA concludes that a statistically significant and clinically relevant treatment effect was demonstrated for elacestrant compared to SOC for the *ESR1*-mut subpopulation. More details on the assessment of PFS are provided below:

- *Treatment benefit in the ITT population was mainly driven by the ESR1-mut subpopulation.*

The Applicant presented the results of PFS per BICR in the *ESR1*-mut subpopulation and ITT population. Results of PFS per BICR in the *ESR1*-mut-nd subpopulation are summarized in **Table 23** and **Figure 10**. The KM curves for the two arms were close to each other. The medians in the two arms were almost the same, and the percentage of the patients with progressive disease or who died was greater in the elacestrant arm compared with the SOC arm. The results of PFS in the *ESR1*-mut subpopulation, *ESR1*-mut-nd subpopulation, and ITT population indicated that the treatment benefit in the ITT population was mainly driven by the *ESR1*-mut subpopulation.

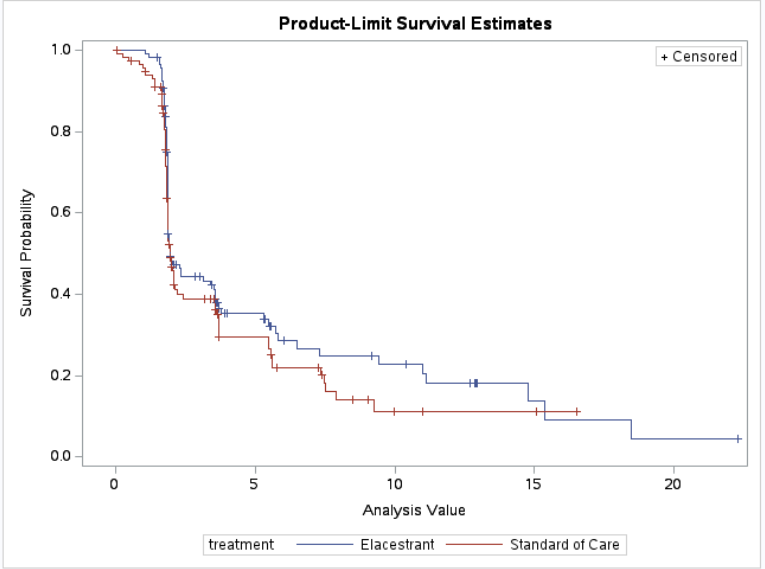
Table 23 BICR Assessment of PFS in *ESR1*-mut-nd subpopulation

	Elacestrant (N = 124)	**SOC** (N = 126)
Event, n (%)	82 (66%)	78 (62%)
Median (95% CI)	1.9 (1.9, 3.6)	2.0 (1.9, 2.2)
Hazard Ratio (95% CI)	0.86 (0.63, 1.19)	

3-month PFS rate (95% CI)	0.50 (0.43, 0.57)	0.39 (0.32, 0.46)
6-month PFS rate (95% CI)	0.34 (0.27, 0.41)	0.20 (0.14, 0.27)
12-month PFS rate (95% CI)	0.22 (0.15, 0.29)	0.09 (0.04, 0.15)
18-month PFS rate (95% CI)	0.17 (0.09, 0.25)	NE

Source: FDA analysis

Figure 10 KM Curves of PFS per BICR in *ESR1*-mut-nd Subpopulation



Source: FDA analysis

- *Non-Proportional Hazards*

The KM plots of PFS indicated that the assumption of exponential distribution was not met in study RAD1901-308, and the interpretation of hazard ratios from the Cox PH analysis is subject to the issue of non-proportional hazards. Unlike a typical oncology trial, the estimates of median and hazard ratio are challenging to interpret with non-proportional hazards, and it is recommended that multiple statistical measures, such as KM estimate at landmark time, restricted mean survival time (RMST), etc. should be considered when evaluating the efficacy of elacestrant.

Table 24 summarizes the FDA's RMST analysis of PFS per BICR in the *ESR1*-mut population, *ESR1*-mut-nd population, and ITT population. Similar to the primary analysis, the mean difference of the RMST between the two treatment arms is only one month in the *ESR1*-mut-nd subpopulation, and the RMST analysis results indicate that the treatment benefit in the ITT population was mainly driven by the *ESR1*-mut subpopulation (Figure 11).

The choice of the timing in the RMST analysis is 16.5 months for the *ESR1*-mut-nd subpopulation, 13.1 months for the *ESR1*-mut subpopulation, and 16.5 months for the ITT population, which is the smallest value among the largest observed times across the treatment

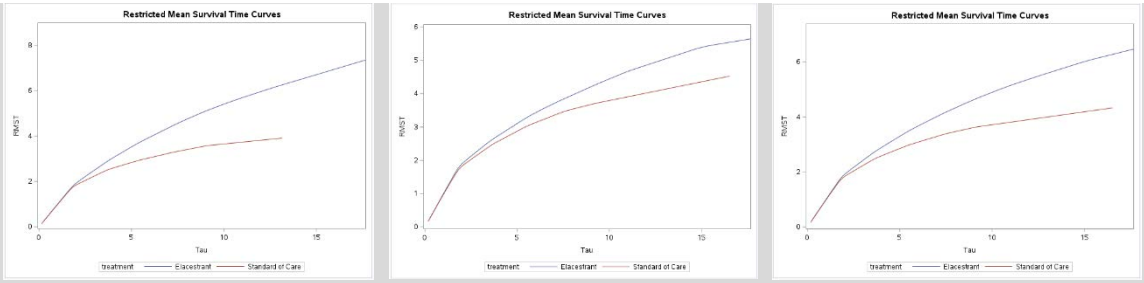
groups. Note that the choice of the timing in the RMST analysis is subjective, and the RMST results could potentially change if a different time was chosen; therefore, the RMST analysis is considered exploratory.

Table 24 Restricted Mean Survival Time (RMST) Analysis of PFS per BICR

	***ESR1*-mut**		***ESR1*-mut-nd**		**ITT**	
	Elacestrant (N = 115)	SOC (N = 113)	Elacestrant (N = 124)	SOC (N = 126)	Elacestrant (N = 239)	SOC (N = 239)
Mean (SE) (months)	6.3 (0.5)	3.9 (0.4)	5.5 (0.6)	4.5 (0.6)	6.3 (0.45)	4.3 (0.37)
RMST difference (SE) (months)	2.3 (0.6)		1.0 (0.8)		1.9 (0.6)	
Nominal p value	0.0003		0.21		0.001	

Source: FDA analysis

Figure 11 RMST Plots of PFS per BICR in (a) *ESR1*-mut Subpopulation, (b) *ESR1*-mut-nd Subpopulation, and (c) ITT Population



(a) (b) (c)

- *High Discordance Rate Between IRC and INV Assessment*

The concordance and discordance of PFS assessment between IRC and INV were examined and summarized in Table 25. The early discordance rate (EDR) and late discordance rate (LDR) was calculated for each arm. EDR is the frequency that the investigator declares recurrence earlier than IRC, and LDR is the frequency that investigator declares recurrence later than IRC. A negative differential discordance for the EDR and/or a positive differential discordance for the LDR between the experimental arm and the control arm beyond a threshold would suggest a bias in the investigator assessment favoring the elacestrant arm. Threshold values ranging from 0.075 to 0.100 were recommended based on simulation studies in Amit et al. 2011.

Table 25 Concordance and Discordance of IRC and INV Assessment of PFS in All Patients

INV Assessment	IRC Assessment			
	Elacestrant (N = 239)		SOC (N = 239)	
	Event	Censor	Event	Censor
Event	132 (55.2%)	60 (25.1%)	146 (61.1%)	43 (18.0%)
Censor	12 (5.0%)	35 (14.6%)	10 (4.2%)	40 (16.7%)

Source: FDA analysis

In all patients, the concordance was 69.9% (95% CI: 63.6%, 75.6%) for elacestrant arm and 77.8% (95% CI: 72.0%, 82.9%) for SOC arm. The EDR was 33.9% for the elacestrant arm and 24.3% for the SOC arm, a difference of 9.6%. The LDR was 42.0% for the elacestrant arm and 50.0% for the SOC arm, a difference of -8.0%. Neither of the differences for EDR or LDR was greater than the threshold recommended in Amit et al. to demonstrate investigator assessment bias in favor of elacestrant. However, the results indicated that there was a difference in the IRC and INV assessments, which increased the uncertainty in the efficacy analysis results.

Due to the high percentage of discordance rate of IRC and INV assessment of PFS, it is meaningful to assess its impact on the primary PFS analysis results. FDA performed a sensitivity analysis of PFS per BICR by considering the patients who considered events per INV but censored by IRC as events instead. The results were summarized in Table 29.

Note that in the *ESR1*-mut-nd population, the percentage of patients who progressed or died was higher in the elacestrant arm than the SOC arm (90.3% vs. 81.6%), and the overlapped KM curves indicated that there was no treatment benefit of elacestrant in the sensitivity analysis. In the *ESR1*-mut population, the sensitivity analysis showed consistent results with the primary analysis. Overall, the treatment benefit in PFS in the ITT population was mainly driven by the *ESR1*-mut subpopulation.

- *Results Not Robust to Palliative Radiation Therapy (RT)*

During the review, FDA noticed that the palliative radiation therapy was permitted in the Study RAD1901-308. The Applicant clarified in an information request that there were 17 patients (12 on elacestrant arm vs. 5 in SOC arm) who received RT on trial treatment. Among these 17 patients, only 3/17 patients had PD or were censored prior to receiving the RT, and 14 out of 17 patients had PD or were censored after RT. The range of the gap between the RT time and PD/censor time per BICR is between 0.2 and 10.4 months.

Due to the imbalance in the percentage of the patients who received RT between the two arms and the large gap of the time between the RT time and PD/censor time, FDA performed sensitivity analyses to assess the impact of the RT on the PFS analysis results. The sensitivity analysis was for PFS per INV with date of RT called PD (unless PD recorded prior to RT). The results are summarized in Table 26.

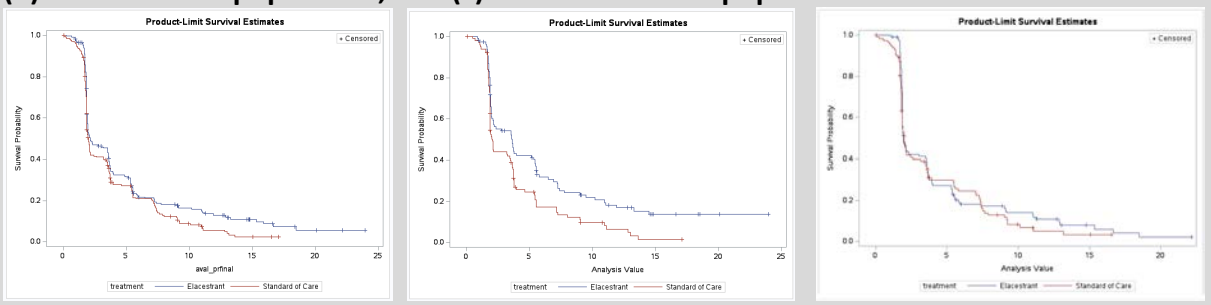
The sensitivity analysis results (Table 26 and Figure 12) showed that in the *ESR1*-mut-nd population, the percentage of patients who progressed or died was higher in the elacestrant arm than in the SOC arm (86.3% vs. 79.2%), and the KM curves indicated that there was no treatment benefit of elacestrant. In the *ESR1*-mut population, the sensitivity analysis showed consistent results with the primary PFS analysis. Overall, the treatment benefit in PFS in the ITT population was mainly driven by the *ESR1*-mut subpopulation.

Table 26 Sensitivity Analysis of PFS per INV by Considering Palliative RT as Event

	ITT		***ESR1*-mut**		***ESR1*-mut-nd**	
	Elacestrant (N = 239)	SOC (N = 239)	Elacestrant (N = 115)	SOC (N = 113)	Elacestrant (N = 124)	SOC (N = 126)
Event, # (%)	194 (81.2%)	190 (79.5%)	85 (73.9%)	90 (80.7%)	107 (86.3%)	99 (78.6%)
Median (95% CI)	2.2 (1.9, 3.5)	1.9 (1.9, 2.1)	3.6 (2.1, 5.4)	2.1 (1.9, 3.5)	1.9 (1.9, 3.0)	2.0 (1.9, 2.4)
HR (95% CI)	0.79 (0.65, 0.97)		0.65 (0.48, 0.89)		0.88 (0.66, 1.17)	

Source: FDA analysis

Figure 12 KM Plots of PFS per INV by Considering Palliative RT as Event in (a) ITT Population, (b) *ESR1*-mut Subpopulation, and (c) *ESR1*-mut-nd Subpopulation



(a) (b) (c)

- *Early censoring*

Overall, in the ITT population, 91 out of 177 censored patients (51%) were censored within 2 months. Table 27 summarizes the number patients censored within 2 months within each patient population, indicating imbalanced censoring between the two arms in the *ESR1*-mut-nd subpopulation, with almost twice as many patients censored in the SOC arm.

Table 27 Number of Patients Censored for PFS per BICR within 2 Months

***ESR1*-mut**		***ESR1*-mut-nd**		**ITT**	
Elacestrant (N = 115)	SOC (N = 113)	Elacestrant (N = 124)	SOC (N = 126)	Elacestrant (N = 239)	SOC (N = 239)
25 (21.7%)	23 (20.3%)	15 (12.1%)	28 (22.2%)	40 (16.7%)	51 (21.3%)

Source: Applicant IR response

The main reasons for the initial drop in the KM curves in both arms were due to the majority of

PFS events occurring within 2 months and early censoring. The most common cause of early censoring was a patient experiencing PD per INV but not per IRC. Because no further tumor assessments were collected, the IRC would censor the patient. Early censoring lends to issues with interpretability of survival estimates.

The FDA disagrees with the Applicant's characterization of this initial drop in the KM curves in both arms. The Applicant states that this drop is "probably reflecting endocrine resistance in a subgroup of patients." Given the number of patients who left the trial after first scan, the initial drop is showing that rather than a small subgroup, a notable proportion of the study population had disease unresponsive to endocrine therapy.

Table 28 summarizes the reason for censoring overall (censored at any time point during the study). The most common reason for censoring was due to patients being censored due to patients experiencing PD per INV but not per IRC. The percentages of patients censored due to PD per INV but not per IRC were relatively balanced between treatment arms for the *ESR1*-mut subpopulation (57% [30/53] elacestrant vs. 54% [19/35] SOC). However, more of an imbalance was observed for the *ESR1*-mut-nd subpopulation (71% [30/42] elacestrant vs. 50% [24/48] SOC), which increases uncertainty in the robustness of PFS estimates for this subpopulation.

Table 28 Censoring Reason for PFS per BICR

	ITT		***ESR1*-mut**		***ESR1*-mut-nd**	
Description	**Elacestrant (N=95 Censored)**	**SOC (N=83 Censored)**	**Elacestrant (N=53 Censored)**	**SOC (N=35 Censored)**	**Elacestrant (N=42 Censored)**	**SOC (N=48 Censored)**
Patients censored for IRC but events for INV	60	43	30	19	30	24
Progression: RECIST	*57*	*40*	*29*	*19*	*28*	*21*
Progression: CLINICAL	*3*	*3*	*1*	*0*	*2*	*3*
No documented progression and no death (with a post-baseline tumor	22	15	17	5	5	10

assessment)						
No post-baseline assessments and no death	6	15	4	8	2	7
Censored progression or death after taking new anti-cancer therapies	4	8	2	3	2	5
Lost to follow-up or withdrew consent before documented progression or death	2	1	0	0	2	1
No baseline measurable or evaluable lesion	1	0	0	0	1	0
Censored progression or death after missing >=2 consecutive post-baseline tumor assessments	0	1	0	0	0	1

Source: FDA analysis

Sensitivity Analyses

FDA believes there is uncertainty regarding the clinical meaningfulness and reliability of PFS in

the ITT population for several reasons: (1) PFS analysis was performed early, (2) limited number of patients left on trial after first scan due to early censoring and dropout, (3) events of the start of new anticancer therapy, and (4) discordance between IRC- and INV-assessed PFS.
FDA conducted several sensitivity analyses to address these concerns (Table 29).

Table 29 PFS Sensitivity Analyses

Sensitivity Analysis Description	***ESR1*-mut HR (95% CI)**	***ESR1*-mut-nd HR (95% CI)**
New anticancer therapy considered an event	0.55 (0.39, 0.76)	0.84 (0.62, 1.14)
Patients with no post-baseline assessments and no death excluded	0.55 (0.39, 0.77)	0.86 (0.63, 1.19)
Patients who were considered events per INV and therefore censored by IRC are considered events	0.64 (0.48, 0.86)	0.89 (0.68, 1.17)
Palliative therapy considered an event	0.60 (0.43, 0.84)	0.85 (0.62, 1.17)

The sensitivity analyses showed that the observed PFS difference remained consistent with the treatment effect in the primary analysis for the *ESR1*-mut subpopulation indicating robustness of PFS estimates and a clear treatment benefit. For the *ESR1*-mut-nd subpopulation, the KM curves were generally overlapping indicating no treatment effect between arms. Due to the lack of clear benefit compared to SOC in the *ESR1*-mut-nd population, FDA believes the indication should be limited to the *ESR1*-mut population.

- *Landmark PFS analyses*

Landmark analyses for time-to-event endpoints are considered exploratory only since specific time points are used as opposed to assessing the entire survival distribution. It is difficult to interpret clinical meaningfulness of landmark estimates as time points chosen for such analyses do not have adequate clinical justification. Early censoring affects the robustness of the estimates reported. In addition, later separation of PFS survival curves seen in the KM plots are not adequately characterized from landmark analyses.

- *Long tail for KM curve in* ESR1-*mut subpopulation*

For the *ESR1*-mut subpopulation, 7 patients were censored after 14 months of follow-up, which created a long tail in the KM curve. All patients were administratively censored except for one on the elacestrant arm who was censored due to clinical disease progression per INV. A

sensitivity analysis excluding these 7 patients showed a consistent treatment effect with the primary analysis: PFS HR 0.65 (95% CI: 0.46, 0.91).

Data Quality and Integrity

The Applicant's Position:

The conduct of the study with regard to protocol adherence and validity of data were recorded in the clinical database. Data were reviewed at regular intervals in order to verify adherence to the protocol and for completeness, consistency, and accuracy of the data, study source documents, and drug accountability records. Data were verified against the original medical records and laboratory results as part of source document verification to ensure its validity. Any issues detected in the course of a monitoring visit were resolved.

To ensure compliance with GCP and all applicable regulatory requirements, quality assurance audits were conducted.

Site audits were conducted at 8 study sites, 1 site each in Australia, Belgium, Italy, the USA, France, and Spain, and at 2 sites in the Republic of Korea. Audit certificates detailing the scope of audit conducted at each site are provided in CSR RAD1901-308, Appendix 16.1.8.

The investigator and study staff were required to maintain a complete and accurate filing system of all study-related documentation that was suitable for inspection at any time by the Sponsor, its designees, and/or regulatory agencies. On signing the protocol, the investigator understood and agreed to give access to study-related documentation and files to the CRA, The Sponsor, other authorized representatives of the Sponsor, representatives of the IRB/IEC, and regulatory agencies.

The FDA's Assessment:

Clinical Audits

The FDA audited some of the clinical data included in the Applicant's submission, particularly information regarding tumor assessments. The FDA examined information in the CRFs and JMP datasets. The audits did not yield any disagreements with the Applicant's tumor assessments.

Clinical Inspections

Refer to Section 4.1 for more detailed information of FDA clinical inspections.

Efficacy Results – Secondary and other relevant endpoints

Data:

Key Secondary Endpoint: Overall Survival

In all subjects, the HR for death under elacestrant versus SOC treatment was 0.742 (95% CI: 0.536 to 1.025), stratified log-rank test p-value = 0.0697 (Source: Updated Table 14.2.2.1.2). At a prospectively defined interim analysis with adjusted alpha level of 0.0001, the difference in

OS between the elacestrant and SOC groups was not statistically significant. A Kaplan-Meier plot is shown in Figure 13.

In *ESR1*-mut subjects, the HR for death for the elacestrant treatment group versus the SOC treatment group was 0.592 (95% CI: 0.361 to 0.958), stratified log-rank test p-value = 0.0325 (Source: Updated Table 14.2.2.1.1). At an alpha level of 0.0001, the difference in OS between the elacestrant and SOC groups was not statistically significant. A Kaplan-Meier plot is shown in Figure 14.

The numbers of subjects with any individual reason for censoring were generally similar across treatment groups. Among all subjects, 30 subjects (12.6%) in the SOC group compared to 18 subjects (7.5%) in the elacestrant group were censored due to withdrawal of consent. A majority of subjects in all groups were censored as they were still alive at data cutoff (CSR RAD1901-308, Table 14.2.2.1.2).

Among all subjects, systemic therapy for breast cancer after study treatment discontinuation was reported for 181 subjects (75.7%) in the elacestrant group and 183 subjects (76.6%) in the SOC group. Chemotherapy was the most frequently reported poststudy treatment, in 114 subjects in the elacestrant group and 120 subjects in the SOC group. The poststudy treatment characteristics were similar between all subjects and *ESR1*-mut subjects (CSR RAD1901-308, Table 14.1.17).

Landmark analysis was conducted at 3, 6, 12, and 18 months and the estimates at each of the timepoints consistently favored the elacestrant arm.

- In all subjects, the 6- and 12-month OS rates were 93.01% and 79.27%, respectively, in the elacestrant arm as compared to 84.84% and 73.00% in the SOC arm (Source: Updated Table 14.2.2.1.2).
- In the *ESR1*-mut subjects, the 6- and 12-month OS rates were 92.79% and 82.64%, respectively, in the elacestrant arm as compared to 84.36% and 73.58% in the SOC arm (Source: Updated Table 14.2.2.1.1).

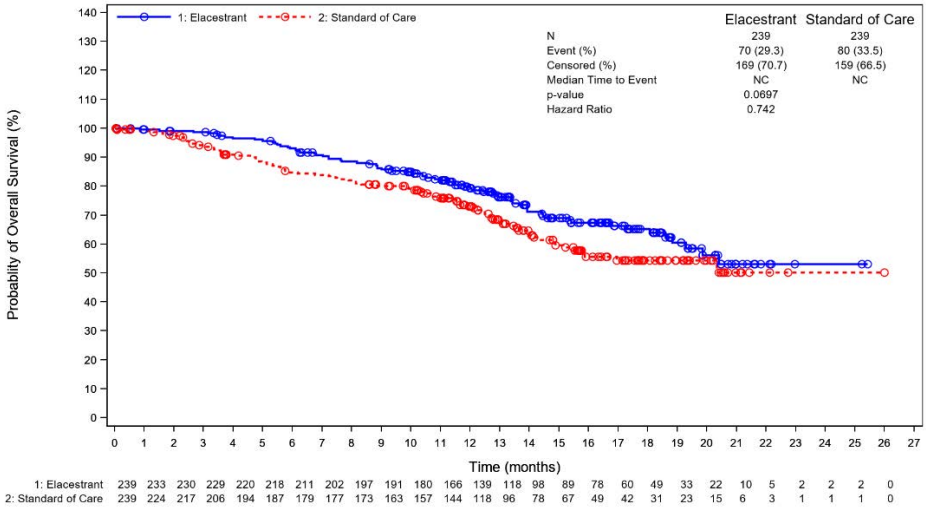
Additional landmark OS estimates are provided in the Source Tables.

Simulation results for OS are described in CSR RAD1901-308, Section 11.6.1.2.

Conditional power was calculated based on the number of deaths observed at the data cutoff date (06 September 2021). This approach estimated the power to observe statistically significant results to be 65.6% for all subjects and 90.4% for subjects with *ESR1*-mut. Additionally, a simulation model based on 10,000 conditional simulations estimated that the probability of success is 68.81% for the all-subject population and 90.78% for the *ESR1*-mut subject population.

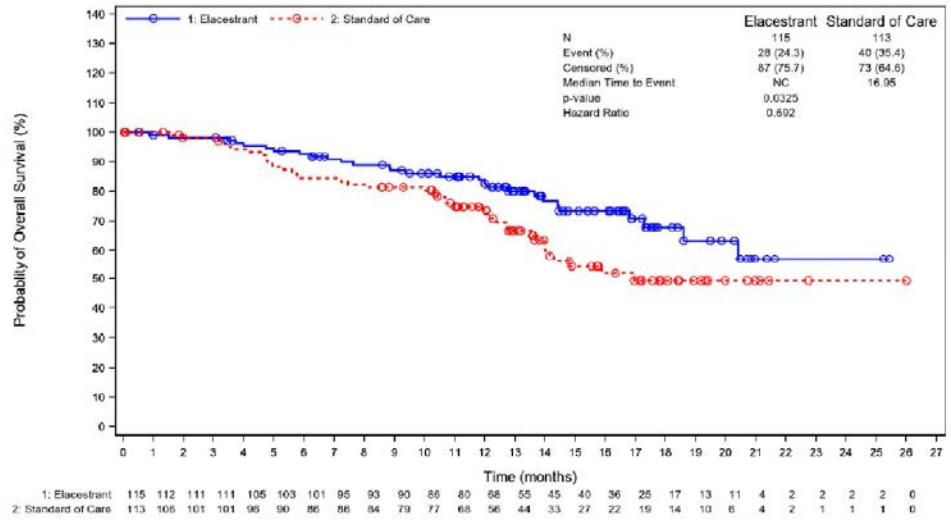
The observed results and the conditional power calculations indicate that the PFS observed results are likely to translate into survival benefit at the time of the final OS analysis which is planned when 239 events are reached.

Figure 13: Kaplan-Meier Plot for Overall Survival in All Subjects (Intent-to-Treat Population)



Abbreviations: N = total number of subjects in group.
Source: CSR RAD1901-308, Figure 14.2.2.1.2

Figure 14: Kaplan-Meier Plot for Overall Survival in ESR1-mut Subjects (Intent-to-Treat Population)



Abbreviations: *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; N = total number of subjects in group.
Source: CSR RAD1901-308, Figure 7

Table 30: Overall Survival (Intent-to-Treat Population)

	All Subjects		*ESR1*-mut Subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
HR (95% CI)	0.742 (0.536–1.025)		0.592 (0.361–0.958)	
p (stratified log-rank test)	0.0697		0.0325	
Median OS (months)	NC	NC	NC	16.95
95% CI	19.29–NC	15.80–NC	18.60–NC	14.00–NC
3-month OS rate	98.72	94.18	98.24	98.09
95% CI	97.28-100.00	91.11-97.25	95.82-100.0	95.46-100.00
6-month OS rate	93.01	84.84	92.79	84.36
95% CI	89.71-96.32	80.07-89.61	87.97-97.60	77.32-91.40
12-month OS rate	79.27	73.00	82.64	73.58
95% CI	73.84-84.71	66.90-79.11	75.28-90.00	64.80-82.37
18-month OS rate	65.24	54.38	67.81	49.36
95% CI	57.85-72.64	46.18-62.57	56.22-79.40	37.03-61.70

Abbreviations: CI = confidence interval; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; HR = hazard ratio; n = number of subjects with the observed group characteristic; N = total number of subjects in group; NC = not calculable; OS = overall survival; SOC = standard of care;

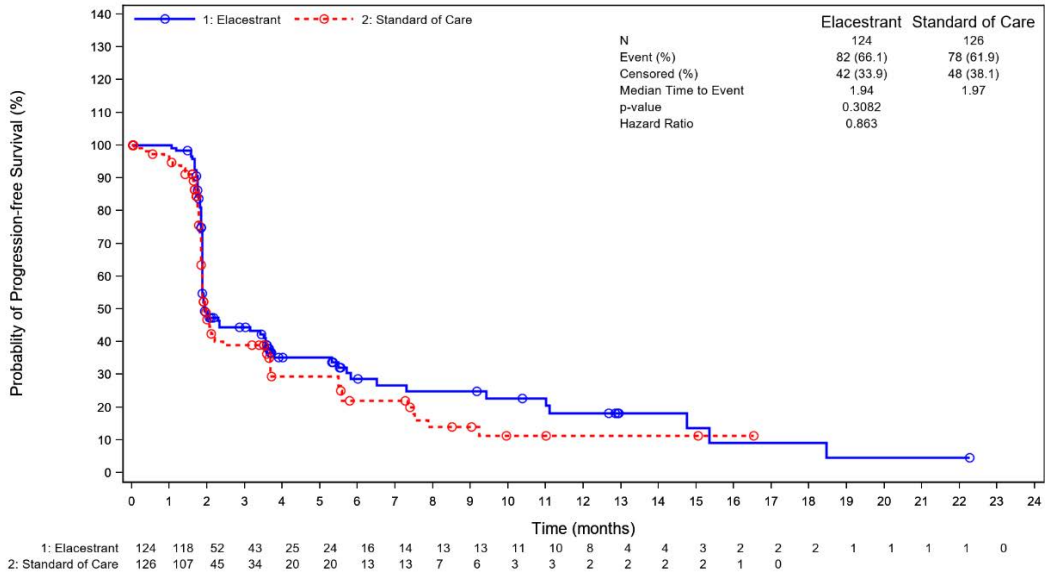
Source: Updated Table 14.2.2.1.1 and Table 14.2.2.1.2

Other Secondary Endpoint: Progression Free Survival in ESR1-mut-nd Subjects (Imaging Review Committee Assessment

In *ESR1*-mut-nd subjects, the observed HR for progression under elacestrant versus SOC treatment was 0.863 (95% CI: 0.628 to 1.186), stratified log-rank test p-value = 0.3082 (Updated Table 14.2.1.1.3). Median PFS values were 1.94 months (95% CI: 1.87 to 3.55) versus 1.97 months (95% CI: 1.87 to 2.20) for the elacestrant versus SOC arms, respectively (Updated Table 14.2.1.1.3). A Kaplan-Meier plot of PFS is shown in Figure 15.

Landmark analysis at 3, 6, 12, and 18 months were conducted (Updated Table 14.2.1.1.3), and the estimates also numerically favored the elacestrant arm and were consistent with the results in the overall population. The 6- and 12-month PFS rates were 28.58% and 18.16%, respectively, in the elacestrant arm as compared to 21.85% and 11.22% in the SOC arm. The 18-month PFS rate was 9.08% on elacestrant and 'data not available' in the SOC arm.

Figure 15: Kaplan-Meier Plot for Blinded Imaging Review Committee Assessment of Progression-free Survival in ESR1-mut-nd Subjects (Intent-to-Treat Population)



Abbreviations: *ESR1* = estrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected (includes samples where *ESR1* mutation was not detected and where *ESR1* mutation status could not be determined); N = total number of subjects in group.

Source: Updated Figure 14.2.1.1.3

Table 31: Blinded Imaging Review Committee Assessment of Progression-free Survival in ESR1-mut-nd subjects (Population)

	Elacestrant N = 124		SOC N = 126	
HR (95% CI)	0.863 (0.628–1.186)			
p (stratified log-rank test)	0.3082			
Median PFS (months)	1.94		1.97	
95% CI	1.87–3.55		1.87–2.20	
Events, n (%)	82	(66.1)	78	(61.9)
Death	2	(1.6)	5	(4.0)
Progression	80	(64.5)	73	(57.9)
3-month PFS rate	44.30		38.92	
95% CI	34.98-53.62		29.16-48.67	
6-month PFS rate	28.58		21.85	
95% CI	18.98-38.18		12.71-30.99	
12-month PFS rate	18.16		11.22	
95% CI	8.60-27.73		2.82-19.62	
18-month PFS rate	9.08		-	
95% CI	0.00-19.19		-	

Abbreviations: CI = confidence interval; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected; HR = hazard ratio; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.

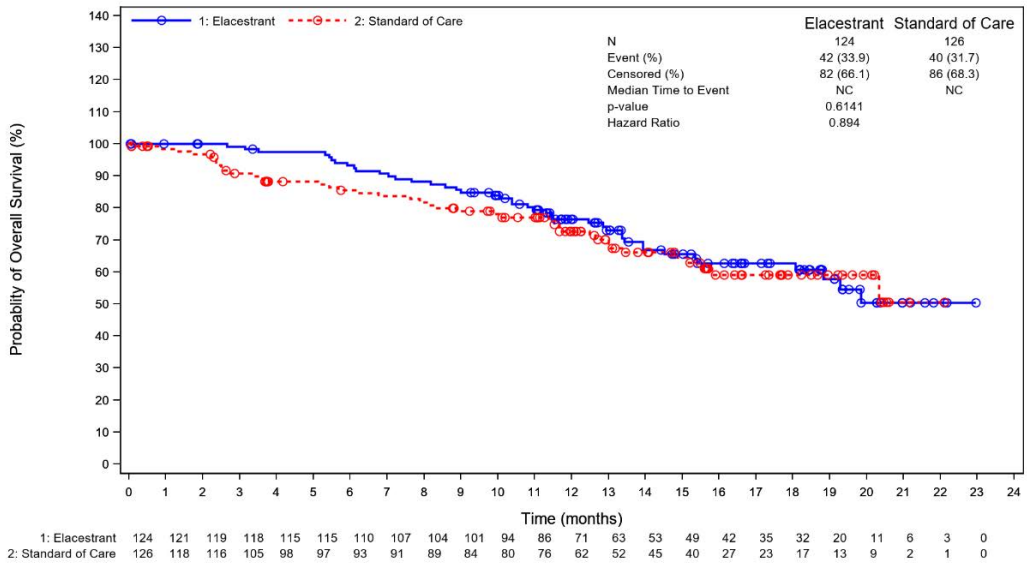
Source: Updated Table 14.2.1.1.3

Other Secondary Endpoint: Overall Survival in ESR1-mut-nd Subjects

In *ESR1*-mut-nd subjects, the HR for death under elacestrant versus SOC treatment was 0.894 (95% CI: 0.577 to 1.386), stratified log-rank test p-value = 0.6141 (Table 32). A Kaplan-Meier plot is shown in Figure 16.

Landmark OS analysis at 3, 6, 12, and 18 months were conducted, and the estimates also numerically favored the elacestrant arm and were consistent with the results in the overall population. The 6- and 12-month OS rates were 93.23% and 76.37%, respectively, in the elacestrant arm as compared to 85.45% and 72.67% in the SOC arm (Table 32).

Figure 16: Kaplan-Meier Plot for Overall Survival in ESR1-mut-nd Subjects (Intent-to-Treat Population)



Abbreviations: *ESR1* = estrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected (includes samples where *ESR1* mutation was not detected and where *ESR1* mutation status could not be determined); N = total number of subjects in group.

Source: Updated Figure 14.2.2.1.3

Table 32: Overall Survival in ESR1-mut-nd Subjects (Intent-to-Treat Population)

	Elacestrant N = 124	SOC N = 126
HR (95% CI)	0.894 (0.577–1.386)	
p (stratified log-rank test)	0.6141	
Median OS (months)	NC	NC
95% CI	18.83–NC	15.80–NC
Deaths, n (%)	42 (33.9)	40 (31.7)
3-month OS rate	99.16	90.77
95% CI	97.52-100.00	85.56-95.97
6-month OS rate	93.23	85.45
95% CI	88.71-97.76	79.04-91.85
12-month OS rate	76.37	72.67
95% CI	68.55-84.20	64.23-81.11
18-month OS rate	62.67	59.01
95% CI	52.88-72.46	48.30-69.73

Abbreviations: CI = confidence interval; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected; HR = hazard ratio; n = number of subjects with the observed group characteristic; N = total number of subjects in group; NC = not calculable; OS = overall survival; SOC = standard of care.

Source: Updated Table 14.2.2.1.3

Other Secondary Endpoint: Progression-Free Survival (Investigator Assessment)

In all subjects, the HR for progression as assessed by the investigators under elacestrant versus SOC treatment was 0.769 (95% CI: 0.625 to 0.945), stratified log-rank test p-value = 0.0097 (Table 33). A Kaplan-Meier plot of PFS for all subjects is shown in Figure 17.

In *ESR1*-mut subjects, the HR for progression as assessed by the investigators under elacestrant versus SOC treatment was 0.647 (95% CI: 0.477 to 0.876), stratified log-rank test p-value = 0.0049 (Table 33). A Kaplan-Meier plot of PFS is shown in Figure 18.

In *ESR1*-mut-nd subjects, the HR for progression as assessed by the investigators under elacestrant versus SOC treatment was 0.892 (95% CI: 0.673 to 1.183), stratified log-rank test p-value = 0.3596 (Table 34). A Kaplan-Meier plot of PFS for *ESR1*-mut-nd subjects is shown in Figure 19.

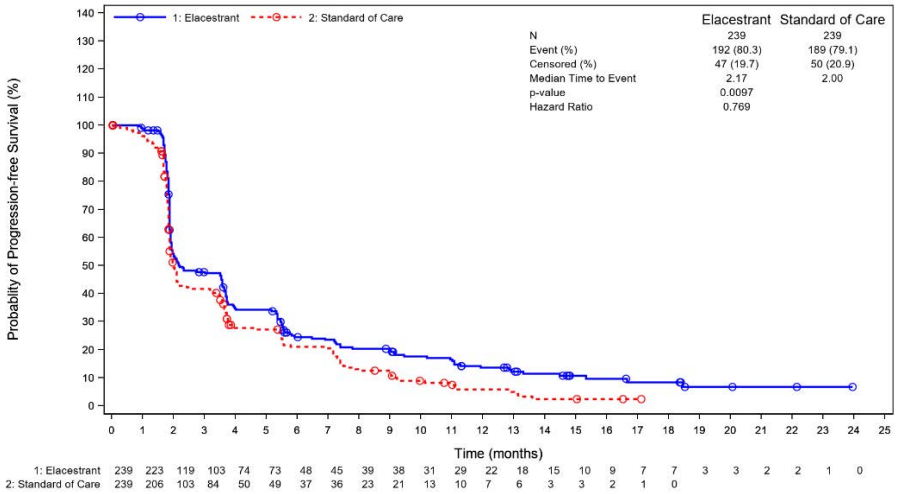
Therefore, the results of PFS analysis based on investigator's assessment for all, *ESR1*-mut and *ESR1*-mut-nd subjects were consistent with the results of PFS based on the assessment of the IRC.

Landmark analysis at 3, 6, 12, and 18 months were conducted. With the exception of the 6-month estimate of PFS in the *ESR1*-mut-nd group, all other PFS estimates at the various time points numerically favored elacestrant.

- In all subjects, the 6- and 12-month PFS estimates were 24.52% and 13.56%, respectively, in the elacestrant arm as compared to 20.98% and 5.75% in the SOC arm.
- In *ESR1*-mut subjects, the 6- and 12-month PFS estimates were 31.79% and 16.87%, respectively, in the elacestrant arm as compared to 17.10% and 6.51% in the SOC arm.

- In *ESR1*-mut-nd subjects, the 6- and 12-month PFS estimates were 18.14% and 10.71%, respectively, in the elacestrant arm as compared to 24.51% and 5.09% in the SOC arm.

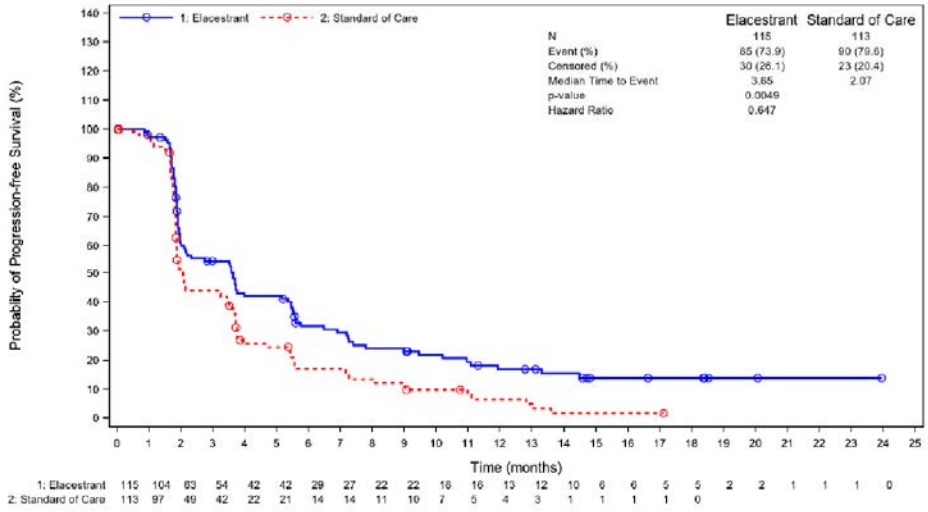
Figure 17: Kaplan-Meier Plot for Investigator Assessment of Progression-free Survival in All Subjects (Intent-to-Treat Population)



Abbreviations: N = total number of subjects in group.

Source: Updated Figure 14.2.1.2.2

Figure 18: Kaplan-Meier Plot for Investigator Assessment of Progression-free Survival in ESR1-mut Subjects (Intent-to-Treat Population)



Abbreviations: *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = no *ESR1* mutation; N = total number of subjects in group.

Source: CSR RAD1901-308, Figure 11

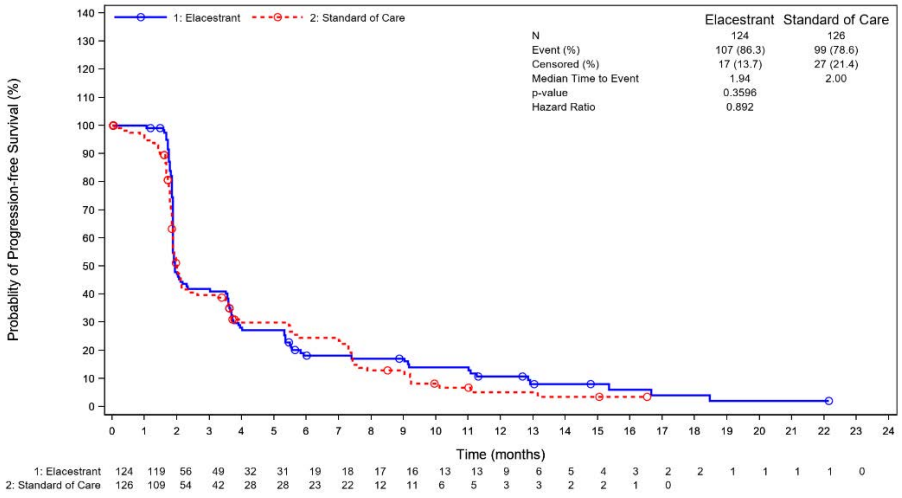
Table 33: Investigator Assessment of Progression-free Survival (Intent-to-Treat Population)

	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 239		SOC N = 239		Elacestrant N = 115		SOC N = 113	
HR (95% CI)	0.769 (0.625–0.945)				0.647 (0.477–0.876)			
p (stratified log-rank test)	0.0097				0.0049			
Median PFS (months)	2.17		2.00		3.65		2.07	
95% CI	1.94–3.58		1.87–2.14		2.10–5.36		1.87–3.48	
Events, n (%)	192	(80.3)	189	(79.1)	85	(73.9)	90	(79.6)
Death	5	(2.1)	6	(2.5)	3	(2.6)	1	(0.9)
Progression	187	(78.2)	183	(76.6)	82	(71.3)	89	(78.8)
3-month PFS rate	47.72		41.73		54.24		43.99	
95% CI	41.14-54.30		34.99-48.47		44.68-63.79		34.13-53.84	
6-month PFS rate	24.52		20.98		31.79		17.10	
95% CI	18.74-30.29		15.22-26.75		22.66-40.91		9.28-24.93	
12-month PFS rate	13.56		5.75		16.87		6.51	
95% CI	8.74-18.37		2.08-9.41		9.18-24.57		0.93-12.10	
18-month PFS rate	8.41		-		13.81		-	
95% CI	3.86-12.96		-		6.43-21.18		-	

Abbreviations: CI = confidence interval; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; HR = hazard ratio; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.

Source: Updated Table 14.2.1.7.1 and Table 14.2.1.7.2

Figure 19: Kaplan-Meier Plot for Investigator Assessment of Progression-free Survival in ESR1-mut-nd Subjects (Intent-to-Treat Population)



Abbreviations: *ESR1* = estrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected (includes samples where *ESR1* mutation was not detected and where *ESR1* mutation status could not be determined); N = total number of subjects in group.

Source: Updated Figure 14.2.1.2.3

Table 34: Investigator Assessment of Progression-free Survival in ESR1-mut-nd Subjects (Intent-to-Treat Population)

	Elacestrant N = 124		SOC N = 126	
HR (95% CI)	0.892 (0.673–1.183)			
p (stratified log-rank test)	0.3596			
Median PFS (months)	1.94		2.00	
95% CI	(1.87–3.02)		(1.87–2.43)	
Events, n (%)	107	(86.3)	99	(78.6)
Death	2	(1.6)	5	(4.0)
Progression	105	(84.7)	94	(74.6)
3-month PFS rate	41.89		39.72	
95% CI	32.95-50.83		30.50-48.94	
6-month PFS rate	18.14		24.51	
95% CI	11.05-25.23		16.18-32.85	
12-month PFS rate	10.71		5.09	
95% CI	4.75-16.66		0.22-9.96	
18-month PFS rate	4.01		-	
95% CI	0.00-8.82		-	

Abbreviations: CI = confidence interval; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut-nd = no *ESR1* mutation detected; HR = hazard ratio; n = number of subjects with the observed group characteristic; N = total number of subjects in group; PFS = progression-free survival; SOC = standard of care.

Source: Updated Table 14.2.1.7.3

Other Secondary Endpoint: Objective Response Rate

For all subjects in the RE population, there was no difference in the ORR (8 subjects [4.5%] in the elacestrant group versus 8 subjects [4.4%] in the SOC group).

For *ESR1*-mut subjects, the ORR (based on confirmed partial response [PR] as assessed by the blinded IRC for the RE population) was slightly higher in the elacestrant group (6 subjects [7.1%]) than in the SOC group (4 subjects [4.7%]). There was no statistically significant difference in ORR between the elacestrant and SOC groups either for all or just *ESR1*-mut subjects (Table 35). No subjects had a CR.

Among *ESR1*-mut-nd subjects, objective responses (all PR) were observed in 2 (2.1%) subjects in the elacestrant group and 4 subjects (4.2%) in the SOC group (CSR RAD1901-308, Table 14.2.3.1.6).

The RE population is smaller than the ITT Population, partly due to the exclusion of subjects with bone-only disease who cannot be classified per RECIST into the response categories shown here. Overall, fewer than 5% of subjects in the RE population were not evaluable. Reasons for nonevaluability included not having a postbaseline assessment, and diagnosis of clinical progression by the investigator prior to the first postbaseline radiological assessment.

Results based on local investigator's assessment were consistent with the results reported by the blinded IRC for both groups (Table 36).

Table 35: Blinded Imaging Review Committee Assessment of Objective Response Rate (Response Evaluable Population)

	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 179		SOC N = 182		Elacestrant N = 85		SOC N = 86	
ORR, n (%)	8	(4.5)	8	(4.4)	6	(7.1)	4	(4.7)
95% CI	1.95–8.62		1.92–8.48		2.63–14.73		1.28–11.48	
p	0.959				0.499			
Best OR, n (%)								
CR (confirmed)	–	–	–	–	–	–	–	–
PR (confirmed)	8	(4.5)	8	(4.4)	6	(7.1)	4	(4.7)
SD ≥ 6 weeks	75	(41.9)	55	(30.2)	42	(49.45)	22	(25.6)
PD	89	(49.7)	110	(60.4)	32	(37.6)	55	(64.0)
NE[a]	7	(3.9)	9	(4.9)	5	(5.9)	5	(5.8)

Abbreviations: CI = confidence interval; CR = complete response; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; n = number of subjects with the observed group characteristic; N = total number of subjects in group; NE = not evaluable; OR = overall response; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; SOC = standard of care.

Source: Updated Table 14.2.3.1.4 and Table 14.2.3.1.5

Table 36: Investigator Assessment of Objective Response Rate (Response Evaluable Population)

	All Subjects				*ESR1*-mut Subjects			
	Elacestrant N = 189		SOC N = 192		Elacestrant N = 91		SOC N = 92	
ORR, n (%)	13	(6.9)	4	(2.1)	10	(11.0)	3	(3.3)
95% CI	3.71–11.47		0.57–5.25		5.40–19.28		0.68–9.23	
p	0.030				0.054			
Best OR, n (%)								
CR (confirmed)	–	–	–	–	–	–	–	–
PR (confirmed)	13	(6.9)	4	(2.1)	10	(11.0)	3	(3.3)
SD	67	(35.4)	75	(39.1)	37	(40.7)	36	(39.1)
PD	103	(54.5)	112	(58.3)	40	(44.0)	53	(57.6)
NE	6	(3.2)	1	(0.5)	4	(4.4)	-	-

Abbreviations: CI = confidence interval; CR = complete response; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; n = number of subjects with the observed group characteristic; N = total number of subjects in group; NE = not evaluable; OR = overall response; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease; SOC = standard of care.

Source: Updated Table 14.2.3.2.4 and Table 14.2.3.2.5

Other Secondary Endpoint: Clinical Benefit Rate and Duration of Response

The CBR, as assessed by the IRC:

- Among all subjects, the CBR was 18.4% in the elacestrant group and 13.5% in the SOC group (Source: Updated Table 14.2.5.1.2).
- Among *ESR1*-mut subjects, the CBR was 24.1% in the elacestrant group and 11.5% in the SOC group (Source: Updated, Table 14.2.5.1.1).

Similarly, the CBR, as assessed by the investigator:

- Among all subjects, the CBR was 20.6% in the elacestrant group and 13.7% in the SOC group (Source: Updated Table 14.2.5.2.2).
- Among *ESR1*-mut subjects, the CBR was 25.0% in the elacestrant group and 11.0% in the SOC group (Source: Updated Table 14.2.5.2.1).

In all subjects, as per the IRC assessment, the median DoR could not be calculated in the elacestrant group for any group of subjects, as all subjects with response were censored without progression or death as of the cut-off date (Source: Updated Table 14.2.4.1.2).

The median DoR, as per investigator's assessment for the 13 subjects with conformed PR was 9.23 months with approximately half of the responders progression-free at 18 months (Source: Updated Table 14.2.4.2.2).

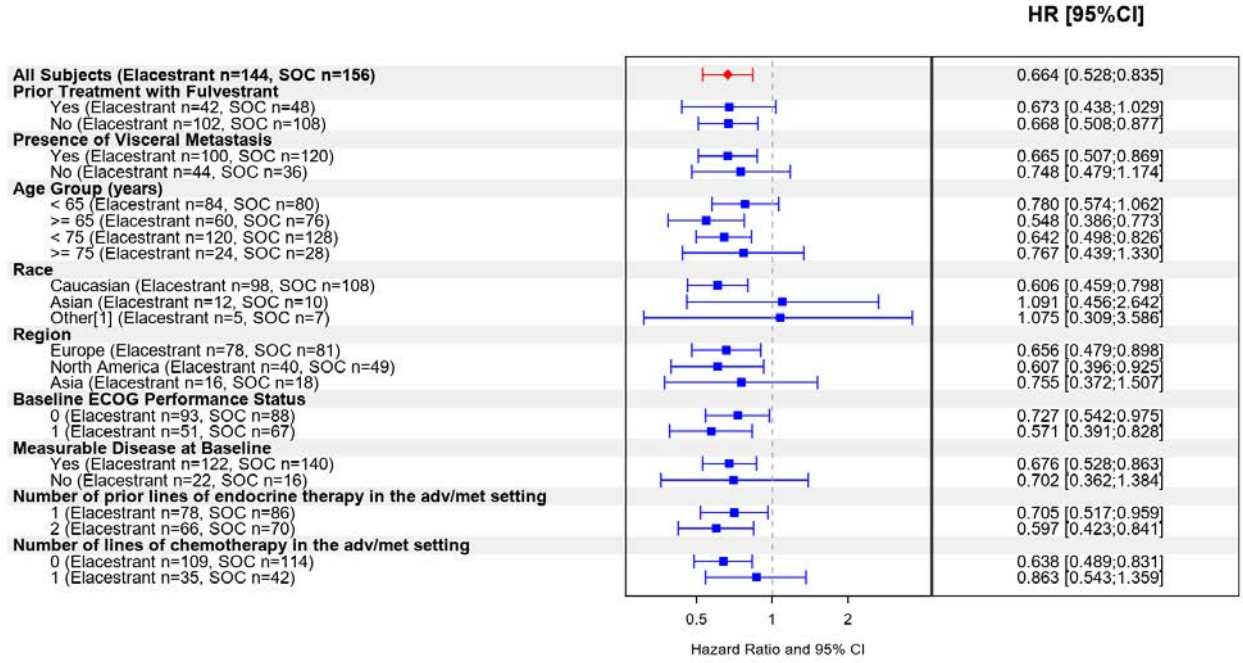
Consistency of Progression Free Survival Results Across Subpopulations

Prespecified subgroup analyses were conducted and displayed by forest plot. As shown in Figure 20: Forest Plot of Blinded IRC Assessment of PFS in All Subjects (N = 478) (Study RAD1901-308 - ITT Population) and Figure 21: Forest Plot of Blinded IRC Assessment of PFS in ESR1-mut Subjects (N = 228) (Study RAD1901-308 - ITT Population), the results in individual subgroups consistently favored elacestrant as compared to SOC in both all subjects and in subjects with *ESR1*-mut. However, results should be interpreted with caution as the study was not powered for the investigation of subgroups, and some HRs are calculated based on low numbers of subjects or events.

Details for age groups and for number of prior hormonal therapy in the advanced/metastatic setting are presented in Table 37.

The forest plots (Figure 20 and Figure 21) were produced based on the subjects who were classified in each subgroup at baseline. The "n's" displayed in the following plots represent the number of events in each subgroup and treatment (rather than the number of subjects) due to the limited space in the figures. However, both the number of events and the number of subjects are presented in the associated subgroup tables (CSR RAD1901-308, Table 14.2.1.8.1 and Table 14.2.1.8.2).

Figure 20: Forest Plot of Blinded IRC Assessment of PFS in All Subjects (N = 478) (Study RAD1901-308 - ITT Population)



Abbreviations: adv/met = advanced/metastatic; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; n = number of PFS events; PFS = progression-free survival; SOC = standard of care.

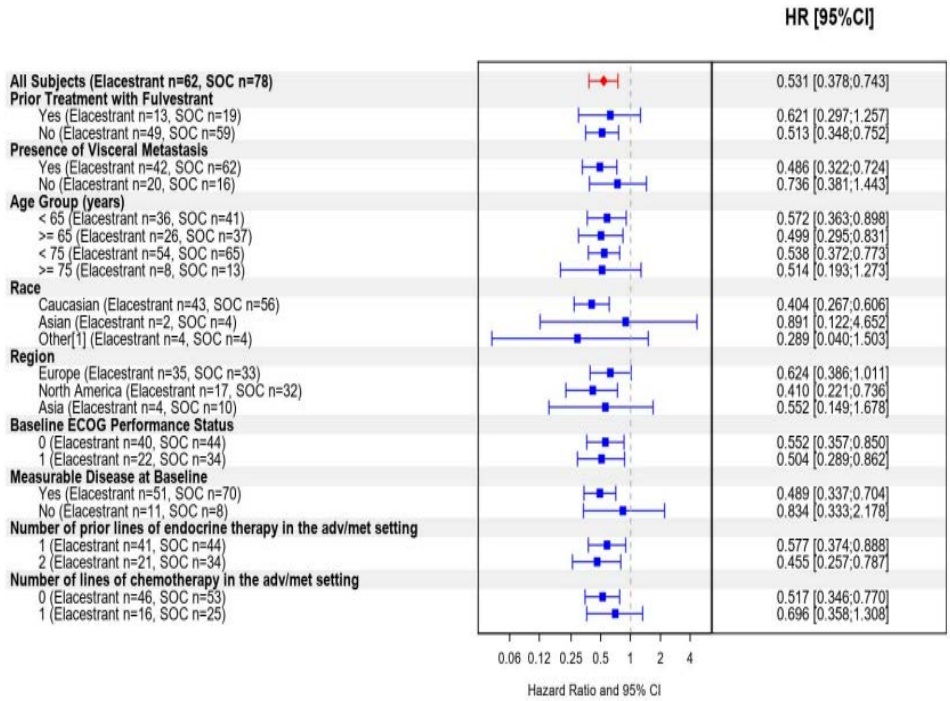
Note: Includes subjects with multiple races

HR is calculated using an unstratified Cox proportional hazards model with ties = Efron. The CI is calculated using a profile likelihood approach.

Number of events are reported in brackets

Source: Updated Figure 14.2.1.3.2

Figure 21: Forest Plot of Blinded IRC Assessment of PFS in ESR1-mut Subjects (N = 228) (Study RAD1901-308 - ITT Population)



Abbreviations: adv/met = advanced/metastatic; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; HR = hazard ratio; IRC = imaging review committee; ITT = intent-to-treat; n = number of PFS events; PFS = progression-free survival; SOC = standard of care.

Note: Includes subjects with multiple races

HR is calculated using an unstratified Cox proportional hazards model with ties = Efron. The CI is calculated using a profile likelihood approach.

Number of events are reported in bracket

Source: CSR RAD1901-308, Figure 16

Table 37: Blinded Imaging Review Committee Assessment of Subgroup Analysis for Progression-free Survival (Intent-to-Treat Population)

	All Subjects		*ESR1*-mut Subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
Age group (years)				
< 65				
HR (95% CI)	0.780 (0.574–1.062)		0.572 (0.363–0.898)	
Median PFS	2.00	1.87	3.75	1.87
95% CI	1.91–3.71	1.87–3.45	2.10–5.45	1.84–3.45
Events/subjects	84/135	80/128	36/62	41/62
≥ 65				
HR (95% CI)	0.548 (0.386–0.773)		0.499 (0.295–0.831)	
Median PFS	3.68	1.97	7.79	1.94
95% CI	2.33–7.79	1.87–2.14	1.94–10.84	1.87–3.71

	All Subjects		*ESR1*-mut Subjects	
	Elacestrant N = 239	SOC N = 239	Elacestrant N = 115	SOC N = 113
Events/subjects	60/104	76/111	26/53	37/51
< 75				
HR (95% CI)	0.642 (0.498–0.826)		0.538 (0.372–0.773)	
Median PFS	2.79	1.87	3.78	1.87
95% CI	1.94–4.14	1.87–2.07	2.17–7.26	1.84–2.14
Events/subjects	120/199	128/193	54/98	65/96
≥ 75				
HR (95% CI)	0.767 (0.439–1.330)		0.514 (0.193–1.273)	
Median PFS	3.42	2.10	2.33	2.10
95% CI	1.87–7.39	1.91–4.76	1.87–NC	1.87–4.76
Events/subjects	24/40	28/46	8/17	13/17
Number of prior lines of endocrine therapy in the adv/met setting				
1				
HR (95% CI)	0.705 (0.517–0.959)		0.577 (0.374–0.888)	
Median PFS	3.52	1.94	4.14	1.87
95% CI	1.97–4.99	1.87–3.55	2.10–8.61	1.84–3.68
Events/subjects	78/129	86/142	41/73	44/69
2				
HR (95% CI)	0.597 (0.423–0.841)		0.455 (0.257–0.787)	
Median PFS	2.33	1.87	3.78	2.00
95% CI	1.87–5.45	1.84–2.10	1.91–7.79	1.84–3.52
Events/subjects	66/110	70/97	21/42	34/44

Abbreviations: adv/met = advanced/metastatic; CI = confidence interval; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; HR = hazard ratio; N= total number of subjects in group; NC = not calculable; PFS = progression-free survival; SOC = standard of care.

Source: Updated Table 14.2.1.8.1, Updated Table 14.2.1.8.2, Updated Table 14.2.1.1.1, and Updated Table 14.2.1.1.2

The Applicant's Position:

The patient population evaluated in Study RAD1901-308 represents patients with the highest unmet medical need among ER+/HER- mBC, with limited treatment options after prior therapy with the combination of a CDK4/6 inhibitor and either fulvestrant or an AI.

Elacestrant showed clear advantage versus SOC in terms of PFS (e.g., a hazard reduction of 33% in all subjects and 45% in subjects with *ESR1* mutation) in addition to a clear advantage in PFS estimates at the different time points. In all subjects at 12 months, it is estimated that 1 in 5 subjects on elacestrant will be alive and progression-free as compared to 1 in 10 subjects in the SOC arm. In the *ESR1*-mut group, the corresponding estimates are 1 in 4 on elacestrant versus 1 in 12 on SOC. This protocol-prespecified landmark analysis is especially important as the median PFS values are heavily impacted by the steep drop in the Kaplan-Meier plots in the first 2 months after randomization.

Results of post hoc exploratory PFS and OS analyses of elacestrant versus fulvestrant were consistent with the results in the overall population in terms of median values, hazard ratios, and landmark estimates. These results are of special interest for 3 reasons:

a. Fulvestrant is the most commonly used hormonal monotherapy after failure of the combination of a CDK4/6 inhibitor and AIs, and alternative combination therapy options, e.g., everolimus combination with exemestane or with fulvestrant, and alpelisib combination with fulvestrant, have a toxicity profile that leads to approximately 25% discontinuation rate because of AEs (everolimus USPI; alpelisib USPI).
b. The efficacy advantage of elacestrant versus fulvestrant was observed, despite the fact that both drugs share a common mechanism of action, which is ER degradation.
c. If approved, elacestrant will be the first hormonal therapy that showed a statistically significant efficacy in all patients, including patients with *ESR1* mutations, in a randomized setting against SOC (primary analysis), in addition to the efficacy advantage against fulvestrant (post hoc exploratory analysis).

PFS results of elacestrant versus SOC after prior use of fulvestrant in the advanced/metastatic setting were also consistent with the PFS results in all subjects. This is important for patients who receive fulvestrant either as monotherapy or in combination with a CDK4/6 inhibitor as a first- or second-line therapy, as elacestrant, if approved, will be a more tolerable alternative to combination therapy or chemotherapy.

Also, the interim analysis of OS numerically favored elacestrant, both in the overall population and in subjects with *ESR1* mutations

Elacestrant shows statistically significant and clinically relevant benefit in terms of PFS in the all subjects and the *ESR1*-mut group. Additionally, elacestrant displayed an advantage against SOC in the PFS landmark analysis in all subjects, subjects with *ESR1*-mut, and, to a smaller extent, in subjects with *ESR1*-mut-nd. Furthermore, analyses based on local tumor assessments were statistically significant in favor of elacestrant, both in all subjects and in the *ESR1*-mut group. Results of post hoc exploratory PFS analysis of elacestrant versus the fulvestrant and AI subgroups of the control arm, separately, were also consistent with the overall results.

Analysis of secondary endpoints, including OS, numerically favored the elacestrant arm. Consistent with the PFS landmark analysis, estimates of OS at the various timepoints favored elacestrant versus SOC in all subjects and *ESR1*-mut subjects, as well as in subjects with *ESR1*-mut-nd.

Sensitivity and subgroup analyses were also supportive of the analyses of the primary endpoints. Although the benefit observed in the *ESR1*-mut-nd group was smaller than that observed in all subjects and in *ESR1*-mut subjects, results numerically, but not statistically significantly, favored elacestrant versus SOC in this subgroup of patients.

Despite the fact that the development of *ESR1* mutations during earlier treatment settings in ER+/HER2- mBC leads to resistance to further endocrine therapy, data from this study show that elacestrant, and not fulvestrant or AIs, has the potential to overcome this resistance mechanism.

The FDA's Assessment:

The FDA has the following comments on the secondary endpoints.

Overall Survival

The FDA agrees that a statistically significant difference was not observed for the OS analyses in the ITT and *ESR1*-mut populations. The FDA determined that there was no trend towards OS detriment for the *ESR1*-mut subpopulation, but the FDA had some concerns regarding OS in the *ESR1*-mut-nd subpopulation.

At the time of initial submission, the interim OS analysis (40% maturity; DCO: 9/6/21) showed 42 patients (34%) in the elacestrant arm vs. 40 patients (32%) in the SOC arm died in the *ESR1*-mut-nd subpopulation. The percentage of patients died was higher in the elacestrant arm than the SOC arm.

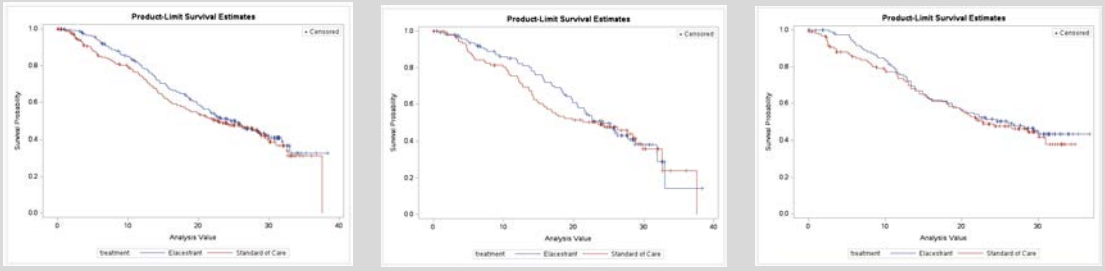
During the review, OS reached the planned final analysis time (DCO: 11/15/22). The Applicant performed the final OS analysis and submitted the results and data to the Agency for review. The following table summarized the final OS results in the *ESR1*-mut subpopulation, *ESR1*-mut-nd subpopulation, and ITT population (Table 38). The KM curves were plotted in the figure below (Figure 22).

There was a higher percentage of deaths in the elacestrant arm than in the SOC arm in the *ESR1*-mut-nd subpopulation, which led to a higher percentage of deaths in the elacestrant arm than in the SOC arm in the ITT population. In addition, while we see some separation of the KM curves for the two arms in the *ESR1*-mut subpopulation, the KM curves for the two arms crossed each other in *ESR1*-mut-nd subpopulation. The results in the interim and final analysis did not indicate a treatment benefit in OS in the *ESR1*-mut-nd subpopulation.

Table 38 Final OS Analysis in (a) ITT population, (b) *ESR1*-mut subpopulation, and (c) *ESR1*-mut-nd subpopulation (DCO: 11/15/22)

	ITT		***ESR1*-mut**		***ESR1*-mut-nd**	
	Elacestrant (N = 239)	SOC (N = 239)	Elacestrant (N = 115)	SOC (N = 113)	Elacestrant (N = 124)	SOC (N = 126)
Event, # (%)	124 (51.9)	121 (50.6)	61 (53.0)	60 (53.1)	63 (50.8)	61 (48.4)
Median in months (95% CI)	24.6 (20.7, 29.5)	22.6 (18.1, 28.9)	24.2 (20.5, 28.7)	23.5 (15.6, 29.9)	26.1 (18.8, NR)	22.6 (18.4, 31.0)
Hazard Ratio (95% CI)	0.91 (0.71, 1.18)		0.90 (0.63, 1.30)		0.92 (0.65, 1.31)	

Figure 22 Final OS KM Curves in (a) ITT population, (b) *ESR1*-mut subpopulation, and (c) *ESR1*-mut-nd subpopulation (DCO: 11/15/22)



(a) (b) (c)

The HRs were consistent across exploratory subgroups in the *ESR1*-mut subpopulation, including age, sex, race, region, prior fulvestrant, visceral metastases, prior chemotherapy, and prior targeted therapy.

However, due to a high proportion of withdrawal of consent and missing vital status for 11% of patients, FDA evaluated several important review issues in detail as articulated below and conducted several sensitivity analyses to address these concerns. Moreover, there were late changes to the OS testing procedure that are discussed below.

Withdrawal of Consent

There were 40 patients (8.4%) in the ITT population who withdrew consent and were censored for OS at that time (Table 39). There was no further follow-up for these 40 patients. This percentage is high for a well-designed and well-conducted clinical trial. The Applicant stated in an IR Response that "10 subjects (9 in the SOC arm and 1 in the ELA arm) were randomized but withdrew consent prior to treatment with study drug (which is probably due to subjects wishing to benefit from the treatment arm rather than the control arm)." This uneven withdrawal of consent, particularly seen within the *ESR1*-mut-nd population, could result in bias.

Refer to the Missing Vital Status and Data Integrity section regarding the IR that was sent regarding retrieval of data for patients who withdrew consent and the Sensitivity Analyses section evaluating robustness of results due to withdrawal of consent for OS.

Table 39 Reasons for Censoring of Final OS (DCO: 9/2/22)

	***ESR1*-mut**		***ESR1*-mut-nd**	
	Elacestrant (N=115)	**SOC (N=113)**	**Elacestrant (N=124)**	**SOC (N=125)**
Total Censored	54 (47.0%)	53 (46.9%)	61 (49.2%)	65 (52.0%)
Withdrawn consent	15 (13.0%)	14 (12.4%)	8 (6.5%)	19 (15.2%)

Still in follow-up	38 (33.0%)	39 (34.5%)	52 (41.9%)	44 (35.2%)
Terminated before death	0	0	0	1 (0.8%)
Lost to follow-up	0	0	1 (0.8%)	0
Other	1 (0.9%)	0	0	1 (0.8%)

Missing Vital Status and Data Integrity

Vital status was missing for 11% of patients. The Applicant also identified a coding error in 16 patients' censoring reason after FDA review team sent an IR.

FDA sent an IR on 12/12/2022 requesting the Applicant make every effort to retrieve missing OS data for reasons such as withdrawal of consent, physician decision, or loss to follow-up. In the IR response, the Applicant stated that all sites were contacted to evaluate feasibility of retrieving missing OS data; however, most of the sites refused to provide information or did not respond.

Although missing OS data increases the uncertainty of the estimates, the FDA review team concluded that there was no trend towards OS detriment for the *ESR1*-mut subpopulation and that the missing vital status does not impact the main OS estimates, particularly given that the reasons for censoring were balanced between treatment arms. However, due to the large imbalance in withdrawal of consent observed between treatment arms for the *ESR1*-mut-nd subpopulation, the robustness of OS results is a concern in this subpopulation. This limits review team's ability to adequately characterize OS, which is an important endpoint for both safety and efficacy.

Sensitivity Analyses

Several sensitivity analyses were conducted to assess the impact of censoring (Table 40). One sensitivity analysis considered all patients who withdrew consent as events at the time of censoring. Additional sensitivity analyses imputed data for patients who withdrew consent in both arms only from the best 20% of patients for OS in both arms and from the best 20% of patients for OS in the SOC arm only. The HR estimate for the *ESR1*-mut-nd subpopulation was greater than 1 when OS data were imputed to be longer for patients who withdrew consent in the SOC arm only; however, these are considered unlikely scenarios.

Table 40 OS Sensitivity Analyses

Sensitivity Analysis Description	***ESR1*-mut HR (95% CI)**	***ESR1*-mut-nd HR (95% CI)**
Assume patients who withdrew consent as events	0.92 (0.66, 1.27)	0.79 (0.57, 1.09)

at the time of censoring		
Impute OS for patients who withdrew consent in both arms from the best 20% for OS in both arms	0.93 (0.65, 1.33)	1.01 (0.71, 1.43)
Impute OS for patients who withdrew consent in both arms from best 20% for OS in SOC arm only	0.98 (0.69, 1.40)	0.97 (0.69, 1.37)
Impute OS for patients who withdrew consent in SOC arm only from best 20% for OS in both arms	1.08 (0.75, 1.55)	1.09 (0.77, 1.55)
Impute OS for patients who withdrew consent in SOC arm only from best 20% for OS in SOC arm only	1.05 (0.74, 1.51)	1.07 (0.76, 1.52)

The Applicant sent an IR Response on 1/11/2022 to provide results on a tipping point analysis that was requested to evaluate the point in which the OS hazard ratio goes above 1 for the *ESR1*-mut subpopulation. The Applicant performed a tipping point analysis by ordering individual time-to-censoring in ascending order for the 15 patients who withdrew consent on the elacestrant arm only in the *ESR1*-mut subpopulation. In a stepwise manner, patients who withdrew consent were turned into events at the time they were censored. This analysis assumes a shorter survival time for patients who withdrew consent in the elacestrant arm only compared to the main OS analysis. This attenuates the OS HR by assuming incremental worsening in the elacestrant arm. The OS HR tipped to 1.01 after 7 of the 15 patients. FDA confirmed the results of the tipping point analysis in the *ESR1*-mut subpopulation and conducted the same analysis in the *ESR1*-mut-nd subpopulation. The OS HR tipped to 1.01 after 6 of the 8 patients who withdrew consent on the elacestrant arm in the *ESR1*-mut-nd subpopulation. This is also an unlikely clinical scenario. Since OS is unknown for patients who withdrew consent, the statistical analysis of OS relies on modeling assumptions for these patients. Shared characteristics of patients who withdrew consent were not clear to better guide these analyses. Therefore, FDA and the Applicant conducted a series of sensitivity analyses under varying assumptions of OS indicating a range of possibilities in the OS treatment effect for the *ESR1*-mut and *ESR1*-mut-nd subpopulations. The larger range in point estimates for OS in the *ESR1*-mut-nd subpopulation indicates less stability in OS estimates due to differing assumptions for patients who withdrew consent. This adds greater uncertainty to the assessment of OS in the *ESR1*-mut-nd subpopulation.

FDA primarily considers the pre-specified main OS analyses when interpreting survival results as sensitivity analyses rely heavily on modeling assumptions. There was a notable imbalance in withdrawal of consent for the *ESR1*-mut-nd subpopulation, which heavily impacts interpretability of OS estimates and lead to a wider variation in the OS HRs from the sensitivity analyses. The percentages of patients who withdrew consent in the *ESR1*-mut subpopulation were balanced between treatment arms. Several of the sensitivity analyses presented in this section are very conservative and are considered unlikely scenarios, including the exploratory tipping point analyses. FDA concluded that there was no trend towards OS detriment demonstrated in the *ESR1*-mut subpopulation.

Landmark OS analyses

Although indicated in the protocol, landmark analyses for time-to-event endpoints are still considered exploratory only since specific time points are used as opposed to assessing the entire survival distribution. Therefore, any differences between treatment arms at these landmarks must be interpreted with caution. Censoring affects the robustness of the estimates reported, particularly for the ESR1-mut-nd subpopulation where an imbalance in censoring was observed.

Secondary Endpoints

The multiplicity plan accounted for the 2 primary endpoints (PFS in all patients and in *ESR1*-mut patients) and the 2 key secondary endpoints (OS in all patients and in *ESR1*-mut patients). There was no formal hypothesis testing of other secondary endpoints. Therefore, p-values presented by the Applicant for the other secondary endpoints such as ORR are difficult to interpret and are considered nominal p-values only.

The FDA notes that the ORRs on the elacestrant arm and SOC arm were low in the ITT population, *ESR1*-mut subpopulation, and the *ESR1*-mut-nd subpopulation. In the *ESR1*-mut-nd subpopulation, there were only 2 responders (2.1%) in the elacestrant arm vs. 4 responders (4.2%) in the SOC arm. The results of ORR did not support the treatment benefit of elacestrant in this subpopulation. CBR is not an endpoint used by the FDA for regulatory decision making.

Overall, the FDA disagrees with the Applicant's conclusion that elacestrant shows statistically significant and clinically meaningful benefit in terms of PFS in all patients and that the results of subgroup analyses and sensitivity analyses support these findings. Landmark analyses are difficult to interpret due to arbitrary choice in analysis time points and early censoring impacting landmark estimates. In the FDA's review, while a statistically significant benefit for PFS was demonstrated in all patients, the benefit was driven by patients in the *ESR1*-mut subpopulation. There was no clear benefit observed in patients in the *ESR1*-mut-nd subpopulation. In addition, the results of the subgroup analyses and particularly the sensitivity analyses increased the uncertainty regarding clinical benefit in the *ESR1*-mut-nd subpopulation.

Please refer to Section 8.1.2 for the FDA's comprehensive assessment of efficacy on Study RAD1901-308.

Dose/Dose Response

Data:

Not applicable

The Applicant's Position:

Applicability of the dose and dose response are discussed in Section 6.3.2.2 and Section 6.2.2.1.

The FDA's Assessment:

Refer to Clinical Pharmacology review in Section 7 for more information regarding dose.

Durability of Response

The Applicant's Position:

Duration of response was investigated as a secondary objective and discussion can be found in Section 8.1.1.

The FDA's Assessment:

Refer to Section 8.1.1.

Persistence of Effect

The Applicant's Position:

No long-term efficacy data with exception of those previously presented are available at the time of the submission of the application.

The FDA's Assessment:

See FDA assessment of OS in Section 8.1.2.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

The completion rate for EQ-5D-5L remained above 70% until Cycle 2 Day 1. For all subjects and *ESR1*-mut subjects, there were no noteworthy differences between groups in change from baseline to EOT in EQ-VAS scores or subscales, and there were no noteworthy changes over time in either group.

The completion rate for the EORTC QLQ-C30 remained above 70% until Cycle 2 Day 1. Noteworthy differences between treatment groups (for *ESR1*-mut subjects) in mean (s.d.) change from baseline through EOT were observed for the following:

- Role functioning: – 10.42 (29.13) in the elacestrant group versus – 0.46 (27.21) in the SOC group
- Fatigue: + 9.72 (24.31) in the elacestrant group versus + 0.77 (17.92) in the SOC group
- Pain: + 9.49 (28.09) in the elacestrant group versus + 1.62 (22.23) in the SOC group
- Appetite loss: + 10.19 (24.15) in the elacestrant group versus 0.00 (19.38) in the SOC group

Similar patterns were observed for all subjects as among the *ESR1*-mut subjects.

There were no noteworthy differences between treatment groups and no noteworthy changes over time in either group, either for all subjects or for *ESR1*-mut subjects for the mixed model repeated measures analysis of QoL through Cycle 6.

There were no noteworthy differences between treatment groups and no noteworthy changes over time in either group for change from baseline in frequency, severity, or interference for any treatment-emergent adverse event (TEAE), either for all or for just *ESR1*-muts subjects for the Patient-reported Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE) results.

The FDA's Assessment:

The FDA disagrees with the Applicant's assessment of patient-reported outcomes. Due to attrition (treatment discontinuation, disease progression, and death) beyond cycle 2 day 1, there are few patients who were expected to respond to PROs, and therefore it is difficult to make conclusions on the tolerability of elacestrant. However, of the patients who were expected to complete a PRO, more than 80% did so through cycle 4 day 1.

In terms of physical and role functioning, FDA examined results from EORTC-QLQ-C30 in both *ESR1*-mut and ITT populations. In general, these analyses are exploratory and difficult to interpret due to attrition as mentioned above. Observed differences between groups are small with large SDs, further limiting interpretability.

The Applicant commented on patient-reported symptoms based on the *ESR1*-mut population using EORTC QLQ-C30 results, however FDA performed additional PRO analysis and interpretation on the entire trial population using PRO-CTCAE results to evaluate tolerability of elacestrant. The main symptoms that descriptively appeared different between arms were decreased appetite (severity) and nausea (frequency) and were measured using the PRO-CTCAE:

- Decreased appetite: throughout the first four cycles, more patients treated with SOC reported no decreased appetite compared to patients treated with elacestrant. At cycle 4 day 1, 78% (58/74) of patients on the SOC arm reported no decreased appetite, while 68% (65/96) of patients in the elacestrant arm reported no decreased appetite.
- Nausea: throughout the first four cycles, there was a substantial difference between

elacestrant and SOC treated patients in terms of frequency of nausea. Although there was nearly identical baseline frequency of nausea between arms, by cycle 1 day 15, 75% of SOC treated patients reported "never" experiencing nausea while only 56% of elacestrant treated patients reported "never" experiencing nausea. This difference was seen throughout the first six cycles, and supports the observed clinician reported nausea. The majority of patients in both arms who reported any frequency of nausea reported it as "rarely" or "occasionally" and less than 10% of those responding to the nausea item responded with "frequently" or "almost constantly" at any given timepoint in the first six cycles.

No other notable differences were obvious between arms in terms of PRO-CTCAE symptoms, again noting the limitations in interpreting the data due to attrition beyond cycle 2.

FDA did not analyze the results of EQ-5D as it is not a PRO measure suitable for assessment of tolerability or disease improvement. FDA focused its analysis on results from EORTC QLQ-C30 and PRO-CTCAE.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

8.1.2. Integrated Review of Effectiveness

The FDA's Assessment:

The FDA's conclusions regarding the efficacy of elacestrant for the treatment of patients with ER+HER2- advanced or metastatic breast cancer were based on results from Study RAD1901-308, a randomized, active-controlled, open-label, multicenter trial examining elacestrant versus SOC endocrine therapy (fulvestrant or AI). The primary endpoint was PFS assessed by IRC in the *ESR1*-mut subpopulation and in the ITT population (*ESR1*-mut and *ESR1*-mut-nd). The secondary endpoint was OS in the *ESR1*-mut subpopulation and in the ITT population.

The PFS endpoint was met in the *ESR1*-mut subpopulation (median PFS 3.8 months vs. 1.9 months, HR 0.55, 95% CI: 0.39-0.77; p-value = 0.0005) and in the ITT population (median PFS 2.8 months vs. 1.9 months, HR 0.70, 95% CI: 0.55-0.88; p-value = 0.0018). The FDA considers the PFS results in the ITT population to be driven by patients with an *ESR1* mutation, who made

up approximately 48% of the population enrolled. In the FDA's assessment, there was uncertainty regarding efficacy for patients in the *ESR1*-mut-nd subpopulation.

Results in the *ESR1*-mut-nd subpopulation were descriptive and must be interpreted with caution since efficacy endpoints in this subpopulation were not formally powered or statistically tested. However, there were differential PFS results in the *ESR1*-mut-nd subpopulation compared to the *ESR1*-mut subpopulation. For patients in the *ESR1*-mut-nd subpopulation, median PFS was 1.9 months on the elacestrant arm compared to 2.0 months on the SOC arm with a HR of 0.86 (95% CI: 0.63-1.19). The KM curves for the two arms were close together, the medians were essentially the same, and the percentage of the patients with an event was higher in the elacestrant arm compared with the SOC arm. A variety of PFS sensitivity analyses to evaluate issues such as early censoring and palliative RT in the *ESR1*-mut-nd subpopulation consistently indicated no clear benefit for the elacestrant arm. For example, FDA performed a sensitivity PFS analysis where patients who were censored due to progressive disease (PD) per investigator assessment (INV) in the primary analysis were considered as events. In the ESR1-mut-nd subpopulation, median PFS was 1.9 (95% CI: 1.9, 2.1) months on the elacestrant arm compared to 1.9 (95% CI: 1.8, 2.0) months on the SOC arm (HR 0.89, 95% CI: 0.68-1.17). Additionally, Kaplan-Meier (KM) curves were widely overlapping indicating no clear benefit in the elacestrant arm for the *ESR1*-mut-nd subpopulation.

Study RAD1901-308 is an active-controlled trial with a replacement design, and to support a favorable regulatory decision, improvement in an efficacy endpoint can be more modest, provided that the control arm is active, and the experimental treatment is not adding toxicity relative to the SOC treatment. In Study RAD1901-308, although the choice of control arm appeared reasonable when the trial was designed and initiated, the performance of the control arm was poor with a shorter median PFS than expected. Most patients appeared to have endocrine-resistant disease and experienced PD at first imaging assessment (~2 months). Therefore, the control arm was not particularly active, and the clinical significance of a marginally positive trend in PFS, as demonstrated in the *ESR1*-mut-nd subpopulation, is uncertain.

Results from secondary efficacy endpoints also did not support clinical benefit in the *ESR1*-mut-nd subpopulation. Although the OS endpoint was not met, there was a trend favoring the elacestrant arm in both the *ESR1*-mut subpopulation (HR 0.90, 95% CI: 0.63-1.30) and in the ITT population (HR 0.91, 95% CI: 0.71, 1.18). However, in the *ESR1*-mut-nd subpopulation, there was a higher percentage of deaths in the elacestrant arm than in the SOC arm, and the KM curves for the two arms crossed each other. There was a notable imbalance in withdrawal of consent for the *ESR1*-mut-nd subpopulation, which adds further uncertainty regarding OS in this group of patients. In addition, in the *ESR1*-mut-nd subpopulation, descriptive ORR estimates were numerically lower on the elacestrant arm compared to the SOC arm: 2.1% vs. 4.2%

Finally, there are publicly available external data to suggest that patients with an *ESR1* mutation may derive greater benefit from elacestrant and other oral SERDs compared to patients without an *ESR1* mutation. Emerging data from other oral SERDs, summarized in Section 2.2, suggest greater benefit for several of these products in patients with an *ESR1* mutation.

The FDA concluded that clinical benefit was demonstrated for patients in the *ESR1*-mut subpopulation. Although the PFS improvement was modest, this was a replacement design trial, the PFS improvement was robust to multiple sensitivity analyses, and it was supported by demonstration of no potential trend towards OS detriment. In contrast, the FDA concluded that clinical benefit was not demonstrated in the *ESR1*-mut-nd subpopulation. In exploratory PFS results, there was a marginally favorable trend in PFS which was not robust to multiple sensitivity analyses and not supported by OS or ORR results. The FDA restricted the indication for elacestrant to patients in the *ESR1*-mut subpopulation only.

Although male patients with breast cancer were included in Study RAD1901-308, there were no male patients in the *ESR1*-mut subpopulation. The FDA included male patients in the indication based on extrapolation from data in female patients and biologic rationale that there were no expected efficacy or safety differences in male and female patients with an *ESR1* mutation (FDA Guidance: Male Breast Cancer, 2020). There were no specific safety concerns noted based on the 7 male patients included in the ITT population, including 6 patients on the elacestrant arm.

8.1.3. Study RAD1901-005

The Applicant's Position:

The open-label Study 005 (NCT02338349) evaluated elacestrant in heavily pretreated women with ER+/HER2- mBC, including those with the estrogen receptor 1 (*ESR1*) mutation. The primary objective was to determine the MTD and/or RP2D. The study consisted of a 3 + 3 design (elacestrant capsules) followed by expansion at RP2D (345 mg capsules, then 345 mg tablets) for the evaluation of safety and antitumor activity. Elacestrant was administered orally QD until progression or intolerability.

Of 57 postmenopausal women enrolled, 50 received the RP2D (345 mg QD): median age, 63 years; median 3 prior anticancer therapies including CDK4/6 inhibitors (52.0%), SERD (52.0%), and *ESR1* mutation (circulating tumor DNA; 50.0%). No dose-limiting toxicities occurred; the most common AEs at RP2D (345 mg tablet; n = 24) were nausea (33.3%) and increased blood triglycerides and decreased blood phosphorus (25.0% each). Most AEs were Grades 1 to 2 in severity. The ORR was 19.4% (n = 31 evaluable subjects receiving the RP2D), 15.0% in subjects with prior SERD (n = 3 out of 20), 16.7% in subjects with prior CDK4/6 inhibitor (n = 3 out of 18), and 33.3% in subjects with *ESR1* mutation (n = 5 out of 15). The CBR at 24 weeks was 42.6% overall (n = 47, subjects receiving the RP2D), 56.5% (n = 23, *ESR1* mutation), and 30.4% (n = 23, prior CDK4/6 inhibitor). Elacestrant CB was associated with decline in *ESR1* mutant allele fraction.

In conclusion, elacestrant 345 mg orally QD had a manageable safety profile and demonstrated single-agent activity with confirmed PRs in heavily pretreated women with ER+/HER2- mBC. Notably, responses were observed in subjects with *ESR1* mutation as well as those with prior CDK4/6 inhibitor and prior fulvestrant.

The FDA's Assessment:

The FDA agrees with the Applicant's description of Study RAD1901-005. Study RAD1901-005 is a small, single arm trial from which limited conclusions can be drawn. In addition, the patient population differed from that of Study RAD1901-308 in that not all patients had received a prior CDK4/6 inhibitor. However, it is notable that most tumor responses occurred in patients with an *ESR1* mutation. This supports the FDA's assessment of results from RAD1901-308 that clinical benefit was demonstrated in the *ESR1*mut subgroup but not in all patients.

8.1.4. Study RAD1901-106

The Applicant's Position:

The open-label, nonrandomized Study 1901-106 (NCT02650817) was initiated to determine the effect of elacestrant on the availability of ER in lesions from 16 postmenopausal women with ER+ advanced breast cancer using 16α-18F-fluoro-17β-estradiol positron emission tomography with low-dose computed tomography (FES-PET/CT). Eligible subjects were postmenopausal women with ER+/HER2- advanced breast cancer; tumor progression after ≥ 6 months of 1 to 3 lines of endocrine treatment for advanced breast cancer; and measurable or evaluable disease. Two 8-subject cohorts were enrolled: one treated with 345 mg elacestrant QD and one treated with 173 mg elacestrant QD with dose escalation to 345 mg QD after 14 days. Elacestrant was dosed continuously until progressive disease, toxicity, or withdrawal. FES-PET/CT was performed pre-dose at baseline and at 4 hours post-dose on Day 14. The primary endpoint was the percentage difference in FES uptake in tumor lesions (maximum of 20) after 14 days of treatment compared to baseline. Overall response was investigator-assessed by RECIST version 1.1.

Sixteen subjects (median age, 53.5 years) had advanced breast cancer with a median 2.5 prior lines of endocrine therapy. Median reduction in tumor FES uptake from baseline to Day 14 was 88.0% (Q1, Q3: 71.3%, 91.8%) and was similar in both cohorts (88.0% in the 200/345 mg cohort and 88.7% in the 345 mg cohort). Residual ER availability (> 25% persistence in FES uptake) on Day 14 was observed in 3 subjects receiving 200/345 mg (3 of 8, 37.5%) and 1 subject receiving 345 mg (1 of 8, 12.5%). The ORR was 11.1% (1 partial response), and the CBR was 30.8%. Median percentage change in FES uptake did not correlate with ORR or CBR. AEs occurring in > 20% of subjects were nausea (68.8%), fatigue (50.0%), dyspepsia (43.8%), vomiting (37.5%), and decreased appetite, dysphagia, and hot flush (31.3% each). Most events were Grade 2 in severity.

In conclusion, elacestrant 173 mg and 345 mg QD greatly reduced ER availability measured by FES-PET/CT. In a heavily pretreated population, elacestrant was associated with antitumor activity.

The FDA's Assessment:

The FDA agrees with the Applicant's description of Study RAD1901-106. FDA did not consider efficacy data from Study RAD 1901-106 as part of our review as the clinical significance of change in FES uptake is unknown.

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

Secondary and Other Endpoints

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

Subpopulations

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.6. Integrated Assessment of Effectiveness

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

8.2. Review of Safety

The Applicant's Position:

The patient population enrolled in the Phase 3 study (Study RAD1901-308) is representative of the target population for which the Sponsor is seeking a marketing authorization.

The Phase 3 study (Study RAD1901-308) included men and postmenopausal women with mBC treated with either 345 mg elacestrant tablet QD or the approved dose of therapy selected in the SOC treatment.

Adverse events in both treatment arms were mainly Grade 1 and 2. The incidence of Grade 3 events was low in both treatment arms and no grade 4 adverse events were reported in the study.

Although the incidence of nausea (all grades, irrespective of relationship to study drug) was higher in the elacestrant arm (35%), it was reported in 25% of subjects receiving an AI and to a lesser extent in subjects receiving fulvestrant (16.1%). The incidence of treatment-related nausea (all grades) was 25.3% in the elacestrant arm, 8.7% among subjects receiving fulvestrant and 8.8% among subjects receiving an AI. The incidence of grade 3, however, was low in both treatment arms (2.5%, 0%, and 2.9% on elacestrant, fulvestrant, and AI, respectively).

On the other hand, the incidence of arthralgia and fatigue was numerically higher among subjects in the fulvestrant arm (17.4% and 21.7%, respectively) relative to subjects who received elacestrant (14.3% and 19.0%, respectively) and those who received an AI (13.2% and 11.8%, respectively). Injection site pain was reported by 8.7% of the subjects receiving fulvestrant.

No AEs of bradycardia/sinus bradycardia or QTc prolongation were reported in the elacestrant arm, both of which are common AEs observed in trials of other novel antiestrogen drugs. QTcF measurements showed that none of the subjects had a QTcF prolongation of ≥ 60 ms relative to baseline.

None of the TEAEs, irrespective of relationship to treatment, had an incidence of Grade 3 that exceeded 5%. In addition, the incidence of Grade 3 AEs that were considered related to study drug was very low in both treatment arms.

None of the AEs that had a fatal outcome (4 on elacestrant and 6 on fulvestrant) was considered related to study drug.

Only 3 subjects had a serious TEAE that was considered related to elacestrant and the incidence of AEs leading to treatment discontinuation was low in both treatment arms (6.3% in elacestrant and 4.4% in the SOC arm).

The safety profile in subjects with *ESR1*-mut and in subjects with *ESR1*-mut-nd was consistent with the safety profile in all subjects.

Overall, elacestrant was well tolerated, and the safety profile was comparable to currently available SOC treatments. Adverse events were manageable with dose adjustments.

The FDA's Assessment:

The FDA agrees with the Applicant that Study RAD1901-308 (EMERALD) is adequate to characterize the safety profile of elacestrant in patients with ER-positive, HER2-negative advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

The FDA's independent analysis of safety is based on the 467 patients who received at least one dose of trial treatment in Study RAD1901-308, including 237 patients who received elacestrant and 230 patients who received SOC (fulvestrant - 162 or AI - 68). The FDA assessed safety in the entire safety population for Study RAD1901-308, as well as separately in patients with *ESR1*-mut and patients with *ESR1*-mut-nd. The FDA agrees with the Applicant that the safety profile was similar among all patients, patients with *ESR1*-mut, and patients with *ESR1*-mut-nd.

Almost all patients enrolled to Study RAD1901-308 experienced at least one TEAE, and the overall incidence of TEAEs was slightly higher in patients who received elacestrant (93%) compared to patients who received SOC (85%). The most common (≥ 10%) TEAEs, including laboratory abnormalities, in patients who received elacestrant were musculoskeletal pain, nausea, increased cholesterol, increased AST, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased ALT, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia. The incidence of Grade 3 TEAEs was slightly higher in patients who received elacestrant (27%) compared to patients who received SOC (21%). The most common (≥5%) grade 3 TEAE in patients who received elacestrant was musculoskeletal pain which occurred in 7% of patients. There were no Grade 4 TEAEs. SAEs were balanced between patients who received elacestrant (12%) and patients who received placebo (11%), and the most common SAEs (≥ 1%) on the elacestrant arm were musculoskeletal pain (1.7%) and nausea (1.3%).

The incidence of TEAEs leading to dosage interruption was higher in patients who received elacestrant (15%) compared to patients who received SOC (5%), and the most common (≥3%) TEAE leading to dosage interruption in patients receiving elacestrant was nausea (3.4%). The incidence of TEAEs leading to drug discontinuation was slightly increased in patients receiving elacestrant (6%) compared to SOC (4.3%). Dose reductions were low (3%) in patients receiving elacestrant and not allowed for aromatase inhibitors per their labeling. Dose reductions were allowed only for hepatic impairment for fulvestrant.

The FDA's safety review focused on understanding the toxicity of elacestrant compared to the toxicities of the treatments on the SOC arm (fulvestrant or AI). Important safety signals for elacestrant included GI TEAEs including nausea, vomiting, decreased appetite, and dyspepsia, and dyslipidemia including hypercholesterolemia and hypertriglyceridemia. Nausea, vomiting, decreased appetite, and dyspepsia occurred in a greater proportion of patients who received elacestrant compared to SOC: 35% vs. 19%, 19% vs. 9%, 15% vs. 10%, and 10% vs. 2.6%, respectively. In addition, the use of serotonin (5HT3) antagonists (e.g., ondansetron) was higher in patients receiving elacestrant compared to SOC: 18% vs. 10%. Furthermore, descriptive PRO data collected using the PRO-CTCAE instrument showed differences in decreased appetite and nausea in patients who received elacestrant compared to SOC.

Hypercholesterolemia and hypertriglyceridemia also occurred in higher frequencies in patients who received elacestrant compared to SOC: 30% vs. 17% and 27% vs. 15%, respectively. The FDA labeled dyslipidemia under Warnings in the USPI given the frequency, association with cardiovascular disease, and the need for increased monitoring and possible treatment.

The FDA disagrees with the Applicant's statement that elacestrant was well tolerated, and the safety profile was comparable to currently available SOC treatments. As noted, GI TEAEs and dyslipidemia occurred in a greater proportion of patients who received elacestrant compared to SOC. Although most TEAEs, including GI TEAEs, were Grade 1-2, the FDA notes that even certain Grade 1-2 TEAEs, e.g., nausea, can adversely impact a patient's quality of life.

In the FDA's analysis, the frequency of fatigue was similar between patients who received elacestrant (26%) vs. SOC (27%). Arthralgia was included in an assessment of musculoskeletal pain and there was a similar frequency of musculoskeletal pain in patients who received elacestrant (41%) compared to SOC (39%). The only TEAE with a notably higher frequency in patients receiving SOC was injection site pain, which occurred in 9% of patients who received fulvestrant. For further details, refer to the FDA's assessment in Section 8.2.4. Finally, the FDA disagrees with the Applicant's assessment of safety based on treatment- related TEAEs. The FDA considers all TEAEs, regardless of attribution, as attribution is subjective and prone to bias.

Overall, the FDA concluded that the toxicities associated with elacestrant (GI toxicity and dyslipidemia) are only justifiable for patients with *ESR1*-mut as this is the group in whom clinical benefit with elacestrant was observed. Given the uncertainty regarding clinical benefit in patients with *ESR1*-mut-nd, exposing these patients to the increased toxicity of elacestrant is not justifiable. The FDA believes that the safety profile of elacestrant is manageable with labeling for the indicated patient population with *ESR1*-mut.

8.2.1. Safety Review Approach

Data:

Safety endpoints included the following:

- Study drug exposure
- TEAEs by system organ class and preferred term (PT)
- Laboratory assessments
- Vital signs
- Electrocardiograms (ECGs)
- ECOG PS

The safety population (defined as all subjects who received at least 1 dose of 345 mg elacestrant or equivalent SOC) was evaluated and used for presentation and analysis of the ISS data and was analyzed according to the treatments they actually received.

Baseline was defined as the last nonmissing assessment prior to or on the first dose date.

All statistical analyses were performed using SAS statistical software (Version 9.4 or higher).

All AEs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 for reporting. In each individual study, the particular version of the MedDRA was declared for coding. After all data were integrated, a listing of the verbatim terms, PTs, and system organ class assigned to each event was reviewed and, if required, adjustments were made in coding of like terms. Likewise, all concomitant medications were mapped to the same version of the World Health Organization Drug Dictionary (September 2018). AEs and laboratory assessments were reported according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.3 for Studies RAD1901-005 and RAD1901-106 and Version 5.0 for Study RAD1901-308; NCI CTCAE grades were not re-mapped to a single version for this SCS.

Treatment-emergent AEs were defined as follows:

- Any AE that was absent (i.e., had not occurred) or had resolved prior to the start of study drug, and which occurred on or after the date of the first dose of study drug and within 30 days after the last dose of study drug, or
- Any AE that started before treatment, was ongoing after treatment was started, and increased in severity after the start of study drug and within 30 days after the last dose of study drug.

In Studies RAD1901-005 and RAD1901-106, study visits were performed on the last day of the treatment cycle; in Study RAD1901-308, visits were performed on the first day of the next cycle. In each study, dosing was continuous but divided into 28-day cycles. For data presented by study visit, the following visits were combined into a single analysis visit across all studies, and were labeled as the first day of next cycle (e.g., data for Study RAD1901-005 Cycle 1 Day 28 and for Study 308 Cycle 2 Day 1 are presented as Cycle 2 Day 1 in all data presentations):

- Cycle 1, Day 14 and Day 15
- Subsequent cycles, Day 28 and Day 1 of the following cycle (e.g., Cycle 2, Day 28 and Cycle 3, Day 1)

Selected safety endpoints (AEs, ECG data, and laboratory assessments) were also presented by subgroups based on the values collected at baseline (i.e., the last nonmissing measurement collected on or before the study drug first dose date/time). Subgroup levels were redefined or combined based on the availability of data. A subgroup analysis was not performed if the number of subjects in the subgroup in each treatment group was not sufficiently large (e.g., < 5%). Because only the Phase 3 Study RAD1901-308 contained males, tabulations by gender are presented for Study RAD1901-308 only. Similarly, because the majority of women enrolled in the Phase 1 studies were White/Caucasian (range: 87.5% to 94.9%; ISS, Table 14.1.2), tabulations for race are presented for Study RAD1901-308 only.

All planned analyses were completed using observed cases from integrated data in the safety population. Missing or partial dates and times were imputed as described in Appendix 7.1 of the ISS SAP.

Data Presentation and Pooling Strategy

The Phase 3 study group includes men and postmenopausal women with mBC treated with 345 mg elacestrant QD tablet (n= 237) and those treated with SOC (n=229) (Study RAD1901-308). Subjects who received at least 1 dose of elacestrant or SOC were categorized into the following treatment groups:

- 345 mg elacestrant tablets
- SOC (fulvestrant or AIs)

Key safety data are also provided for *ESR1*-mut and *ESR1*-mut-nd subjects from Study RAD1901-308.

Since the proposed registration dose for elacestrant is 345 mg per day, as studied in the Phase 3 study, subjects who received this dose in Phase 1 studies were also evaluated for this summary. For this reason, safety data for the 2 Phase 1 studies were combined and these data were presented alongside the elacestrant data from the Phase 3 study for this SCS. Since only 7 subjects in Study RAD1901-005 and 2 subjects in Study RAD1901-106 received a starting dose other than 345 mg QD, these subjects were not included in this SCS data presentation. Based on differences in eligibility criteria, subjects enrolled in the Phase 1 studies represented a more heavily pretreated subject population with more advanced disease than subjects eligible for the Phase 3 study and with resultant potential for increased risk for a worse safety profile. A comparison of eligibility criteria in all 3 studies is presented in Table 2 of the ISS SAP.

The Phase 1 studies pool includes postmenopausal women with mBC treated with 345 mg QD elacestrant (n=64) from 2 Phase 1 studies (Studies RAD1901-005 and RAD1901-106). Subjects were classified into the following treatment groups pooled across both studies:

- 345 mg elacestrant capsules
- 345 mg elacestrant tablets
- 345 mg elacestrant capsule and tablet groups combined

Subjects who received the capsule dosage form but who transitioned from capsule to tablet are included in the capsule group only.

Tabulations were produced for demographic, baseline, and safety parameters.

For categorical variables, the number and percentage within each category were presented, including a category for missing data, if applicable. For continuous variables, descriptive statistics (e.g., n, mean, median, SD, first quartile, third quartile, minimum, and maximum) were presented.

Treatment duration was calculated differently for fulvestrant (3 biweekly doses, followed by monthly doses) and AIs (QD doses); therefore, these 2 groups were not combined into a single SOC group when presenting exposure data. All other tables were based on treated subjects and present a single SOC group comprising fulvestrant and AIs.

The Applicant's Position:

The clinical development of elacestrant evaluated a series of scientific and clinical questions with the goal of understanding the benefits and risks of elacestrant therapy in the intended patient population, as assessed relative to other currently available hormonal monotherapy treatments.

The FDA's Assessment:

The FDA agrees with the Applicant's description of safety assessments in Study RAD1901-308. The FDA's primary analysis of safety focused on the 467 patients who received at least one dose of trial treatment in RAD1901-308, including 237 patients who received elacestrant and 230 patients (not 229 patients as stated by the Applicant) who received SOC - fulvestrant or an AI. There were 221 patients with *ESR1*-mut in the RAD1901-308 safety population, 115 who received elacestrant and 106 who received SOC. There were 246 patients with *ESR1*-mut-nd in the RAD1901-308 safety population, 122 who received elacestrant and 124 who received SOC.

The FDA's safety review of Study RAD1901-308 is based on data submitted with an initial cutoff date of 9/6/2021. The FDA also reviewed the 120 -day safety update with a data cutoff of 7/8/2022 and there were no new safety signals.

The FDA did not review all safety data submitted as part of the Phase 1 studies pool and did not pool those data with data from Study RAD1901-308 as patients in the Phase 1 study pool had more heavily pretreated disease and some patients received a different formulation of elacestrant. If the FDA used certain data from the Phase 1 studies to support safety analyses and conclusions, it is noted in the safety sections below.

The FDA's safety analysis focused on deaths and TEAEs including SAEs, TEAEs leading to trial drug discontinuation, dose reduction, or dosage interruption, grade 3-4 TEAEs, all-grade TEAEs. The FDA also reviewed laboratory data. Although the Applicant did not identify any AEs of special interest, the FDA conducted further assessments of dyslipidemia and grade 3 musculoskeletal pain. The FDA identified dyslipidemia as an important safety signal associated with elacestrant. More details are included in the Analysis of Submission-Specific Safety Issues.

For assessment of TEAEs, the FDA grouped related preferred terms as follows:

- Musculoskeletal pain: back pain, bone pain, musculoskeletal chest pain, arthralgia, musculoskeletal pain, pain in extremity, spinal pain, neck pain, myalgia, musculoskeletal stiffness, non-cardiac chest pain, musculoskeletal discomfort, arthritis
- Vomiting: vomiting, retching
- Fatigue: fatigue, asthenia
- Abdominal pain: abdominal pain, abdominal pain upper, abdominal pain lower, hepatic pain, gastrointestinal discomfort, abdominal discomfort

The FDA found this portion unclear in the Applicant's position statement: "as assessed relative to other currently available hormonal monotherapy treatments." The FDA evaluated elacestrant compared to SOC endocrine therapy in Study RAD1901-308 but did not conduct additional comparisons between safety data for elacestrant and external data for other hormonal monotherapy treatments.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

In Study RAD1901-308, 478 subjects were randomized to treatment, and 466 subjects received treatment. A total of 239 subjects (237 treated) were randomized to the elacestrant group, and 239 subjects (230 treated) were randomized to the SOC group. The SOC group included 166 subjects assigned to fulvestrant treatment (162 treated) and 73 assigned to AI treatment (68 treated).

In Study RAD1901-308, the mean (SD) duration on treatment (in days) was

- in all subjects: 144 (142) on elacestrant, 123 (101) on fulvestrant, and 97 (98) on AI (Source: Updated Table 14.1.16.2).
- in subjects with *ESR1*-mut: 160 (156) on elacestrant, 125 (98) on fulvestrant, and 97 (111) on AI (Source: Updated Table 14.1.16.2).

Table 41: Duration of exposure

	RAD1901-005 and RAD1901-106			RAD1901-308		
	Elacestrant 345 mg Capsules (N=40)	Elacestrant 345 mg Tablets (N=24)	Elacestrant 345 mg Overall (N=64)	Elacestrant 345 mg Tablets (N=237)	SOC-Fulvestrant (N=162)	SOC-AIs (N=68)
Duration on treatment (days)						
n	40	24	64	237	162	68
Mean	215.1	210.9	213.5	144.1	122.6	96.8
SD	264.04	195.77	239.07	141.89	101.16	97.75
Median	117.0	140.0	117.0	84.0	83.5	64.5
Min	5	14	5	13	2	1
Max	1288	760	1288	756	462	554

Source: Updated Table 14.1.16.2

Table 42: Dose

	RAD1901-005 and RAD1901-106			RAD1901-308		
	Elacestrant 345 mg Capsules (N=40)	Elacestrant 345 mg Tablets (N=24)	Elacestrant 345 mg Overall (N=64)	Elacestrant 345 mg Tablets (N=237)	SOC-Fulvestrant (N=162)	SOC-AIs (N=68)
Total dose received (mg)[a]						
n	40	24	64	237	NA	68
Mean	82647.5	83533.3	82979.7	56617.3	NA	1914.0
SD	102532.64	77674.88	93332.01	55315.16	NA	2149.07
Median	45000.0	56000.0	45400.0	33600.0	NA	1400.0
Min	2000	5600	2000	2800	NA	1
Max	515200	304000	515200	302400	NA	12500

	RAD1901-005 and RAD1901-106			RAD1901-308		
	Elacestrant 345 mg Capsules (N=40)	Elacestrant 345 mg Tablets (N=24)	Elacestrant 345 mg Overall (N=64)	Elacestrant 345 mg Tablets (N=237)	SOC-Fulvestrant (N=162)	SOC-AIs (N=68)
Absolute dose intensity (mg/day)[b]						
n	40	24	64	237	NA	68

Source: ISS, Table 14.1.8

The Applicant's Position:

The size of the safety database is sufficient to adequately characterize the safety profile.

The FDA's Assessment:

The FDA notes that there were 467 patients who received trial treatment on RAD1901-308, not 466 patients as stated by the Applicant. Otherwise, the FDA agrees with the Applicant's description of duration of exposure and total dose. All patients enrolled to RAD1901-308 received the elacestrant tablet.

The FDA also assessed duration of exposure in the *ESR1*mut population relative to the overall population in Study RAD1901-308. Duration of exposure was similar in the *ESR1*mut population and in the overall safety population. In the *ESR1*mut population, the mean and median were as follows; 144 days and 84 days for elacestrant, 97 days and 65 days for AIs, and 122 days and 84 days for fulvestrant, respectively. In all patients, the mean and median were as follows; 160 days and 88 days for elacestrant, 97 and 65 days for AIs, and 125 days and 84 days for fulvestrant, respectively.

The FDA agrees with the Applicant's assessment that the size of the safety database is adequate to assess the safety of elacestrant.

Relevant characteristics of the safety population:

Data:

Table 43: Overview of Elacestrant Clinical Studies in Subjects with mBC

Study Number	Phase	Population	N	Primary Objective	Elacestrant Doses/Formulations	Status
RAD1901-308	3	Postmenopausal women and men with mBC	478 (471 female, 7 male; 239 elacestrant, 239 active comparators[a])	Efficacy (PFS in *ESR1*-mut subjects and PFS in all subjects [*ESR1*-mut + *ESR1*-mut-nd]) of elacestrant versus active comparators[a]	345 mg QD starting dose; tablet	Complete for PFS; Ongoing for OS (Data cutoff date: 06 September 2021)
RAD1901-005	1	Postmenopausal women with mBC	57 (33 capsule and 24 tablet)[b] received elacestrant; 50 received 345 mg dose of elacestrant	MTD and/or RP2D of elacestrant	200, 400, and 600 mg QD; capsule (Part A) 345 mg QD; capsule (Part B) 345 mg QD; tablet (Parts C and D)	Completed
RAD1901-106	1b	Postmenopausal women with mBC	16 (16 capsule and 2 tablet[c]) received elacestrant; 14 received 345 mg elacestrant	Effect of elacestrant on the availability of ER binding sites using FES-PET imaging	173 mg QD × 14 days, then escalated to 345 mg QD; or 345 mg QD; capsule and tablet	Completed

Abbreviations: ER = estrogen receptor; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut =with *ESR1* mutation; *ESR1*-mut-nd = no *ESR1* mutation detected (includes samples where *ESR1* mutation was not detected and where *ESR1* mutation status could not be determined); FES-PET = 16α-^{18}F-fluoro-17β-estradiol positron emission tomography; mBC = metastatic breast cancer; MTD = maximum tolerated dose; N = total number of subjects in group; OS = overall survival; PFS = progression-free survival; QD = once daily; RP2D = recommended Phase 2 dose.

[a] Active comparators include standard of care: fulvestrant, anastrozole, letrozole, and exemestane.

[b] Three subjects in Study RAD1901-005 received both capsules and tablets.

[c] Two subjects in Study RAD1901-106 received both capsules and tablets.

Source: Module 2.7.4, Table 2

The Applicant's Position:

Support for the safety of elacestrant in subjects in the proposed indication is primarily based on the 3 clinical studies conducted in subjects with mBC who received elacestrant 345 mg: the Phase 3 study (Study RAD1901-308) and 2 completed Phase 1 studies (Studies RAD1901-005 and RAD1901-106). These studies are summarized in Table 43 and the sections that follow; full details on each study are provided in the individual clinical study reports (CSRs).

As of 06 September 2021, a total of 570 subjects with mBC (543 postmenopausal females and 7 males) were exposed to study treatment (i.e., elacestrant or SOC) across these 3 elacestrant studies (elacestrant: 301 subjects and active comparator: 229 subjects). Of the 570 subjects, 466 subjects (237 elacestrant and 229 active comparator) are from Phase 3 Study RAD1901-308, 40 subjects are from the completed Phase 1 Study 005, and 24 subjects are from the completed Phase 1 Study 106.

The FDA's Assessment:

FDA disagrees with the Applicant's summary of patients with mBC exposed to elacestrant. In Study RAD1901-308, 467 patients were exposed to study treatment (237 elacestrant and 230 SOC). In Study RAD1901-005, 50 patients were exposed to elacestrant at the 345 mg dose (26 capsule, 24 tablet). In Study RAD1901-106, 14 patients were exposed to elacestrant at the 345 mg tablet dose. There were a total of 301 patients who received elacestrant 345 mg in the safety database.

Adequacy of the safety database:

Data:

Not applicable

The Applicant's Position:

The safety profile of elacestrant was characterized in subjects in the proposed indication based primarily on the 3 clinical studies conducted in subjects with mBC who received elacestrant 345 mg (Phase 3 Study: RAD1901-308; Phase1 Study RAD1901-005, Phase 1 Study RAD1901-006) outlined in Table 14. The collective data from these studies show that elacestrant offers a manageable safety profile in the intended patient population.

The FDA's Assessment:

The FDA's independent analysis of safety primarily relied on data from RAD1901-308, as previously stated. In some instances, FDA examined data from RAD1901-005 and RAD1901-106, as noted below. The FDA is unclear regarding the Applicant's definition of a "manageable safety profile." In FDA's review, important safety signals for elacestrant included nausea, vomiting, hypertriglyceridemia, and hypercholesterolemia. The FDA considers these safety risks to be manageable through labeling.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Not applicable

The Applicant's Position:

No meaningful concerns were observed in the quality and integrity of the submitted datasets and individual case narratives. These were sufficiently managed and complete for a thorough review of the safety of elacestrant.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of data quality and integrity for the safety analysis. Refer to Section 4.1 for more details.

Categorization of Adverse Event

Data:

Not applicable

The Applicant's Position:

This is addressed in Section 8.2.1.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Routine Clinical Tests

The Applicant's Position:

Not applicable

The FDA's Assessment:

The FDA performed an independent analysis of some clinical data collected on Study RAD1901-308 such as laboratory test results. Refer to Section 8.2.4 for more details.

8.2.4. Safety Results

Deaths

Data:

In Study RAD1901-308, TEAEs with an outcome of death were infrequent and were generally consistent across treatment groups, regardless of *ESR1* mutation status.

TEAEs of Grade 5 are summarized in Table 44 (all subjects), Table 45 (subjects with *ESR1*-mut) and Table 46 (subjects with *ESR1*-mut-nd). Overall, treatment-emergent Grade 5 AEs were reported in 4 subjects (1.7%) in the elacestrant group, 5 subjects on fulvestrant (3.1%), and

1 subject on AI (1.5%). The incidence of treatment-emergent Grade 5 AEs was too low to determine any pattern (ISS, Table 14.3.1.7).

None of the death cases were assessed as study drug related.

In the Phase 1 studies pool, there were 2 Grade 5 TEAEs, both of which were disease progression and were identified as AEs in error, as disease progression events should not have been captured as AEs per the protocol (Table 44). None of the deaths were assessed as related to treatment (ISS, Table 14.3.1.7).

Table 44: Treatment-emergent Adverse Events with an Outcome of Death (Safety Population)

System Organ Class Preferred Term[a]	Studies 005 and 106				Study 308			
	Elacestrant 345 mg Capsules (N = 40)	Elacestrant 345 mg Tablets (N = 24)	Elacestrant 345 mg Overall (N = 64)		Elacestrant 345 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 162)	AIs (N = 68)	SOC Total (N = 230)
Subjects with any TEAEs of CTCAE Grade 5	1 (2.5)	1 (4.2)	2 (3.1)		4 (1.7)	5 (3.1)	1 (1.5)	6 (2.6)
Blood and lymphatic system disorders	0	0	0		1 (0.4)	0	0	0
Antiphospholipid syndrome	0	0	0		1 (0.4)	0	0	0
Cardiac disorders	0	0	0		1 (0.4)	1 (0.6)	1 (1.5)	2 (0.9)
Cardiac arrest	0	0	0		1 (0.4)	0	0	0
Arrhythmia	0	0	0		0	0	1 (1.5)	1 (0.4)
Myocardial infarction	0	0	0		0	1 (0.6)	0	1 (0.4)
Infections and infestations	0	0	0		2 (0.8)	2 (1.2)	0	2 (0.9)
Diverticulitis	0	0	0		1 (0.4)	0	0	0
Septic shock	0	0	0		1 (0.4)	0	0	0
COVID-19	0	0	0		0	1 (0.6)	0	1 (0.4)
Pneumonia	0	0	0		0	1 (0.6)	0	1 (0.4)
Gastrointestinal disorders	0	0	0		0	1 (0.6)	0	1 (0.4)
Gastric perforation	0	0	0		0	1 (0.6)	0	1 (0.4)
General disorders and administration site conditions	1 (2.5)	1 (4.2)	2 (3.1)		0	0	0	0
Disease progression[b]	1 (2.5)	1 (4.2)	2 (3.1)		0	0	0	0
Nervous system disorders	0	0	0		0	1 (0.6)	0	1 (0.4)
Ischaemic stroke	0	0	0		0	1 (0.6)	0	1 (0.4)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Preferred terms are summarized using AE synonym terms.

[b] Identified as an AE in error, as disease progression should not be captured as an AE.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study RAD1901-308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study RAD1901-308 within each system organ class.

Sources: ISS, Table 14.3.1.6 and updated Table 14.3.1.2.5.2

Table 45: Treatment-emergent Adverse Events with an Outcome of Death (ESR1-mut Subjects in Study RAD1901-308 Safety Population)

System Organ Class Preferred Term	Elacestrant 345 mg Tablets (N = 115)	SOC		
		Fulvestrant (N = 79)	AIs (N = 27)	SOC Total (N = 106)
Any Grade 5 TEAE	3 (2.6)	1 (1.3)	0	1 (0.9)
Cardiac disorders	1 (0.9)	0	0	0
Cardiac arrest	1 (0.9)	0	0	0
Infections and infestations	2 (1.7)	1 (1.3)	0	1 (0.9)
Diverticulitis	1 (0.9)	0	0	0
Septic shock	1 (0.9)	0	0	0
COVID-19	0	1 (1.3)	0	1 (0.9)

Abbreviations: AI = aromatase inhibitor; COVID-19 = coronavirus disease 2019; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group. Preferred terms are sorted by descending order of frequency in the elacestrant group within each system organ class.

Source: Module 2.7.4, Table 25

Table 46: Treatment-emergent Adverse Events with an Outcome of Death (ESR1-mut-nd Subjects in Study RAD1901-308 Safety Population)

System Organ Class Preferred Term	Elacestrant 345 mg Tablets (N = 122)	SOC		
		Fulvestrant (N = 83)	AIs (N = 41)	SOC Total (N = 124)
Subjects with any Grade 5 TEAEs	1 (0.8)	4 (4.8)	1 (2.4)	5 (4.0)
Blood and lymphatic system disorders	1 (0.8)	0	0	0
Antiphospholipid syndrome	1 (0.8)	0	0	0
Cardiac disorders	0	1 (1.2)	1 (2.4)	2 (1.6)
Arrhythmia	0	0	1 (2.4)	1 (0.8)
Myocardial infarction	0	1 (1.2)	0	1 (0.8)
Gastrointestinal disorders	0	1 (1.2)	0	1 (0.8)
Gastric perforation	0	1 (1.2)	0	1 (0.8)
Infections and infestations	0	1 (1.2)	0	1 (0.8)
Pneumonia	0	1 (1.2)	0	1 (0.8)
Nervous system disorders	0	1 (1.2)	0	1 (0.8)
Ischaemic stroke	0	1 (1.2)	0	1 (0.8)

Abbreviations: AI = aromatase inhibitor; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group. Preferred terms are sorted by descending order of frequency in the elacestrant group within each system organ class.

Source: Updated Table 14.3.1.2.5.3

The Applicant's Position:

A review of TEAEs leading to death in all subjects, *ESR1*-mut, and *ESR1*-mut-nd revealed the overall incidence of AEs leading to death was low and similar between the treatment groups in Study RAD1901-308. None of the death cases were considered related to any of the study drugs.

Similar results were observed for the pooled Phase 1 studies with none of the death cases being related to study drug.

The FDA's Assessment:
FDA's independent analysis of deaths in the EMERALD (Study RAD 1901-308) trial is generally consistent with the data the Applicant presented with a few disagreements as noted below. The majority of deaths in both treatment arms were due to disease progression. The FDA reviewed all narratives provided by the Applicant. The FDA agrees with the Applicant that the overall frequencies of deaths were low and were similar between patients who received elacestrant and patients who received SOC.

Below is a summary of the narratives for the 4 deaths associated with TEAEs reported in patients who received elacestrant in Study RA1901-308.

1. Patient (b) (6) This 64-year-old female patient in the United States received her last dose of elacestrant on Day 27. Study drug was discontinued due to Grade 3 fatigue and Grade 2 nausea and thrombocytopenia. On Day 37, the patient experienced the SAEs of Grade 3 hyperbilirubinemia and cardiac arrest. The patient was found to have brain metastases, new liver metastases, and bone marrow infiltration of cancer. The patient became progressively lethargic and was put on comfort care on Day 45. She died on the same day due to Grade 5 cardiac arrest in the setting of disease progression. FDA agrees with the Applicant's assessment. Thrombocytopenia was likely due to bone marrow infiltration of tumor.

2. Patient (b) (6) This 72-year-old female patient in the United States experienced Grade 4 acute kidney injury on Day 16 and was hospitalized. Elacestrant was interrupted due to this AE. On Day 22, patient experienced the SAE of septic shock with hypotension, progressive anuric renal failure, and altered mental status. She also developed recurrent peritoneal effusions due to disease progression. On Day 26, the patient was transitioned to comfort care and died due to Grade 5 septic shock in the setting of an Enterococcus Faecalis septicemia. FDA agrees with the Applicant's assessment of this patient's cause of death.

3. Patient (b) (6) This 71-year-old female patient in Australia experienced Grade 5 diverticulitis. On Day 65, elacestrant was discontinued due to disease progression. On Day 81, patient started next line treatment with paclitaxel and bevacizumab. On Day 85, the patient experienced the SAE of diverticulitis in the setting of underlying diverticulum. On Day 87, a CT scan showed perforated sigmoid diverticulitis and treatment with paclitaxel and bevacizumab was stopped. On Day 113, the patient died of Grade 5 diverticulitis. FDA agrees with the Applicant's assessment of cause of death. Perforated sigmoid diverticulitis could be due to underlying diverticulosis and treatment with bevacizumab and paclitaxel.

4. Patient (b) (6) This 73-year-old female patient in France was initially felt to have

antiphospholipid antibody syndrome (APLS) on Day 449. Treatment with elacestrant was discontinued on this day. The patient developed altered mental status with a normal brain scan. Liver function tests and renal function declined. Liver, chest, and kidney scans were also unremarkable Initial information presented on this death did not support the diagnosis of APLS. FDA requested additional information for clarification on the cause of death. After further review of all available data, there was no support for APLS, and the cause of death was undetermined. There is insufficient information to determine if study treatment contributed to cause of death for this patient.

Below is a summary of deaths associated with TEAEs in patients who received SOC in Study RAD1901-308.

1. Patient (b) (6) This 54-year-old female patient on letrozole in the United States experienced Grade 5 arrhythmia resulting in respiratory arrest on Day 40. Resuscitation attempts were unsuccessful, and the patient died. The Applicant considered this death as unlikely to be related to study treatment. The FDA considers that there is insufficient information to determine if the study treatment contributed to death.

2. Patient (b) (6) This 78-year-old female patient on exemestane in the United States experienced Grade 2 abdominal pain on Day 72 that worsened to Grade 3 SAE on Day 83. The patient was hospitalized and ultimately discharged to home hospice. Test results from hospitalization were not available. Cause of death was undetermined, and the investigator and the Applicant assessed that the cause of the patient's abdominal pain was unrelated to study treatment and possibly due to progression of disease. The FDA considers that there is insufficient information to determine if the study treatment contributed to death and agrees that progression of disease could have contributed.

3. Patient (b) (6) This 67-year-old female patient on fulvestrant in Belgium experienced the SAE of Covid -19 on Day 14. On Day 49 patient died due to Grade 5 COVID-19. COVID-19 was felt to be unrelated to study drug. The FDA agrees with the Applicant's assessment.

4. Patient (b) (6) This 53-year-old female patient on fulvestrant in Hungary experienced the SAE of Grade 3 pulmonary embolism on Day 14. Per the Applicant, the patient presented with angina, fever, and chest pain. Imaging showed bilateral progression of miliary lung foci and atelectasis. Patient diagnosed with pulmonary embolism and was started on lovenox. Fulvestrant treatment was interrupted. On Day 16, the SAE of pulmonary embolism was considered resolved and fulvestrant was restarted. On Day 29, study treatment was discontinued due to disease progression. On Day 44, the patient experienced Grade 3 dyspnea. A CT scan was done but results were not reported. On Day 51, patient died due to disease progression. Based on available information, FDA's analysis questions the diagnosis of pulmonary embolism as imaging does not include this diagnosis. If patient did experience a pulmonary embolism, advanced cancer and progression of disease along with fulvestrant would be risk factors for thrombosis.

Fulvestrant has a small risk of venous thromboembolism and may have contributed to development of pulmonary embolism (Howell, 2004).

5. Patient (b) (6) This 68-year-old female on fulvestrant in Italy experienced a Grade 5 ischemic stroke on Day 54. Her history significant for a pulmonary embolism. Imaging confirmed an ischemic stroke on Day 55. Patient completed study treatment on the same day. She was started on enoxaparin for ischemic stroke. On Day 75, she died of ischemic stroke felt not be unrelated to study treatment. The FDA assesses that death was due to ischemic stroke due to hypercoagulability of malignancy and progression of disease (which was demonstrated on imaging). Fulvestrant also has a small risk of thromboembolism, however usually venous in nature.

6. Patient (b) (6) This 79-year-old female on fulvestrant in Italy experienced the SAE of pneumonia on Day 24 and was hospitalized. On Day 25, patient was transferred to another hospital and died from pneumonia. It was felt that pneumonia was not related to study treatment. The FDA agrees with this assessment.

7. Patient (b) (6) This 74-year-old female on fulvestrant in Argentina on Day 213 experienced the SAE of myocardial infarction. She died on Day 239 due to myocardial infarction. The Applicant did not believe that death was due to study treatment. The FDA considers that there is insufficient information to determine if the study treatment contributed to death

Serious Adverse Events

Data:

Serious TEAEs

In Study RAD1901-308, serious TEAEs (≥ 1% of subjects) are shown in Table 47(all subjects), Table 48(subjects with *ESR1*-mut), and Table 49(subjects with *ESR1*-mut-nd). None of the reported AEs had an incidence that was ≥ 2% in any of the treatment arms.

Among all subjects, only 3 had serious TEAEs that were considered related to elacestrant: 2 subjects with nausea and 1 subject with vomiting, acute cholecystitis, decreased appetite, dehydration, and pulmonary embolism (CSR RAD1901-308, Table 14.3.1.2.8.2). Two of these 3 subjects had *ESR1*-mut (CSR RAD1901-308, Table 14.3.1.2.8.2).

In the Phase 1 studies pool, serious TEAEs were reported in 23.4% of the subjects. Serious AEs reported in more than 1 subject included disease progression (although categorized as a serious TEAE, disease progression does not meet the serious TEAE requirements), syncope, dyspnea, and pulmonary embolism (3.1% each).

Table 47: Serious TEAEs in ≥ 1% of Subjects in Any Study Group (Safety Population)

System Organ Class Preferred Term	Studies 005 and 106				Study 308			
	Elacestrant 345 mg Capsules (N = 40)	Elacestrant 345 mg Tablets (N = 24)	Elacestrant 345 mg Overall (N = 64)		Elacestrant 345 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 162)	AIs (N = 68)	SOC Total (N = 230)
Subjects with any serious TEAEs	7 (17.5)	8 (33.3)	15 (23.4)		29 (12.2)	15 (9.3)	10 (14.7)	25 (10.9)
Gastrointestinal disorders	1 (2.5)	1 (4.2)	2 (3.1)		6 (2.5)	0	3 (4.4)	3 (1.3)
Nausea	0	0	0		3 (1.3)	0	0	0
Abdominal pain	0	0	0		0	0	2 (2.9)	2 (0.9)
Colitis	0	0	0		0	0	1 (1.5)	1 (0.4)
Diarrhoea	0	0	0		0	0	1 (1.5)	1 (0.4)
Enteritis	0	0	0		0	0	1 (1.5)	1 (0.4)
Ileus	0	0	0		0	0	1 (1.5)	1 (0.4)
Infections and infestations	1 (2.5)	3 (12.5)	4 (6.3)		3 (1.3)	5 (3.1)	4 (5.9)	9 (3.9)
Pneumonia	0	1 (4.2)	1 (1.6)		1 (0.4)	2 (1.2)	1 (1.5)	3 (1.3)
Sepsis	0	0	0		0	0	1 (1.5)	1 (0.4)
Urinary tract infection	0	0	0		0	0	2 (2.9)	2 (0.9)
Metabolism and nutrition disorders	1 (2.5)	1 (4.2)	2 (3.1)		4 (1.7)	0	1 (1.5)	1 (0.4)
Hypercalcaemia	0	0	0		1 (0.4)	0	1 (1.5)	1 (0.4)
Hypokalaemia	0	0	0		0	0	1 (1.5)	1 (0.4)
Musculoskeletal and connective tissue disorders	0	0	0		5 (2.1)	1 (0.6)	1 (1.5)	2 (0.9)
Pathological fracture	0	0	0		1 (0.4)	0	1 (1.5)	1 (0.4)
Cardiac disorders	0	0	0		1 (0.4)	2 (1.2)	1 (1.5)	3 (1.3)
Arrhythmia	0	0	0		0	0	1 (1.5)	1 (0.4)
General disorders and administration site conditions	1 (2.5)	2 (8.3)	3 (4.7)		4 (1.7)	1 (0.6)	1 (1.5)	2 (0.9)
Gait disturbance	0	0	0		0	0	1 (1.5)	1 (0.4)
Investigations	0	0	0		1 (0.4)	1 (0.6)	1 (1.5)	2 (0.9)
Neutrophil count decreased	0	0	0		0	0	1 (1.5)	1 (0.4)
Nervous system disorders	1 (2.5)	3 (12.5)	4 (6.3)		4 (1.7)	4 (2.5)	1 (1.5)	5 (2.2)
Cranial nerve paralysis	0	0	0		0	0	1 (1.5)	1 (0.4)
Dysarthria	0	0	0		0	0	1 (1.5)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0		0	0	2 (2.9)	2 (0.9)

System Organ Class Preferred Term	Studies 005 and 106				Study 308			
	Elacestrant 345 mg Capsules (N = 40)	Elacestrant 345 mg Tablets (N = 24)	Elacestrant 345 mg Overall (N = 64)		Elacestrant 345 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 162)	AIs (N = 68)	SOC Total (N = 230)
Malignant neoplasm of pleura	0	0	0		0	0	1 (1.5)	1 (0.4)
Tumor pain	0	0	0		0	0	1 (1.5)	1 (0.4)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Identified as an AE in error, as disease progression should not be captured as an AE.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study RAD1901-308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study RAD1901-308 within each system organ class.

Sources: ISS, Table 14.3.1.8 and Updated Table 14.3.1.2.7.2

Table 48: Serious TEAEs in ≥ 1% of Subjects in Any Group (ESR1-mut Subjects in Study 308 Safety Population)

System Organ Class Preferred Term	Elacestrant 345 mg Tablets (N = 115)	SOC		
		Fulvestrant (N = 79)	AIs (N = 27)	SOC Total (N = 106)
Any serious TEAE	14 (12.2)	7 (8.9)	5 (18.5)	12 (11.3)
Gastrointestinal disorders	3 (2.6)	0	3 (11.1)	3 (2.8)
Nausea	2 (1.7)	0	0	0
Vomiting	2 (1.7)	0	0	0
Abdominal pain	0	0	2 (7.4)	2 (1.9)
Colitis	0	0	1 (3.7)	1 (0.9)
Diarrhoea	0	0	1 (3.7)	1 (0.9)
Enteritis	0	0	1 (3.7)	1 (0.9)
Ileus	0	0	1 (3.7)	1 (0.9)
Infections and infestations	3 (2.6)	4 (5.1)	3 (11.1)	7 (6.6)
Diverticulitis	1 (0.9)	1 (1.3)	0	1 (0.9)
Pneumonia	1 (0.9)	1 (1.3)	0	1 (0.9)
COVID-19	0	1 (1.3)	0	1 (0.9)
Device related sepsis	0	1 (1.3)	0	1 (0.9)
Sepsis	0	0	1 (3.7)	1 (0.9)
Urinary tract infection	0	0	2 (7.4)	2 (1.9)
Investigations	1 (0.9)	1 (1.3)	1 (3.7)	2 (1.9)
Neutrophil count decreased	0	0	1 (3.7)	1 (0.9)
Platelet count decreased	0	1 (1.3)	0	1 (0.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (3.7)	1 (0.9)
Tumor pain	0	0	1 (3.7)	1 (0.9)
Nervous system disorders	1 (0.9)	2 (2.5)	0	2 (1.9)
Meningeal disorder	0	1 (1.3)	0	1 (0.9)
Seizure	0	1 (1.3)	0	1 (0.9)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; COVID-19 = coronavirus disease 2019; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut = with *ESR1* mutation; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group. Preferred terms are sorted by descending order of frequency in the elacestrant group within each system organ class.

Source: Module 2.7.4, Table 28

Table 49: Serious TEAEs in ≥ 1% of Subjects in Any Group (ESR1-mut-nd Subjects in Study RAD1901-308 Safety Population)

System Organ Class Preferred Term	Elacestrant 345 mg Tablets (N = 122)	SOC		
		Fulvestrant (N = 83)	AIs (N = 41)	SOC Total (N = 124)
Subjects with any serious TEAEs	15 (12.3)	8 (9.6)	5 (12.2)	13 (10.5)
Cardiac disorders	0	2 (2.4)	1 (2.4)	3 (2.4)
Angina pectoris	0	1 (1.2)	0	1 (0.8)
Arrhythmia	0	0	1 (2.4)	1 (0.8)
Myocardial infarction	0	1 (1.2)	0	1 (0.8)
General disorders and administration site conditions	2 (1.6)	1 (1.2)	1 (2.4)	2 (1.6)
Gait disturbance	0	0	1 (2.4)	1 (0.8)
General physical health deterioration	0	1 (1.2)	0	1 (0.8)
Infections and infestations	0	1 (1.2)	1 (2.4)	2 (1.6)
Pneumonia	0	1 (1.2)	1 (2.4)	2 (1.6)
Metabolism and nutrition disorders	3 (2.5)	0	1 (2.4)	1 (0.8)
Hypercalcaemia	1 (0.8)	0	1 (2.4)	1 (0.8)
Hypokalaemia	0	0	1 (2.4)	1 (0.8)
Musculoskeletal and connective tissue disorders	2 (1.6)	1 (1.2)	1 (2.4)	2 (1.6)
Back pain	2 (1.6)	0	0	0
Arthritis	0	1 (1.2)	0	1 (0.8)
Pathological fracture	0	0	1 (2.4)	1 (0.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1 (2.4)	1 (0.8)
Malignant neoplasm of pleura	0	0	1 (2.4)	1 (0.8)
Nervous system disorders	3 (2.5)	2 (2.4)	1 (2.4)	3 (2.4)
Spinal cord compression	2 (1.6)	0	0	0
Cerebrovascular accident	0	1 (1.2)	0	1 (0.8)
Cranial nerve paralysis	0	0	1 (2.4)	1 (0.8)
Dysarthria	0	0	1 (2.4)	1 (0.8)
Ischaemic stroke	0	1 (1.2)	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	3 (2.5)	1 (1.2)	0	1 (0.8)
Pulmonary embolism	0	1 (1.2)	0	1 (0.8)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; *ESR1* = estrogen receptor 1 gene; *ESR1*-mut-nd = *ESR1* mutation nondetected (includes samples where *ESR1* mutation was not detected and where *ESR1* mutation status could not be determined); MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group. Preferred terms are sorted by descending order of frequency in the elacestrant group within each system organ class.

Source: Updated Table 14.3.1.2.7.3

The Applicant's Position:

In Study RAD1901-308, none of the reported serious TEAEs had an incidence of ≥ 2% in any of the treatment arms. Among all subjects treatment group, only 3 subjects had a serious TEAE

that was considered related to elacestrant (2 subjects with nausea and 1 subject with vomiting, acute cholecystitis, decreased appetite, dehydration, and pulmonary embolism).

The FDA's Assessment:

The FDA conducted an independent review of SAEs and agrees with the frequencies of SAEs reported by the Applicant. Of note, The FDA considered all SAEs regardless of whether the Applicant considered them related to treatment as attribution of toxicities is challenging and subject to bias. The frequencies of SAEs were similar on both groups, occurring in 29 (12%) of patients who received elacestrant and 25 (11%) of patients who received SOC. SAEs with an incidence of ≥ 1% in patients who received elacestrant were musculoskeletal pain (1.7%) and nausea (1.3%). No SAEs of nausea occurred in patients who received SOC. The FDA also notes that the frequency of SAEs was similar in the *ESR1*-mut population compared to the overall population.

Dropouts and/or Discontinuations Due to Adverse Effects

Data

Not applicable

The Applicant's Position:

Study 308: The frequency of treatment discontinuation due to AEs was low in both treatment arms (elacestrant: 6.3%, fulvestrant: 3.7%, AIs: 5.9%). Individual TEAEs were comparable between the 2 treatment groups, with none reported in ≥ 2% of the subjects (Source: CSR RAD1901-308, Table 14.3.1.2.13.2).

A similar picture was observed in the *ESR1*-mut group (Source: CSR RAD1901-308, Table 14.3.1.2.13.1).

Pooled Phase 1 Studies Subjects: Treatment-emergent AEs leading to treatment discontinuation were experienced by 8 (12.5%) subjects, of which 7 subjects were in the 345 mg capsules group. Overall, in the Phase 1 studies pool, these TEAEs were driven by the gastrointestinal disorders system organ class, with nausea being the only PT reported in more than 1 subject.

The FDA's Assessment:

The FDA conducted an independent review of TEAEs leading to treatment discontinuation in Study RAD1901-308 and agrees with the frequencies reported by the Applicant. In patients who received elacestrant, the most common TEAEs (≥1%) leading to treatment discontinuation were musculoskeletal pain (1.7%) and nausea (1.3%). In the *ESR1*-mut subgroup, the frequencies of TEAEs leading to treatment discontinuation were similar to the overall population: 5% patients receiving elacestrant and 3.8% in patients receiving SOC. The FDA did not independently review the TEAEs leading to treatment discontinuation in the Phase 1 pool.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Not applicable

The Applicant's Position:

Dose Interruption

Study RAD1901-308: Among all subjects, nausea was reported as the reason for dose interruption in a small percentage (3.4%) of the elacestrant subjects as compared to 0.0% on fulvestrant and 2.9% on AIs. Decreased appetite was reported as the reason for dose interruption in 0.8% on elacestrant, 0.0% on fulvestrant, and 4.4% on AI. None of the other AEs leading to dose interruption were reported in ≥ 2% of the subjects in either one of the 2 treatment arms (ISS, Table 14.3.1.10 and Study RAD1901-308, Table 14.3.1.2.9.2).

A similar picture was observed in the *ESR1*-mut group (Study RAD1901-308, Table 14.3.1.2.9.1).

Treatment-related TEAEs leading to dose interruption are shown in Module 2.7.4, Table 33 (all subjects) and Study RAD1901-308, Table 14.3.1.2.10.1 (subjects with *ESR1*-mut).

Pooled Phase 1 Studies Subjects: Twenty subjects (31.3%) experienced TEAEs leading to dose interruption. These TEAEs occurred most often in the system organ class of gastrointestinal disorders, mainly nausea and vomiting (ISS, Table 14.3.1.10). No subject experienced a TEAE leading to dose reduction (ISS, Table 14.3.1.12).

Dose Reduction

Per the PI of AIs, no dose reduction was allowed. For fulvestrant, dose reduction is only allowed in case of liver impairment.

Study RAD1901-308: In the elacestrant group, the incidence of TEAEs leading to dose reduction was low (3.0%). Treatment-related TEAEs leading to dose reduction are shown in ISS, Table 14.3.1.13 and Study RAD1901-308, Table 14.3.1.2.12.2 (all subjects) and Table 14.3.1.2.12.1 (subjects with *ESR1*-mut).

Pooled Phase 1 Studies Subjects: No treatment-related TEAEs leading to dose reduction were reported in the Phase 1 studies.

The FDA's Assessment:

The FDA conducted an independent assessment of TEAEs requiring dosage interruption and TEAEs requiring dose reduction in Study RAD1901-308. TEAEs leading to dosage interruption were more frequent in patients receiving elacestrant vs SOC (15% vs 5.2). The most commonly occurring TEAEs (≥1%) requiring dosage interruption were nausea (3.4%), musculoskeletal pain (1.7%), and increased ALT (1.3%).

TEAEs leading to dose reductions only occurred in 3% of patients receiving elacestrant. No dose reductions were observed in patients receiving SOC. As noted by the Applicant, dose reduction

was only allowed for fulvestrant and only in the case of hepatic impairment. The most common TEAE (≥1%) leading to dose reduction of elacestrant was nausea (1.7%).

The frequencies of TEAEs leading to dosage interruptions and dose reductions were generally similar in the *ESR1*mut subgroup compared to all patients.

As stated previously, FDA considers all TEAEs leading to dosage interruptions or dose reductions regardless of attribution as attribution is subjective and prone to bias.

The FDA did not conduct an independent assessment of TEAEs leading to dosage interruptions or reductions in the Phase 1 pool.

Treatment-Emergent Adverse Events and Adverse Reactions

Data:

Overview of TEAEs

Exposure among *ESR1*-mut subjects was similar to that among all subjects.

There was a low incidence of Grade ≥ 3 events that were considered related to study therapy: 7.2% on elacestrant and 3.1% on SOC. Only 3 subjects on elacestrant and none on SOC had a serious AE that was considered related to trial therapy (Table 50).

The incidence of treatment-related TEAEs leading to dose interruption was also low: 6.3% and 1.7% on elacestrant and SOC, respectively, and the incidence of treatment-related TEAEs leading to dose reduction was only 2.5% on elacestrant and none on SOC (Table 50). Of note, as per the PI of AIs, no dose reduction is allowed, and dose reduction is only allowed for fulvestrant in case of hepatic impairment. Similarly, the incidence of treatment-related TEAEs leading to discontinuation of study drug was low in both arms: 3.4% and 0.9% on elacestrant and SOC, respectively.

Generally, the patterns of TEAE observed for all subjects were also observed in the *ESR1*-mut and *ESR1*-mut-nd subject groups individually.

Serious TEAEs were reported in 29 (12.2%) subjects in the elacestrant group and in 25 (10.9%) subjects in the SOC group, including 15 (9.3%) in the fulvestrant group and 10 (14.7%) in the AI group (Table 50). None of the reported AEs had an incidence of ≥ 2% in any of the treatment arms. Three subjects had related serious TEAEs in the elacestrant group: 2 subjects had nausea, and 1 subject had vomiting, acute cholecystitis, decreased appetite, dehydration, and pulmonary embolism.

Among all subjects, nausea was reported as the reason for dose interruption in 3.4% of the elacestrant subjects as compared to none on fulvestrant and 2.9% on AIs. Decreased appetite was reported as the reason for dose interruption in 0.8% on elacestrant and 4.4% on AI. None of the other TEAEs leading to dose interruption were reported in ≥ 2% of the subjects in either of the 2 treatment arms.

As per the PI of AIs, no dose reduction is allowed. For fulvestrant, dose reduction is only allowed in case of liver impairment. In the elacestrant group, TEAEs leading to dose reduction were reported for 7 subjects (3.0%) (Table 50).

A similar picture was observed in the *ESR1*-mut and the *ESR1*-mut-nd groups.

Adverse Drug Reactions

ADRs are defined as treatment-related TEAEs. Table 51 presents treatment-related TEAEs with an incidence of ≥ 5% in any group in descending order by the Study RAD1901-308 elacestrant group. For Study RAD1901-308, the PTs reported in ≥ 5% of subjects in the elacestrant group were nausea (25.3%), fatigue (11.0%), vomiting (11.0%), hot flush (9.7%), diarrhea (7.6%), decreased appetite (7.6%), and dyspepsia (5.9%).

None of the ADRs observed in Study RAD1901-308 and the Phase 1 pooled studies were elevated to the level of a contraindication in the proposed elacestrant labeling.

Table 50: Overview of TEAEs (Safety Population)

	Studies 005 and 106				Study RAD1901-308			
	Elacestrant 345 mg Capsules (N = 40)	Elacestrant 345 mg Tablets (N = 24)	Elacestrant 345 mg Overall (N = 64)		Elacestrant 345 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 162)	AIs (N = 68)	SOC Total (N = 230)
Number of subjects with at least 1 TEAE	39 (97.5)	22 (91.7)	61 (95.3)		218 (92.0)	145 (89.5)	53 (77.9)	198 (86.1)
Any treatment-related TEAEs	37 (92.5)	19 (79.2)	56 (87.5)		150 (63.3)	72 (44.4)	28 (41.2)	100 (43.5)
Any NCI CTCAE Grade 3 and Grade 4 TEAEs	15 (37.5)	10 (41.7)	25 (39.1)		64 (27.0)	34 (21.0)	14 (20.6)	48 (20.9)
Any treatment-related NCI CTCAE Grade 3 and Grade 4 TEAEs	8 (20.0)	1 (4.2)	9 (14.1)		17 (7.2)	5 (3.1)	2 (2.9)	7 (3.0)
Any fatal (Grade 5) TEAEs	1 (2.5)	1 (4.2)	2 (3.1)		4 (1.7)	5 (3.1)	1 (1.5)	6 (2.6)
Any treatment-related fatal (Grade 5) TEAEs	0	0	0		0	0	0	0
Any serious TEAEs	7 (17.5)	8 (33.3)	15 (23.4)		29 (12.2)	15 (9.3)	10 (14.7)	25 (10.9)
Any treatment-related serious TEAEs	1 (2.5)	1 (4.2)	2 (3.1)		3 (1.3)	0	0	0
Any TEAEs leading to dose interruption	12 (30.0)	8 (33.3)	20 (31.3)		36 (15.2)	5 (3.1)	7 (10.3)	12 (5.2)
Any treatment-related TEAEs leading to dose interruption	8 (20.0)	1 (4.2)	9 (14.1)		15 (6.3)	0	4 (5.9)	4 (1.7)

	Studies 005 and 106				Study RAD1901-308			
	Elacestrant 345 mg Capsules (N = 40)	Elacestrant 345 mg Tablets (N = 24)	Elacestrant 345 mg Overall (N = 64)		Elacestrant 345 mg Tablets (N = 237)	SOC		
						Fulvestrant (N = 162)	AIs (N = 68)	SOC Total (N = 230)
Any TEAEs leading to dose reduction	0	0	0		7 (3.0)	0	NA	0
Any treatment-related TEAEs leading to dose reduction	0	0	0		6 (2.5)	0	NA	0
Any TEAEs leading to discontinuation of study drug	7 (17.5)	1 (4.2)	8 (12.5)		15 (6.3)	6 (3.7)	4 (5.9)	10 (4.3)
Any treatment-related TEAEs leading to discontinuation of study drug	6 (15.0)	0	6 (9.4)		8 (3.4)	1 (0.6)	1 (1.5)	2 (0.9)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; NA = not applicable; NCI = National Cancer Institute; SOC = standard of care; TEAE = treatment-emergent adverse event.

Note: MedDRA Version 23.0 was used; NCI CTCAE Version 4.3 was used for Studies 005 and 106, and NCI CTCAE Version 5.0 was used for Study RAD1901-308. If a subject experienced more than 1 event in a given category, that subject was counted only once in that category. A TEAE was considered treatment-related if its causality was "possibly related," "definitely related," or "related" on the AE eCRF pages from each study.

Source: ISS, Table 14.3.1.1.1 and Updated Table 14.3.1.1.2

Table 51: Treatment-related TAEs in ≥ 5% of Subjects in Any Study Group (Safety Population)

System Organ Class Preferred Term[a]	**Studies 005 and 106**			**Study RAD1901-308**	
	Elacestrant 400 mg Capsules (N = 40)	**Elacestrant 400 mg Tablets (N = 24)**	**Elacestrant 400 mg Overall (N = 64)**	**Elacestrant 400 mg Tablets (N = 237)**	**SOC (N = 230)**
Subjects with any treatment-related TEAEs	37 (92.5)	19 (79.2)	56 (87.5)	150 (63.3)	100 (43.5)
Gastrointestinal disorders	**35 (87.5)**	**11 (45.8)**	**46 (71.9)**	**102 (43.0)**	**29 (12.6)**
Nausea	23 (57.5)	7 (29.2)	30 (46.9)	60 (25.3)	20 (8.7)
Vomiting	14 (35.0)	2 (8.3)	16 (25.0)	26 (11.0)	6 (2.6)
Diarrhoea	6 (15.0)	0	6 (9.4)	18 (7.6)	8 (3.5)
Dyspepsia	17 (42.5)	4 (16.7)	21 (32.8)	14 (5.9)	2 (0.9)
Abdominal pain	2 (5.0)	0 (0.0)	2 (3.1)	4 (1.7)	4 (1.7)
General disorders and administration site conditions	**8 (20.0)**	**2 (8.3)**	**10 (15.6)**	**43 (18.1)**	**42 (18.3)**

Fatigue	7 (17.5)	1 (4.2)	8 (12.5)		26 (11.0)	18 (7.8)
Injection site pain	0	0	0		0	13 (5.7)
Vascular disorders	**6 (15.0)**	**3 (12.5)**	**9 (14.1)**		**23 (9.7)**	**14 (6.1)**
Hot flush	5 (12.5)	3 (12.5)	8 (12.5)		23 (9.7)	14 (6.1)
Metabolism and nutrition disorders	**4 (10.0)**	**2 (8.3)**	**6 (9.4)**		**19 (8.0)**	**7 (3.0)**
Decreased appetite	4 (10.0)	2 (8.3)	6 (9.4)		18 (7.6)	7 (3.0)
Nervous system disorders	**7 (17.5)**	**3 (12.5)**	**10 (15.6)**		**17 (7.2)**	**15 (6.5)**
Headache	3 (7.5)	2 (8.3)	5 (7.8)		10 (4.2)	10 (4.3)
Musculoskeletal disorders and connective tissue	**2 (5.0)**	**2 (8.3)**	**4 (6.3)**		**18 (7.6)**	**41 (17.8)**
Myalgia	0	2 (8.3)	2 (3.1)		2 (0.8)	12 (5.2)

Abbreviations: AE = adverse event; AI = aromatase inhibitor; eCRF = electronic case report form; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in group; SOC = standard of care; TEAE = treatment-emergent adverse event.

[a] Preferred terms are summarized using AE synonym terms.

Note: MedDRA Version 23.0 was used. Subjects with 1 or more AEs within a system organ class of MedDRA were counted only once. A TEAE is considered treatment related if its causality was "possibly related," "definitely related," or "related" on the AE eCRF pages from each study. System organ classes are sorted by descending order of frequency of preferred terms in the elacestrant group in Study 308. Preferred terms are sorted by descending order of frequency in the elacestrant group in Study 308 within each system organ class.

Sources: ISS, Table 14.3.1.3 and Updated Table 14.3.1.2.2.2.

The Applicant's Position:

Safety and tolerability were assessed by TEAEs (including serious TEAEs, treatment-related TEAEs, outcome of TEAEs, and TEAEs by grade), clinical laboratory data, ECGs, ECOG PS, and vital signs. There were no new or unexpected safety observations in this study.

AEs in both treatment arms were mainly Grades 1 and 2 and could be managed by routine safety monitoring and dose modifications. The incidence of Grades 3 was low in both treatment arms and no grade 4 AEs were reported in the Phase 3 Study. None of the TEAEs, irrespective of relationship to treatment, had an incidence of Grades 3 that exceeded 5%. In addition, the incidence of Grades 3 AEs that were considered related to study drug was very low in both treatment arms.

Although the incidence of nausea (all grades, irrespective of relationship to study drug) was higher in the elacestrant arm (35.0%), it was reported in 25.0% of subjects receiving an AI and to a lesser extent in subjects receiving IM fulvestrant (16.1%). The incidence of treatment-related nausea (all grades) was 25.3% in the elacestrant arm, 8.7% among subjects receiving fulvestrant, and 8.8% among subjects receiving an AI. The incidence of Grades 3 or 4, however, was low in both treatment arms (2.5%, 0%, and 2.9% on elacestrant, fulvestrant, and AIs, respectively).

On the other hand, the incidence of arthralgia and fatigue was numerically higher among subjects in the fulvestrant arm (17.4% and 21.7%, respectively) relative to subjects who received elacestrant (14.3% and 19.0%, respectively) and those who received an AI (13.2% and

11.8%, respectively). Injection site pain was reported by 8.7% of the subjects receiving fulvestrant.

No AEs of bradycardia/sinus bradycardia or QTc prolongation were reported in the elacestrant arm, both of which are common AEs observed in trials of other novel antiestrogen drugs. QTcF measurements showed that none of the subjects had a QTcF prolongation of ≥ 60 ms, relative to baseline.

None of the AEs that had a fatal outcome (4 on elacestrant and 5 on fulvestrant) were considered related to study drug.

Only 3 subjects had a serious TEAE that was considered related to elacestrant, and the incidence of AEs leading to treatment discontinuation was low in both treatment arms (6.3% on elacestrant and 4.4% on the SOC arm).

The safety profile in subjects with *ESR1*-mut and in subjects with *ESR1*-mut-nd was consistent with the safety profile in all subjects.

Overall, the safety of elacestrant in the Phase 1 studies was consistent with the safety observed in the Phase 3 study.

In conclusion, based on available data in the target patient population, elacestrant has a manageable safety profile and its safety is comparable to the safety of current SOC hormonal monotherapy.

The FDA's Assessment

The FDA conducted an independent analysis of TEAEs in Study RAD1901-308. The FDA agrees with the Applicant that the safety profiles for patients in the *ESR1-mut* and *ESR1-nd* populations were similar to the safety profile for all patients in Study RAD1901-308. The FDA also agrees with the frequencies of all-grade TEAEs, grade 3-4 TEAEs, SAEs, TEAEs leading to death, and TEAEs leading to dosage interruption, dose reduction, and drug discontinuation presented in the Applicant's Overview of TEAEs table. The FDA disagrees with the Applicant's focus on treatment-related TEAEs and the inclusion of treatment-related TEAEs in Table 50 and Table 51. As previously stated, the FDA considered all TEAEs which occurred in Study RAD1901-308 during the review as attribution of TEAEs is subjective and prone to bias. The FDA's analysis of all-grade and grade 3-4 TEAEs is shown in Table 52 below and this information is also included in Section 6 of the elacestrant USPI.

The FDA considers some of the information presented by the Applicant in this section to be redundant with other sections of the Assessment Aid. For the FDA's assessment of exposure, deaths, SAEs, dosage modifications, and ECG/QTc findings, please refer to those specific subsections (clearly marked with headings) throughout Section 8.2.4. The FDA will focus only on all-grade TEAEs and grade 3-4 TEAEs in this subsection.

The FDA disagrees with the Applicant's assessment that "there were no new or unexpected safety observations in this study." Elacestrant is an NME, and this is the first assessment of this drug's safety database. All safety findings are new.

The FDA agrees with the Applicant that no Grade 4 TEAEs occurred in Study RAD1901-308. The FDA disagrees with the Applicant's statements regarding Grade 3 TEAEs. Grade 3 TEAEs

occurred in >20% of patients in Study RAD1901-308, with a higher frequency in patients who received elacestrant vs. SOC: 27% vs. 21%. The difference in frequencies of Grade 3 TEAEs is due to a higher frequency of Grade 3 musculoskeletal pain in patients who received elacestrant compared to SOC. After further investigation, the FDA concluded that there was no clear evidence to suggest that exposure to elacestrant predisposed patients to Grade 3 musculoskeletal events. Refer to the subsection on Analysis of Submission-Specific Safety Issues for more details.

The FDA agrees with the Applicant that the frequency of all-grade nausea was higher in patients who received elacestrant compared to SOC: 35% vs. 19%. The frequencies of other GI TEAEs were also higher in patients who received elacestrant compared to SOC: vomiting – 19% vs. 9%, decreased appetite – 15% vs. 10%, and dyspepsia – 10% vs. 2.6%. Furthermore, the use of serotonin (5HT3) antagonists (e.g., ondansetron) was higher in patients receiving elacestrant compared to SOC: 18% vs. 10%. Although the frequencies of Grade 3 nausea and other GI TEAEs were low, the FDA notes that even Grade 1-2 GI toxicity, e.g., nausea, can be quite bothersome to patients. There was a >10% higher incidence of nausea and vomiting in patients who received elacestrant vs. SOC which is notable.

The FDA disagrees with the Applicant's assessment of fatigue. The FDA considers the terms "fatigue" and "asthenia" to both indicate fatigue. When grouping these terms together, the FDA concluded that the frequency of fatigue was similar in patients who received elacestrant compared to SOC: 26% vs. 27%.

The FDA considered "arthralgia" as one term indicative of musculoskeletal pain. After grouping together all terms indicative of musculoskeletal pain, the FDA found a similarly frequency of musculoskeletal pain in patients who received elacestrant compared to SOC: 41% vs. 39%.

The FDA agrees with the Applicant's description of injection site pain in patients who received fulvestrant and also notes that no patients who received elacestrant experienced injection site pain.

The FDA did not consider information from the Phase 1 pool as part of the assessment of all-grade and grade 3-4 TEAEs. However, the FDA notes that GI toxicity, particularly nausea and dyspepsia, occurred in higher frequencies of patients who received the capsule formulation of elacestrant. All patients who received elacestrant in Study RAD1901-308 received the tablet formulation.

Table 52: Adverse Reactions (>10%) in Patients with ER-positive, HER2-negative, Advanced or Metastatic Breast Cancer Who Received ORSERDU in EMERALD

Adverse Reaction†	ORSERDU (n=237)		Fulvestrant or an Aromatase Inhibitor (n=(b) (4))	
	All Grades (%)	Grade 3 or 4 c (%)	All Grades (%)	Grade 3 or 4 c (%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[b]	41	7	39	1

Gastrointestinal disorders				
Nausea	35	2.5	19	0.9
Vomiting[b]	19	0.8	9	0
Diarrhea	13	0	10	1
Constipation	12	0	6	0
Abdominal pain[b]	11	1	10	0.9
Dyspepsia	10	0	2.6	0
General disorders				
Fatigue[b]	26	2	27	1
Metabolism and nutrition disorders				
Decreased appetite	15	0.8	10	0.4
Nervous system				
Headache	12	2	12	0
Vascular disorders				
Hot flush	11	0	8	0

[a] Adverse reactions were graded using NCI CTCAE version 5.0.
[b] Includes other related terms
[c] Only includes Grade 3 adverse reactions.

Laboratory Findings

Data:

No significant or clinically meaningful changes in clinical laboratory evaluations were observed in subjects treated with elacestrant, regardless of *ESR1* mutation status. Clinical laboratory evaluations in the Phase 1 studies pool were generally consistent with those in Study 308.

Study RAD1901-308: No significant or clinically meaningful changes in clinical laboratory evaluations were observed in subjects treated with elacestrant in Study RAD1901-308.

Shifts from NCI CTCAE Grades 0, 1, or 2 at baseline to any incidence of Grades 3 or 4 on treatment were infrequent, occurring in 7 subjects or less in any group for hematology variables, 5 subjects or less in any group for chemistry variables, and 2 subjects or less in any group for coagulation variables.

High cholesterol, creatinine, and triglycerides and low bicarbonate were more common in the elacestrant group, and high alanine aminotransferase (ALT), AST, alkaline phosphatase (ALP), and bilirubin were more common in the SOC group. Grades 3 or 4 abnormalities were rare in both groups (Table 53). The only Grade 3 laboratory abnormality reported in ≥ 5% of subjects in any group was low lymphocytes (6.3% for elacestrant subjects and 3.9% for SOC subjects). No Grade 4 laboratory abnormalities were reported in ≥ 5% of subjects in any group.

Markers of liver dysfunction were generally similar between the treatment groups; however, more subjects in the SOC group had elevations in ALP than in the elacestrant group (18.6% in the fulvestrant group, 25.0% in the AI group, versus 10.5% subjects, respectively).

The pattern of laboratory abnormalities in subjects with *ESR1*-mut was similar to that observed in all subjects.

Pooled Phase 1 Studies Subjects: In the Phase 1 studies pool, no significant or clinically meaningful changes were observed from baseline over time in any laboratory variable. Shifts from NCI CTCAE Grades 0, 1, or 2 at baseline to any incidence of Grades 3 or 4 on treatment were infrequent.

Table 53: Select Laboratory Abnormalities that worsened from baseline in patients with ER-positive, HER2-negative Advanced or Metastatic Breast Cancer who received Elacestrant in EMERALD (ITT population N=478)

	ORSERDU[1]		SOC[1]	
Laboratory Abnormality	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Eosinophils (10/L)	10 (4.9)	0	15 (8.2)	0
Eosinophils/Leukocytes (%)	3 (10.3)	0	10 (27.0)	0
Hemoglobin (g/L)	63 (26.7)	3 (1.3)	46 (20.5)	4 (1.8)
Leukocytes (10/L)	32 (13.6)	0	33 (14.7)	1 (0.4)
Lymphocytes (10/L)	49 (23.8)	7 (3.4)	34 (18.7)	1 (0.5)
Neutrophils, Segmented (10/L)	14 (6.8)	1 (0.5)	16 (8.7)	1 (0.5)
Platelets (10/L)	18 (7.6)	0	27 (12.1)	3 (1.3)
Chemistry				
Alanine Aminotransferase (U/L)	39 (16.5)	1 (0.4)	54 (24.2)	3 (1.3)
Albumin (g/L)	27 (11.5)	0	23 (10.3)	1 (0.4)
Alkaline Phosphatase (U/L)	39 (16.5)	0	58 (25.9)	3 (1.3)
Aspartate Aminotransferase (U/L)	67 (28.5)	1 (0.4)	77 (34.4)	3 (1.3)
Bicarbonate (mmol/L)	40 (18.1)	0	24 (11.6)	0
Bilirubin (umol/L)	7 (3.0)	0	22 (9.9)	1 (0.4)
Calcium (mmol/L)	45 (19.1)	0	38 (17.0)	0
Cholesterol (mmol/L)	70 (30.6)	2 (0.9)	34 (16.7)	0
Creatinine (umol/L)	37 (15.7)	1 (0.4)	13 (5.8)	0
Magnesium (mmol/L)	27 (11.5)	0	25 (11.4)	0
Potassium (mmol/L)	28 (11.9)	2 (0.9)	23 (10.3)	2 (0.9)
Sodium (mmol/L)	40 (16.9)	2 (0.8)	39 (17.4)	0
Triglycerides (mmol/L)	61 (26.8)	5 (2.2)	31 (15.1)	1 (0.5)
Coagulation				
Activated Partial Thromboplastin Time (sec)	8 (3.9)	0	13 (6.9)	1 (0.5)
Prothrombin Intl. Normalized Ratio (RATIO)	9 (3.8)	1 (0.4)	14 (6.4)	2 (0.9)

	ORSERDU[1]		SOC[1]	
Laboratory Abnormality	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)

[1] The denominator used to calculate the rate varied from 29 to 236 for Elacestrant and from 37 to 225 for SOC based on the number of patients with a baseline value and at least one post-treatment value.
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Database cut-off date: 06SEP2021, Database extraction date: 07OCT2021. Source: Table 3 Worsening Lab ITT (478_Clean) Page 1 of 1

The Applicant's Position:

No significant or clinically meaningful changes in clinical laboratory evaluations were observed in subjects treated with elacestrant, regardless of *ESR1* mutation status. Clinical laboratory evaluations in the Phase 1 studies pool were generally consistent with those in Study RAD1901-308.

The FDA's Assessment:

The FDA conducted an independent analysis of laboratory abnormalities in Study RAD1901-308 based on laboratory values that worsened from baseline and disagrees with the Applicant's description of laboratory data. The Applicant's laboratory table does not include directionality for the laboratory abnormalities (increased or decreased) and so it is not possible to interpret the information. The FDA includes results from our laboratory analysis in Table 54 below which is also included in the Section 6 of the elacestrant USPI. The FDA disagrees with the Applicant that no clinically meaningful changes in laboratory evaluations occurred. Patients who received elacestrant had higher frequencies of serum cholesterol elevation and serum triglyceride elevation relative to patients who received SOC. For additional information on dyslipidemia, refer to section on Analysis of Submission-Specific Safety Issues.

Table 54: Select Laboratory Abnormalities (>10%) That Worsened from Baseline in Patients with ER-positive, HER2-negative, Advanced or Metastatic Breast Cancer Who Received Elacestrant

Laboratory Abnormality	ORSERDU[a]		Fulvestrant or an Aromatase Inhibitor[a]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Cholesterol increased	30	1	17	0
Aspartate aminotransferase increased	29	0	34	1
Triglycerides increased	27	2	15	1
Alanine aminotransferase increased	17	0	24	1
Sodium decreased	16	1	15	0
Creatinine increased	16	0	6	0
Hematology				
Hemoglobin decreased	26	1	20	2

[a] The denominator used to calculate the rate varied from 29 to 236 for ORSERDU and from 37 to 225 for fulvestrant or an aromatase inhibitor based on the number of patients with a baseline value and at least one post-treatment value.

Vital Signs

The Applicant's Position:

In Study RAD1901-308, no significant or clinically meaningful changes in vital signs were observed in subjects treated with elacestrant, regardless of *ESR1* mutation status. Vital signs in the Phase 1 studies pool were generally consistent with those in Study RAD1901-308.

All Phase 3 Study Subjects

No significant or clinically meaningful changes in vital signs were observed in subjects treated with elacestrant in Study RAD1901-308.

In Study RAD1901-308, no trends over time or differences between groups were observed in vital signs or blood pressure. No meaningful difference in abnormal vital signs was observed between the elacestrant and SOC groups.

No trends over time or differences between groups for either all subjects or the *ESR1*-mut subgroup were observed for vital signs and blood pressure.

Pooled Phase 1 Study Subjects

Among pooled Phase 1 studies subjects, no significant or clinically meaningful changes in vital signs or blood pressure from baseline were observed in subjects.

The FDA's Assessment:

The FDA did not conduct an independent analysis of vital sign data collected on Study RAD1901-308 as FDA believes that any clinically significant changes would be captured as TEAEs. The FDA did not consider vital sign data from the Phase 1 pool.

Electrocardiograms (ECGs)

The Applicant's Position:

In Study RAD1901-308, no significant or clinically meaningful changes in ECG parameters were observed in subjects treated with elacestrant, regardless of *ESR1* mutation status. Electrocardiogram parameters in the Phase 1 studies pool were generally consistent with those in Study RAD1901-308.

Phase 3 Study

No significant or clinically meaningful changes in ECG parameters were observed in subjects treated with elacestrant in Study RAD1901-308. Notably, there were no significant shifts in QTcF during treatment with elacestrant.

In Study RAD1901-308, no subject had a change from baseline in QTcF that was > 60 ms. No trends over time or meaningful differences between groups were observed.

No TEAEs of bradycardia/sinus bradycardia or QTc prolongation were observed in the elacestrant group, both of which are common AEs observed in trials of other oral novel antiestrogens currently under development.

Similar results were observed for *ESR1*-mut subjects. No trends over time or differences between groups for the *ESR1*-mut subgroup were observed.

Pooled Phase 1 Studies Subjects

No significant or clinically meaningful changes in ECG parameters were observed in subjects treated with elacestrant in the Phase 1 studies pool. Notably, there were no significant shifts in QTcF during treatment with elacestrant.

In the Phase 1 studies pool, 13 (20.3%) subjects had a QTcF value > 450 ms. Twenty-one (32.8%) subjects had a change from baseline in QTcF of > 30 ms, and 2 (3.1%) subjects had a change of baseline in QTcF of > 60 ms. One subject (1.6%) had a worst postbaseline value of

> 500 ms QTc, and 2 (3.2%) subjects had a worst postbaseline ≥ 480 to ≤ 500 ms. No trends over time or meaningful differences between groups were observed.

The FDA's Assessment:

The FDA agrees with the Applicant's statements that there were no notable changes in ECG parameters in patients receiving elacestrant. In the elacestrant group, there was one patient with a cardiac arrest (in the setting of disease progression) and this patient did not have significant QTc prolongation. Please refer to Section 6.2.1 for more details regarding FDA's assessment QTC including E-R analysis with respect to QTc. The FDA agrees that there were no TEAEs of bradycardia recorded in patients receiving elacestrant in Study RAD1901-308. There was one TEAE of sinus bradycardia recorded in a patient receiving SOC.

QT

The Applicant's Position:

Refer to the ECG section above.

The FDA's Assessment:

Refer to the ECG section above.

Immunogenicity

The Applicant's Position:

Not applicable as immunogenicity was not assessed nor expected with elacestrant treatment.

The FDA's Assessment:

Not applicable

Analysis of Submission-Specific Safety Issues

The Applicant's Position:

There were no prespecified AEs of special interest in the ISS or Study RAD1901-308.

Safety assessment did not reveal any potential signal after database lock.

The FDA's Assessment:

Although the Applicant did not designate any prespecified AEs of special interest, the FDA conducted an independent safety analysis focused on two safety signals: dyslipidemia (hypercholesterolemia and hypertriglyceridemia) and severe musculoskeletal pain.

Dyslipidemia - Hypercholesterolemia and hypertriglyceridemia

Dyslipidemia has been reported in association with other endocrine therapies to treat breast cancer, including both aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs). The mechanism is thought to be due to dysregulation of lipid metabolism (Bhatnagar, 2022). AIs are associated predominantly with dyslipidemia, and SERMs are predominantly associated with hepatic steatosis and elevated triglycerides (Okwuosa, 2021). The USPI for

letrozole (FEMARA) reports hypercholesterolemia in 52% of patients receiving letrozole and 29% of patients receiving tamoxifen in the BIG 1-98 trial. The USPI for tamoxifen (SOLTAMOX) lists elevated serum triglycerides, sometimes associated with pancreatitis, under Postmarketing Experience.

In RAD1901-308, hypercholesterolemia and hypertriglyceridemia occurred in patients taking elacestrant at an incidence of 30% and 27%, respectively. The incidence of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia were 0.9% and 2.2%, respectively. One patient who received elacestrant had Grade 4 hypertriglyceridemia but did not have any further sequelae (e.g., pancreatitis). In the SOC arm, hypercholesterolemia and hypertriglyceridemia occurred at an incidence of 17% and 15%, respectively. The incidence of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia were 0% and 0.5%.

Hypercholesterolemia and hypertriglyceridemia were observed in at least one earlier trial of elacestrant. In RAD1901-005, the incidences of hypercholesterolemia and hypertriglyceridemia were 14% and 24%, respectively (as reported in the CSR). These values were reported based on collection of TEAEs, not laboratory data, which may result in underreporting. The incidences of Grade 3 and 4 hypercholesterolemia and hypertriglyceridemia based on laboratory data were 11% and 3.6%, respectively. In RAD1901-106, summarized information regarding hypercholesterolemia and hypertriglyceridemia based on either TEAEs or laboratory data is not included in the CSR and it is not clear if these toxicities occurred.

The FDA included dyslipidemia in labeling as a Warning given its frequency in patients who received elacestrant (~30%), potential association with cardiovascular disease, and the need for increased monitoring as well as possible treatment with medications or adjustments to existing medications. Prescribers are recommended to monitor the lipid panel in patients at baseline and periodically throughout treatment with elacestrant.

Musculoskeletal Pain

The FDA conducted an independent analysis of Grade ≥ 3 musculoskeletal pain (limits activities of daily living). Although the frequencies of all-grade musculoskeletal pain were similar in patients who received elacestrant and SOC: 41% vs. 39%, there was a higher frequency of grade 3 events in patients who received elacestrant versus SOC. (In CTCAE v5.0, the maximum grade for musculoskeletal pain TEAEs is Grade 3.) In patients who received elacestrant compared to SOC, 7% vs. 0.9% experienced Grade 3 musculoskeletal pain. The frequencies of Grade 3 musculoskeletal pain were similar in patients in the *ESR1*mut group who received elacestrant and SOC. The FDA reviewed narratives for all patients with Grade 3 musculoskeletal pain which included 16 patients who received elacestrant and 2 patients who received SOC treatment (summarized below). Due to several instances where grade 3 musculoskeletal pain was associated with fracture, the FDA also assessed fracture events in patients who received elacestrant vs. SOC. The frequencies were similarly low on both arms: 1.3% vs. 2.2%.

Ultimately, the FDA did not find clear evidence to suggest that exposure to elacestrant predisposed patients to Grade 3 musculoskeletal events. Most patients who developed Grade 3 events had pre-existing musculoskeletal pain, many of the events occurred at the time of disease progression, and several events occurred after elacestrant had been discontinued. In addition, assessment of the events was confounded because elacestrant was rarely interrupted and most patients received concomitant pain medication. In nearly all cases, it was not possible to assess whether the toxicity stopped/recurred following dechallenge/rechallenge with elacestrant. Furthermore, the term "musculoskeletal pain" encompasses a broad range of toxicities including bone pain, leg pain, shoulder pain, back pain, etc. which may have differing causes and differing pathophysiology. Finally, the frequency of all-grade musculoskeletal pain was similar in patients who received elacestrant vs. SOC.

Narratives for Patients with Grade 3 Musculoskeletal Pain

Patient ID (b) (6) (elacestrant)

This 63-year-old female patient initially experienced Grade 2 pain in right extremity and Grade 2 arthralgia on Day 476. On Day 567, the patient was not able to walk due to this leg pain and was started on a fentanyl patch for pain control. On Day 574, the patient was hospitalized due to worsening pain to Grade 3. The patient had a known history of intervertebral disc protrusion, rheumatoid arthritis, and bone pain. Treatment with elacestrant was interrupted on the day of hospitalization. Hip and femur x-ray showed no fractures. On Day 578, study treatment was discontinued due to disease progression. On Day 582, the patient was discharged from the hospital and on Day 595, the SAE of right extremity pain was considered resolved. The nonserious AE of arthralgia was not yet resolved. In the FDA's assessment, the patient had underlying medical conditions that could have contributed to her musculoskeletal pain and the role of elacestrant is unclear.

Patient ID (b) (6) (elacestrant)

This 24-year-old female patient experienced Grade 3 back pain and Grade 3 dyspnea on Day 104. Elacestrant was discontinued on Day 103 due to disease progression. Along with back pain, the patient also presented with chest pain with muscle spasms in the back. Chest CT and other diagnostic results were not reported. The patient was treated with methocarbamol and oxycodone for back pain. No treatment was reported for dyspnea. On Day 105, back pain and dyspnea were resolved. FDA agrees that this patient's back pain was unlikely related to study treatment with elacestrant as back pain started after study treatment was discontinued.

Patient ID (b) (6) (elacestrant)

This 57-year-old female patient experienced Grade 3 bone pain on Day 110. She was hospitalized on the same day with hypercalcemia of 14.6 mg/dL along with Grade 2 abdominal pain, Grade 2 chills, Grade 2 muscular weakness, Grade 3 hypertension, Grade 2 nausea and vomiting. The patient was treated with oxycodone for bone pain. Chills and hypertension

resolved within the day. Patient received treatment for hypercalcemia. Elacestrant was interrupted due to the SAE of hypercalcemia on Day 113. On Day 114, bone scan showed increase in bone metastases. At the time of report, bone pain had not yet resolved. The FDA analysis agrees that this patient's bone pain was likely due to progression of bone metastases and unlikely related to study treatment with elacestrant.

Patient ID (b) (6) (elacestrant)

This 28-year-old female in Argentina experienced Grade 3 bone pain on Day 175 and was hospitalized. The patient has a history of bone pain and her existing bilateral hip pain worsened and was no longer responding to usual pain regimen. Results of diagnostic evaluation of this hip pain were not provided. The patient was treated with morphine. Elacestrant treatment was interrupted due to this event. On Day 176, study treatment was discontinued due to disease progression. On Day 177, and MRI of both hips and femoral bones showed "comminuted bilateral femoral bone." On Day 178, bone pain resolved and patient was discharged from the hospital. The FDA agrees that this patient's bone pain was unlikely related to elacestrant given disease progression with femoral bone fracture.

Patient ID (b) (6) (elacestrant)

This 82-year-old female patient with metastatic disease in the spleen, liver, and bone, and a past medical history of leg pain experienced Grade 3 leg pain on day 7 of elacestrant. The investigator determined that this event was unrelated to study drug and the dose of elacestrant was not changed. The patient was treated with oxycodone, gabapentin, and morphine. The event was reported as resolved on Day 78. No other details regarding leg pain are provided. The patient discontinued study drug on Day 52 due to disease progression. The FDA agrees that this patient had pre-existing leg pain and the role of elacestrant in the leg pain is unclear.

Patient ID (b) (6) (elacestrant)

This 59-year-old female patient experienced Grade 3 back pain on Day 116 which resolved on Day 216 and Grade 3 hip pain on Day 280 which resolved on Day 315. The patient was treated with hydrocodone/acetaminophen and ibuprofen. The patient was taking hydrocodone/acetaminophen at trial entry. The patient has a past medical history significant for limb, hip, and rib pain. The patient had baseline bone metastases. Study treatment was discontinued on Day 318 due to disease progression. The FDA agrees underlying bone metastases could have contributed to this patient's pain and the role of elacestrant is unclear.

Patient ID (b) (6) (elacestrant)

This 80-year-old female developed Grade 3 bone pain on Day 130. Bone pain was treated with etoricoxib on Day 184 after study drug discontinuation. The patient discontinued study drug on Day 175 due to disease progression in bone. She had bone metastases at baseline and past medical history significant for bone pain. The FDA agrees that this patient's bone pain could be related to bone metastases and progression of disease; the role of elacestrant is unclear.

Patient ID (b) (6) (elacestrant)

This 44-year-old female patient with past medical history significant for bone pain and osteoporosis developed Grade 3 lumbar bone pain on Day 82. She had bone metastases at baseline. She was treated with meloxicam, cyclobenzaprine, tapentadol, pregabalin, tramadol, and diclofenac. The patient discontinued study treatment on Day 106 for progression of disease and bone pain was reported as resolved on Day 107. The FDA considers that this patient's bone pain could be related to bone metastases and progression of disease and also notes that the bone pain was reported as resolved on the day study treatment was discontinued. The timing of administration of the medications to treat pain is unclear.

Patient ID (b) (6) (elacestrant)

This 41-year-old female patient with past medical history significant for bone pain developed Grade 3 right hip pain on Day 1. Elacestrant was interrupted though the investigator felt the event was unlikely to be unrelated to study drug. The patient was treated with ketoprofene and IZALGY for pain until DAY 29. The pattern of pain and date of resumption of elacestrant are unknown. Hip pain was reported as resolved on Day 72. The patient discontinued study drug on Day 211 due to progression of disease. The FDA agrees that this patient's hip pain could be due to underlying bone metastases and the contribution of elacestrant is unknown. It appears that the patient was able to resume elacestrant without further pain and without need for additional pain medications after Day 72.

Patient ID (b) (6) (elacestrant)

This 75-year-old female patient developed Grade 3 back pain on Day 78 which was treated with oxycodone/acetaminophen and dexamethasone. The dose of elacestrant was not changed and the event resolved on Day 119. The patient discontinued study drug on Day 87 due to disease progression (unknown sites). This patient did not have baseline bone metastases. In the FDA's assessment, it is unclear what role disease progression, elacestrant, and other factors may have played in this patient's back pain.

Patient ID (b) (6) (elacestrant)

This 51-year-old female with baseline bone metastases developed Grade 3 bilateral shoulder pain on Day 13. The event resolved on the same day and the dose of elacestrant was not changed. On Day 53, the patient developed Grade 3 pain in both arms. On Day 56, patient developed Grade 3 bone pain. On Day 54, the patient underwent intramedullary rod insertion to the left humerus for impending pathological fracture. The investigator and the Applicant felt that these events were unrelated to study drug. Elacestrant was withdrawn on Day 55 for disease progression. The patient received treatment with diclofenac, oxycodone, buprenorphine, paracetamol, a lidocaine patch, and codeine on overlapping dates between Day 13 and Day 64. The FDA agrees that progression of disease and impending fracture could have contributed to bone pain; the role of elacestrant is unclear.

Patient ID (b) (6) (elacestrant)

This 64-year-old female patient had baseline bone metastases, chest wall pain, back pain, and spinal stenosis, and developed Grade 3 chest wall pain and Grade 3 back pain on Day 8. She was treated with oxycodone with resolution of these adverse events on Day 12. The investigator considered theses adverse events unrelated to elacestrant and study treatment was continued. The patient discontinued treatment on Day 56 due to progression of disease in the liver. In the FDA's assessment, it is unclear if elacestrant played a role in the patient's chest wall pain and back pain.

Patient ID (b) (6) (elacestrant)

This 50-year-old female patient with past medical history significant for fibromyalgia, leg/joint pain, peripheral neuropathy, and cancer pain experienced Grade 3 bone pain on Day 12 which was treated with morphine. The patient had been taking acetaminophen and hydrocodone for cancer pain. The patient withdrew consent for continued treatment on Day 14 and discontinued study treatment. The event was reported as unresolved, and the patient was reported as receiving treatment with morphine until Day 27.

Patient ID (b) (6) (elacestrant)

This 47-year-old female patient developed Grade 3 leg pain on Day 50 in the setting of spinal cord compression. She had bone metastases at baseline and past medical history was significant for back pain, buttock pain and nerve pain. She had discontinued study treatment on Day 49 due to progression of disease. Pt had already been taking acetaminophen, gabapentin, ibuprofen and cannabis for back pain, buttock pain and nerve pain. She underwent L2-L4 laminectomy for spinal cord compression on Day 50. Per the investigator and the Applicant, the leg pain was felt to be unrelated to study drug as it had been discontinued the day before for progression of disease. The FDA generally agrees with the Applicant's assessment.

Patient ID (b) (6) (elacestrant)

This 59-year-old female developed Grade 3 back pain on Day 55. Study drug was discontinued on Day 54 for disease progression in the lung. Back pain resolved on Day 72 with hydrocodone/acetaminophen. FDA's independent analysis of back pain disagrees that it is not related to study treatment. Based on the information provided, the patient did not have bone metastases at baseline, disease progression did not occur in the bones, and no underlying conditions exist that may have contributed to bone pain.

Patient ID (b) (6) (elacestrant)

This 57-year-old female developed Grade 3 bone pain on Day 109. Elacestrant had been discontinued on Day 104 for disease progression in the bone and liver, and bone pain was felt to be unrelated to study drug. The FDA agrees with this assessment.

Patient ID (b) (6) (elacestrant)

This 58-year-old female developed Grade 3 shoulder pain on Day 2. She did not have bone metastases at baseline. This AE was felt to be unrelated to study drug and was treated with fentanyl. Study drug was discontinued on Day 56 for disease progression in the lung, liver, and lymph nodes. The FDA disagrees and believes it possible that elacestrant could have played a role in the shoulder pain. Based on the information provided, the patient did not have bone metastases at baseline, disease progression did not occur in the bones, and no other underlying conditions related to shoulder pain.

Patient ID (b) (6) (fulvestrant)

This 76-year-old female patient experienced Grade 3 back pain on Day 133. Her past medical history was significant for polymyalgia rheumatica and open fracture of one leg. At initial presentation of her disease, the patient had bone metastases and underwent intramedullary nail placement in the femur and radiation. From the narrative, it is unclear if the patient experienced another pathologic fracture while receiving treatment. Grade 3 back pain was treated with paracetamol and tramadol. The patient discontinued study treatment on Day 141 due to progressive disease. The FDA agrees that the back pain in this patient could be due to progression of disease and the role of fulvestrant is unclear.

Patient ID (b) (6) (exemestane)

This 63-year-old female patient developed Grade 3 bone pain on Day 39. She had bone metastases at baseline and past medical history significant for bone and tumor pain. She was taking opioid analgesics for bone pain upon entry into the trial. Morphine was added at onset of Grade 3 bone pain. Study drug was discontinued on Day 93 for clinical disease progression. Bone pain is reported as unresolved. In the FDA's assessment, the patient's bone pain could be related to underlying bone metastases and the role of exemestane is unclear.

Patient ID (b) (6) (exemestane)

This 59-year-old female developed the SAE of bone pain due to pathologic fracture of the right femoral head. CT scan on Day 118 showed disease progression. She underwent gamma medullary nailing and radiation therapy. She discontinued study treatment due to disease progression in the bone on Day 139. She did have bone metastases at baseline. FDA agrees that the SAE of bone pain in this patient is due to progression of disease and resulting pathologic fracture.

8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Patient-reported outcomes have been previously discussed in Section 8.1.1.

The FDA's Assessment:

See FDA Assessment of patient-reported outcomes in 8.1.1 above.

8.2.6. Safety Analyses by Demographic Subgroups

Data:

Not applicable

The Applicant's Position:

There was a limited number of males (n = 7) enrolled in the clinical development program. Given the small number, no detailed assessment of safety by gender group was feasible.

There were no clinically meaningful differences in the elacestrant safety profile based on intrinsic factors of age, gender, race, or baseline disease characteristics (including ECOG PS, *ESR1* mutant status, and measurable disease) in Study RAD1901-308 or the Phase 1 studies pool.

There were no clinically meaningful differences in the elacestrant safety profile based on extrinsic factors of region or prior therapies (i.e., number of prior lines of endocrine therapy or chemotherapy).

The FDA's Assessment:

The FDA agrees that there were too few male patients included in the safety database to assess for differences by sex.

The FDA performed an independent analysis of safety based on age ≤ 65 years and >65 years and age≤75 years and >75 years. The FDA agrees there were no significant differences in the safety profile of elacestrant based on age using an age cutoff of 65 years. There were too few patients >75 years to assess for differences in safety using an age cutoff of 75 years.

The FDA disagrees that there were no clinically meaningful differences in the safety profile of elacestrant based on race. Given the amount of missing data on race of patients, an adequate assessment of safety based on race was not feasible.

FDA did not conduct an analysis of safety based on measurable disease, ECOG PS, region, or prior therapies. The FDA examined safety in the *ESR1*-mut subgroup and the entire Study RAD1901-308 safety population and did not note major differences in safety. Details regarding assessment in the *ESR1*-mut subgroup compared to the entire population are noted in relevant portions of the FDA's safety review.

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not applicable.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Human carcinogenicity studies have not been conducted with elacestrant.

The FDA's Assessment:

The FDA agrees that no human carcinogenicity studies have been conducted.

Human Reproduction and Pregnancy

The Applicant's Position:

Based on findings in animals, elacestrant may impair fertility in females and males of reproductive potential. There have been no known incidences of elacestrant administration in women who were pregnant and/or lactating. Elacestrant should not be given to women who are pregnant or breastfeeding. Therefore, verification of pregnancy status in females of reproductive potential prior to initiating elacestrant treatment is warranted.

The proposed elacestrant labeling includes a Warning and Precaution regarding embryo-fetal toxicity, pregnancy, and contraception.

> *Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ORSERDU and for 1 week after the last dose. Advise male patients with female partners of reproductive potential to use* (b) (4) *effective contraception during treatment with ORSERDU and for 1 week after the* (b) (4) *dose.*

The FDA's Assessment:

FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

An agreed initial Pediatric Study Plan for elacestrant, granting a full waiver for all pediatric subjects < 18 years of age (all subsets) for treatment of mBC was received from the FDA on 19 December 2018.

(b) (4)

The FDA's Assessment:

The FDA has the following clarification regarding the Applicant's Agreed initial Pediatric Study Plan (iPSP). The FDA agreed with the Applicant's Agreed iPSP under IND 124748 which was communicated on December 19, 2018. A full waiver was not granted then, but will be granted at time of approval of elacestrant.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There were no known cases of overdose with elacestrant in humans. If an overdose occurred, supportive treatment and monitoring was recommended. Animal studies suggested that no effects other than those related directly or indirectly to antiestrogenic activity were evident with higher doses of elacestrant.

There have been no known incidences of drug abuse with elacestrant. There is no expectation of drug abuse with elacestrant.

There have been no known incidences of withdrawal or rebound with elacestrant. There is no expectation of withdrawal or rebound with elacestrant.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Elacestrant is not currently registered or approved in the US or in any other country.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance practices will be conducted to monitor for unexpected events.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment. The FDA will continue to monitor post-marketing reports and safety reports submitted after approval.

8.2.10. Integrated Assessment of Safety

Data:

Not applicable

The Applicant's Position:

Overall, the safety of elacestrant in the Phase 1 studies was consistent with the safety observed in the Phase 3 study.

The FDA's Assessment:

The FDA disagrees with the Applicant's assessment regarding the similarity with the safety observed in the Phase 1 studies compared with the Phase 3 study. Some patients in the Phase 1 studies received the capsule formulation of elacestrant which is associated with a higher frequency of GI toxicities such as nausea and dyspepsia compared to the tablet formulation. For details, refer to Section 8.2.4. The Phase 1 studies were not a focus of the FDA's review. For the FDA's conclusions regarding safety, please refer to the beginning of Section 8.2.

SUMMARY AND CONCLUSIONS

Applicant Position:

The PFS benefit in favor of elacestrant was statistically significant in all subjects and in subjects with *ESR1*-mut and was supported by statistically significant results from all sensitivity analyses. In addition, the landmark analysis at different time points for both PFS and OS showed clear differences in favor of elacestrant.

All subjects:

- The IRC-assessed PFS estimates at 3, 6, 12, and 18 months were 49.75% versus 39.29%, 34.32 versus 20.38%, 22.32% versus 9.42% and 16.82% versus 0%, in the elacestrant and SOC arms, respectively (Updated Table 14.2.1.1.2).
- Overall survival estimates at 3, 6, 12, and 18 months were 98.72% versus 94.18%, 93.01% versus 84.84%, 79.27% versus 73.00%, and 65.24% versus 54.38%, in the elacestrant and SOC arms, respectively (Updated Table 14.2.2.1.2).

ESR-mut group:

- The IRC-assessed PFS estimates at 3, 6, 12, and 18 months were 55.93% versus 39.55%, 40.76% versus 19.14%, 26.76% versus 8.19% and 24.33% versus 0%, in the elacestrant and SOC arms, respectively (Updated Table 14.2.1.1.1).
- Overall survival estimates at 3, 6, 12, and 18 months were 98.24% versus 98.09%, 92.79% versus 84.36%, 82.64% versus 73.58%, and 67.81% versus 49.36%, in the elacestrant and SOC arms, respectively (Updated Table 14.2.2.1.1).

The results of all subgroup analyses were also supportive and consistent with the overall results.

Post hoc exploratory analysis of elacestrant versus fulvestrant and post hoc subgroup analysis based on one of the stratification factors (prior fulvestrant therapy in the advanced/metastatic

setting) showed that PFS estimates of elacestrant against SOC, were consistent with the results in all subjects.

In addition, the oral route of administration is more convenient and acceptable relative to the IM administration of fulvestrant.

Although the trial was not powered to detect a statistically significant difference in the *ESR1*-mut-nd group, the efficacy benefit was also observed to a smaller extent in this group, both in terms of PFS HR and, more clearly, in terms of landmark analysis.

- IRC-assessed PFS estimates at 3, 6, 12, and 18 months were 44.30% versus 38.92%, 28.58% versus 21.85%, 18.16% versus 11.22%, and 9.08% versus 0%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308, Table 14.2.1.1.3).
- Overall survival estimates at 3, 6, 12, and 18 months were 99.16% versus 90.77%, 93.23% versus 85.45%, 76.37% versus 72.67%, and 62.67% versus 59.01%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308, Table 14.2.2.1.3).

Despite a smaller efficacy benefit compared to SOC, the convenience of the oral route of administration compared to the IM administration of fulvestrant constitutes an additional benefit for these patients.

The safety profile of elacestrant, relative to SOC, was almost identical in all 3 groups. To date, no important identified or potential risks have been determined for elacestrant in the target population. Of note, elacestrant was not associated with cardiac safety issues, and hematological AEs were rare.

For all subjects, mean duration on treatment was highest for subjects in the elacestrant group at 144.1 days and lowest in subjects receiving AIs in the SOC group at 96.8 days. Dose reductions due to TEAEs were reported for 7 subjects (3.0%) in the elacestrant group and 0 subjects in the SOC group (Table 27; PP and the relevant PI, dose reduction was not allowed for subjects receiving AIs and only under limited circumstances for subjects receiving fulvestrant).

The favorable benefits of PFS and OS profiles of elacestrant versus SOC, added to the convenience of an oral administration, outweigh the risks in the proposed patient population in all subjects, including both subjects with *ESR1*-mut and subjects with *ESR1*-mut-nd. These results are clinically relevant for the patient population under study.

In conclusion, the benefit-risk assessment for elacestrant for the treatment of postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer who have progressed following at least 1 line of endocrine therapy is positive in all subjects, irrespective of the *ESR1* mutation status.

8.3. Statistical Issues

The FDA's Assessment:

The EMERALD trial demonstrated a statistically significant improvement in PFS in the ITT and *ESR1*-mut subpopulation; however, the treatment effect from the ITT population was driven by the *ESR1*-mut subpopulation. The PFS analysis in the *ESR1*-mut population was pre-specified and formally powered, while analyses for the *ESR1*-mut-nd population were not. Therefore, PFS

results in the *ESR1*-mut-nd population should be interpreted with caution. However, it is reassuring that the large number of patients in the *ESR1*-mut-nd population (52% of the ITT population) is adequate for estimation of the treatment effect. Interpretation of the PFS results was more challenging due to the high degree of censoring, which leads to uncertainty in the estimation of the magnitude of the PFS treatment effect. Sensitivity analyses were supportive of a robust and statistically persuasive improvement in PFS in the *ESR1*-mut subpopulation but did not show any clear benefit for the *ESR1-mut-nd* subpopulation. The conclusion of the statistical review is that the PFS results did not appear to be compromised by early dropout in the *ESR1*-mut subpopulation. However, there was no obvious benefit in the *ESR1*-mut-nd subpopulation.

The key secondary endpoint of OS, while not statistically significant, did not show a trend towards OS detriment for the *ESR1*-mut subpopulation at the final analysis. KM curves for the *ESR1*-mut-nd subpopulation were heavily overlapping. FDA was concerned that early censoring due to withdrawal of consent and potential informative censoring would impact efficacy results. In addition, there was an imbalance of withdrawal of consent, particularly for the *ESR1*-mut-nd subpopulation, which could result in biased results for OS. A variety of conservative and worst-case sensitivity analyses for OS were performed to evaluate the potential impact of withdrawal of consent. The main and sensitivity analyses showed no clear benefit for the *ESR1*-mut-nd subpopulation. Therefore, FDA recommends that the indication be limited to the *ESR1*-mut subpopulation.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Study RAD1901-308, a randomized, active-controlled, open-label, multicenter trial in 478 patients with ER-positive, HER2-negative advanced or metastatic breast cancer, demonstrated a statistically significant and clinically meaningful improvement in PFS by IRC which was supported by a favorable OS HR trend in patients in the *ESR1*-mut subpopulation. Study RAD1901-308 did not demonstrate a clinically meaningful improvement in PFS in patients in the *ESR1*-mut-nd subpopulation. In addition, elacestrant was associated with increased GI toxicity and higher incidences of hypercholesterolemia and hypertriglyceridemia compared to SOC.

The FDA disagrees with several statements made by the Applicant in Summary and Conclusions:

- The Applicant stated that sensitivity analyses of PFS were statistically significant and supportive of primary PFS results. All sensitivity analyses performed by the Applicant and FDA were exploratory and therefore not statistically significant. PFS results in the *ESR1*-mut subpopulation were robust to multiple sensitivity analyses performed by the FDA. Sensitivity analyses of PFS in the *ESR1*-mut-nd subpopulation consistently indicated no clear benefit for the elacestrant arm.
- The Applicant states that landmark analyses of PFS and OS showed clear differences in favor of elacestrant. Landmark analyses for time-to-event endpoints (PFS and OS) are exploratory and any differences between treatment arms at these landmarks must be interpreted with caution. Censoring also affects the robustness of the estimates reported.

- The Applicant states that an efficacy benefit was observed for patients in the *ESR1*-mut-nd subpopulation. Clinical benefit was not demonstrated in the *ESR1*-mut-nd subgroup.
- The Applicant implies an oral route of administration is always preferred. An oral route of administration is not inherently superior to other routes of administration. Orally administered drugs may be associated with increased GI toxicity, as seen with elacestrant, and may also lead to challenges with adherence for patients.
- The Applicant stated that there were no important safety signals associated with elacestrant. Hypercholesterolemia and hypertriglyceridemia were important safety signals identified for elacestrant in the FDA's review and labeled under Warnings and Precautions.

The FDA disagrees with the Applicant that the overall benefit-risk assessment was favorable for all patients. The review team determined that the benefit-risk assessment is favorable for patients in the *ESR1*-mut subpopulation and not favorable for patients in the *ESR1*-mut-nd subpopulation.

The review team recommends regular approval for elacestrant for following indication:

Elacestrant (ORSERDU) is indicated for the treatment of postmenopausal women or adult men with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, ESR1-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

X	X

Primary Statistical Reviewer: Haley Gittleman, Xin (Cindy) Gao
Statistical Team Leader: Mallorie Fiero

X	X

Primary Clinical Reviewer: Danielle Krol Clinical Team Leader: Mirat Shah

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The FDA did not refer this application to an advisory committee as there were no efficacy or safety issues identified during the review which required external input for the proposed indication.

10 Pediatrics

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA agreed with the Applicant's Initial Pediatric Study Plan (iPSP) submitted under IND on December 19, 2018. In the iPSP, the Applicant requested a full waiver which the FDA granted at time of approval.

11 Labeling Recommendations

The Applicant's Position:

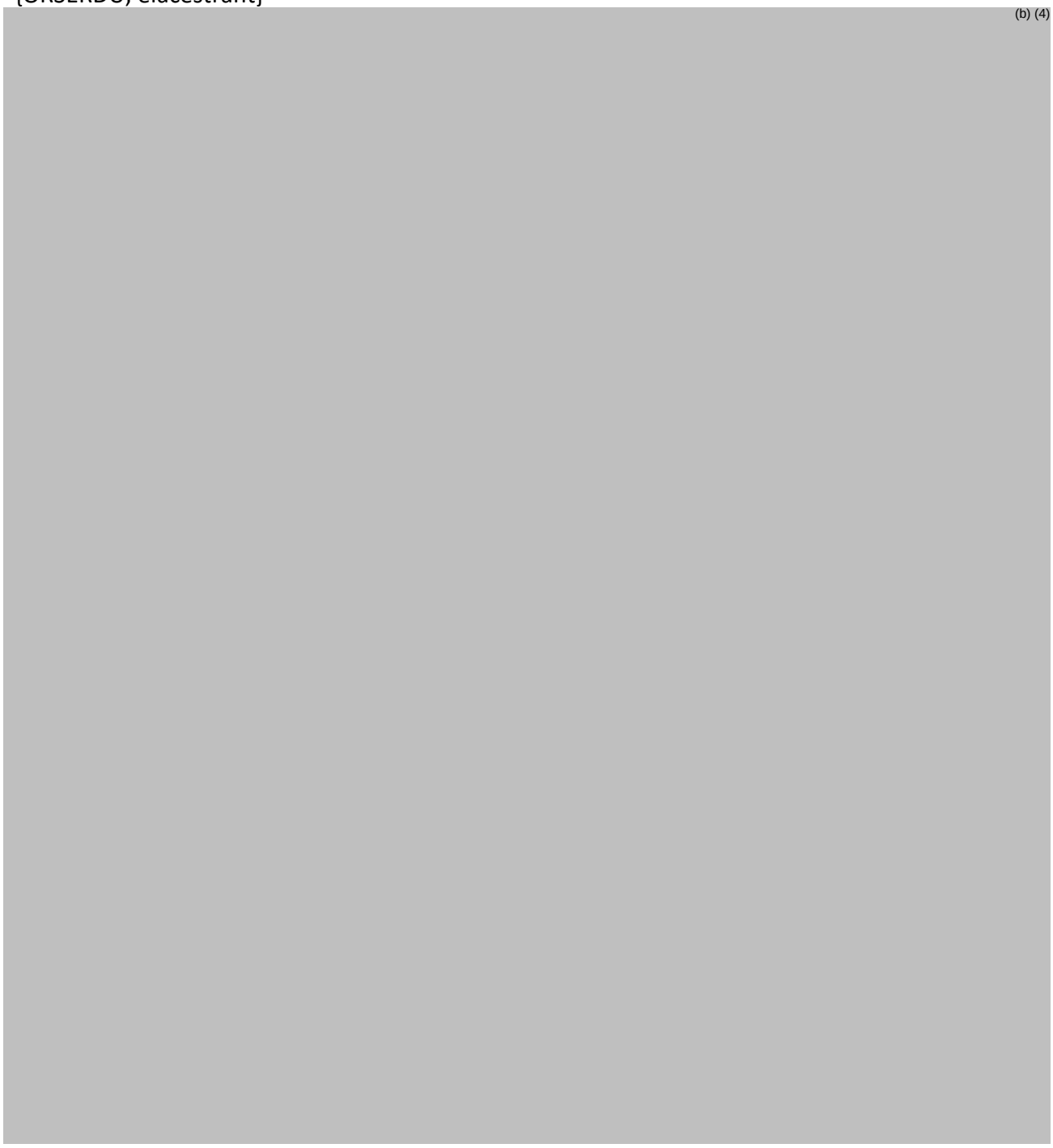
This is the first proposed label submitted for elacestrant. Therefore, a summary of the significant labeling changes is not provided.

The FDA's Assessment:

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)



12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
Based on the benefit-risk profile of elacestrant, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
The following PMRs and PMCs were agreed upon at the time of approval:

Clinical Pharmacology PMR: Hepatic Impairment

Complete a pharmacokinetic trial to determine an appropriate dose of elacestrant in patients with severe hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf.

Draft Protocol Submission: 05/2023
Final Protocol Submission: 10/2023
Study Completion: 12/2025
Final Report Submission: 06/2026

Clinical PMC: Race and Ethnicity

Conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of elacestrant in patients from racial and ethnic minority groups. The analyses should support comparative safety and efficacy outcome analyses between the aforementioned populations and White patients.

Draft Protocol Submission: 06/2023
Final Protocol Submission: 12/2023
Study Completion: 12/2027
Final Report Submission: 06/2028

14 Division Director (DHOT) (NME ONLY)

X

John Leighton

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

Laleh Amiri-Kordestani

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:

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19.2. Financial Disclosure

The Applicant's Position:

The applicant provided financial disclosure for all clinical investigators involved in the studies included in the submission on Form 3455. No financial disclosure concerns were raised regarding study and data integrity.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding Study RAD1901-308. The FDA did not review financial disclosures for investigators involved in RAD1901-116, which was a BE and food effect study.

Covered Clinical Study (Name and/or Number):* RAD1901-308

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 229		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number): * RAD1901-116

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason?	Yes ☐	No ☐ (Request explanation from Applicant) N/A

*The table above should be filled by the applicant and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

None

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of bioanalytical method validation and performance

Table 1a. Summary method performance of a bioanalytical method to measure Elacestrant (RAD-1901) in human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	RDU724UL-157247-B: Validation of a Method for the Determination of RAD1901 in Human K3-EDTA Plasma Samples by LC-MS/MS Amendment No. 01 Amendment No. 02 Assay Method Code: (b) (4) 0185 M5>5314>rdu724ul-157247-b
Method description	This method is used for the quantification of RAD-1901 free form in human plasma using RAD-1901-D5 free form as internal standard (IS). The test item and IS are extracted from 50 µL of plasma by solid-phase extraction. Analysis is performed by LC-MS/MS (API6500, Sciex, operating in MRM positive ion mode)

Materials used for calibration curve & concentration	K_3-EDTA Human Plasma 0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0 and 50.0 ng/mL		
Validated assay range	0.0500 to 50.0 ng/mL		
Material used for QCs & concentration	K3-EDTA Human Plasma LLOQ: 0.0500 ng/mL QCL: 0.150 ng/mL QCM: 2.50 ng/mL QCH: 40.0 ng/mL Amendment No. 01: added QC: 20.0 ng/mL		
Minimum required dilutions (MRDs)	Not Applicable (n/a)		
Source & lot of reagents (LBA)	n/a		
Regression model & weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	9	Table 2 of report rdu724ul-157247-b M5>5314>rdu724ul-157247-b
	Cumulative accuracy (%bias) from LLOQ to ULOQ RAD-1901	-3.1 to 2.2%	Table 2 of report rdu724ul-157247-b M5>5314>rdu724ul-157247-b
	Cumulative precision (%CV) from LLOQ to ULOQ RAD-1901	≤ 3.9%	Table 2 of report rdu724ul-157247-b M5>5314>rdu724ul-157247-b
QCs performance during accuracy & precision	**<u>Cumulative accuracy (%bias) in 18 QCs</u>** QCs: RAD-1901	-3.6 to 1.2%	Table 5 of report rdu724ul-157247-b M5>5314>rdu724ul-157247-b
	<u>Inter-batch %CV</u> QCs: RAD-1901	≤ 6.4%	Table 5 of report rdu724ul-157247-b M5>5314>rdu724ul-157247-b
	<u>Total Error (TE)</u> QCs:	n/a	-
Selectivity & matrix effect	Number of total lots tested: 6 independent sources of blank plasma Range of observed bias: At the LLOQs the overall bias was 10.6% State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		n/a
Hemolysis effect	No effect of hemolysis on the quantitation of RAD-1901		-
Lipemic effect	No effect of lipemia on the quantitation of RAD-1901		
Dilution linearity & hook effect	Dilution Integrity Highest concentration tested: 400 ng/mL		-

	Number of dilution factors: 1 (dilution factor, 10) Range of observed bias: overall bias was -12.7%	
Bench-top/process stability	Bench-top stability: up to 44 hours at room temperature Autosampler stability: up to 123 hours at +10°C Reinjection reproducibility: up to 46 hours at +10°C RAD-1901	-
Freeze-Thaw stability	3 cycles from -70°C to room temperature 5 cycles from -20°C to room temperature RAD-1901	-
Long-term storage	Up to 424 days at -20°C Up to 380 days at -70°C Amendment No. 02: Up to 1890 days at -20°C RAD-1901	-
Parallelism	n/a	-
Carry over	No carry-over was observed	-
Method performance in study RAD1901-109: A Randomized, Open-Label, Single-Dose, Three-Period Crossover Study to Evaluate the Effect of Food on the Bioavailability of Elacestrant Tablets in Healthy Men and Postmenopausal Women M5>5311> rad1901-109		
Assay passing rate	100% (7 out of 7 analytical runs)	
Standard curve performance	● Cumulative bias range: -1.3 to 1.0% ● Cumulative precision: ≤ 5.7% CV	
QC performance	● Cumulative bias range: -4.7 to 0.0 % ● Cumulative precision: ≤ 6.9% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 11.6% of study samples and 97.6% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-110: An Open-Label, Single-Sequence, One-Way Crossover Study to Evaluate the Effect of Multiple Doses of the Cyp3a4 Inhibitor Itraconazole on the Steady State Pharmacokinetics of Elacestrant in Healthy Male and Postmenopausal Female Volunteers M5>5334> rad1901-110		
Assay passing rate	87.5% (7 out of 8 analytical runs)	
Standard curve performance	● Cumulative bias range: -1.0 to 2.0% ● Cumulative precision: ≤ 7.2% CV	
QC performance	● Cumulative bias range: -4.4 to 0.0 % ● Cumulative precision: ≤ 8.9% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 10.4% of study samples and 84.9% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-112: A Pilot, Randomized, Open-label, Single-dose, 3-Period Crossover Study to Evaluatethe Relative Bioavailability of 2 Elacestrant Prototype Tablets Compared to the Elacestrant Clinical Tablet in Healthy Men and Postmenopausal Women M5>5312> rad1901-112		
Assay passing rate	100% (20 out of 20 analytical runs)	

Standard curve performance	● Cumulative bias range: -0.7 to 0.6% ● Cumulative precision: ≤ 3.4% CV	
QC performance	● Cumulative bias range: -0.7 to 2.3 % ● Cumulative precision: ≤ 4.8% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 7.6% of study samples and 100% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-113: An Open-Label Study to Evaluate the Effect of the CYP3A4 Inducer Rifampin on the Pharmacokinetic Profile of Elacestrant in Healthy Men and Postmenopausal Women M5>5334> rad1901-113		
Assay passing rate	100% (6 out of 6 analytical runs)	
Standard curve performance	● Cumulative bias range: -3.3 to 3.2% ● Cumulative precision: ≤ 5.4% CV	
QC performance	● Cumulative bias range: -2.7 to 2.3 % ● Cumulative precision: ≤ 7.2% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 11.1% of study samples and 98.3% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-114: A Randomized, Open-label, Single-dose, 3-Period Crossover Study to Evaluate the Potential Drug-Drug Interaction Between 2 Highly Protein-bound Drugs, Elacestrant and Warfarin, in Healthy Men and Postmenopausal Women M5>5334> rad1901-114		
Assay passing rate	85.7% (6 out of 7 analytical runs)	
Standard curve performance	● Cumulative bias range: -2.4 to 3.5% ● Cumulative precision: ≤ 4.8% CV	
QC performance	● Cumulative bias range: -0.7 to 2.5 % ● Cumulative precision: ≤ 6.0% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 10.6% of study samples and 94.7% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-115: An Open-Label Study to Evaluate the Effect of the Proton Pump Inhibitor Omeprazole on the Pharmacokinetic Profile of Elacestrant in Healthy Men and Postmenopausal Women M5>5334> rad1901-115		
Assay passing rate	100% (6 out of 6 analytical runs)	
Standard curve performance	● Cumulative bias range: -2.0 to 2.4% ● Cumulative precision: ≤ 4.6% CV	
QC performance	● Cumulative bias range: 2.0 to 3.3 % ● Cumulative precision: ≤ 3.6% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 11.1% of study samples and 95.0% of samples met the pre-specified criteria	

Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-116: A Phase 1, Randomized, Open-label, Single-dose, Crossover Study to Evaluate the Bioequivalence of the Elacestrant Commercial Tablet Compared to the Elacestrant Clinical Tablet, Including an Assessment of the Food-Effect on the Commercial Tablet, in Healthy Men and Postmenopausal Women M5>5312> rad1901-116		
Assay passing rate	100% (42 out of 42 analytical runs)	
Standard curve performance	● Cumulative bias range: -3.1 to 1.8% ● Cumulative precision: ≤ 5.9% CV	
QC performance	● Cumulative bias range: -2.0 to 1.0 % ● Cumulative precision: ≤ 7.9% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 7.5% of study samples and 98.4% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-117: A Phase 1, Open-label, Single-dose Study to Evaluate the Pharmacokinetics of Elacestrant in Subjects with Mild or Moderate Hepatic Impairment Compared to Healthy Subjects M5>5333> rad1901-117		
Assay passing rate	85.7% (6 out of 7 analytical runs)	
Standard curve performance	● Cumulative bias range: -1.2 to 1.0% ● Cumulative precision: ≤ 4.1% CV	
QC performance	● Cumulative bias range: 3.3 to 4.5 % ● Cumulative precision: ≤ 5.3% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 11.3% of study samples and 100% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	
Method performance in study RAD1901-308: Elacestrant Monotherapy vs. Standard of Care For the Treatment of Patients with Er+/Her2- Advanced Breast Cancer Following Cdk4/6 Inhibitor Therapy: a Phase 3 Randomized, Open-Label, Active-Controlled, Multicenter Trial (Emerald) M5>5314> rdu138ul-181387-a		
Assay passing rate	100% (16 out of 16 analytical runs)	
Standard curve performance	● Cumulative bias range: -2.6 to 1.6% ● Cumulative precision: ≤ 6.2% CV	
QC performance	● Cumulative bias range: 2.0 to 4.8 % ● Cumulative precision: ≤ 5.4% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of study samples and 98.3% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	

Table 1b. Summary method performance of a bioanalytical method to measure RAD-1901 in human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	RDU2022A-2022AX-B: Validation and Cross-Validation of a Method for the Determination of RAD1901 in Human K3-EDTA Plasma Samples by LC-MS/MS (Triple Quad 6500) Assay Method Code: (b) (4) 0604 M5>5314>study-rdu2022a-2022a		
Method description	This method is used for the quantification of RAD-1901 free form in human plasma using RAD-1901-D5 free form as internal standard (IS). The test item and IS are extracted from 50 µL of plasma by solid-phase extraction. Analysis is performed by LC-MS/MS (API6500, Sciex, operating in MRM positive ion mode)		
Materials used for calibration curve & concentration	K_3-EDTA Human Plasma 0.300, 0.600, 1.50, 6.00, 15.0, 60.0, 150, 240 and 300 ng/mL		
Validated assay range	0.300 to 300 ng/mL		
Material used for QCs & concentration	K3-EDTA Human Plasma LLOQ: 0.300 ng/mL QCL: 0.900 ng/mL QCM: 90 ng/mL and 150 ng/mL QCH: 225 ng/mL		
Minimum required dilutions (MRDs)	Not Applicable (n/a)		
Source & lot of reagents (LBA)	n/a		
Regression model & weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	9	Table 2 of report rdu2022a-2022ax-b M5>5314>study-rdu2022a-2022a
	Cumulative accuracy (%bias) from LLOQ to ULOQ RAD-1901	-3.2 to 1.9%	Table 2 of report rdu2022a-2022ax-b M5>5314>study-rdu2022a-2022a
	Cumulative precision (%CV) from LLOQ to ULOQ RAD-1901	≤ 4.6%	Table 2 of report rdu2022a-2022ax-b M5>5314>study-rdu2022a-2022a
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 18 QCs** QCs: RAD-1901	-13.8 to -7.1%	Table 6 of report rdu2022a-2022ax-b M5>5314>study-rdu2022a-2022a
	Inter-batch %CV QCs: RAD-1901	≤ 7.7%	Table 6 of report rdu2022a-2022ax-b M5>5314>study-rdu2022a-2022a
	Total Error (TE) QCs:	n/a	-
Selectivity & matrix effect	Number of total lots tested: 6 independent sources of blank plasma Range of observed bias: At the LLOQs the overall bias was 10.6% State any issue		-
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		n/a

Hemolysis effect	No effect of hemolysis on the quantitation of RAD-1901	-
Lipemic effect	No effect of lipemia on the quantitation of RAD-1901	
Dilution linearity & hook effect	Dilution Integrity Highest concentration tested: 2250 ng/mL Number of dilution factors: 1 (dilution factor, 10) Range of observed bias: overall bias was -10.8%	-
Bench-top/process stability	Bench-top stability: up to 26 hours at room temperature Autosampler stability: up to 215 hours at +10°C Reinjection reproducibility: up to 187 hours at +10°C RAD-1901	-
Freeze-Thaw stability	5 cycles from -70°C to room temperature 5 cycles from -20°C to room temperature RAD-1901	-
Long-term storage	Up to 76 days at -20°C Up to 76 days at -70°C RAD-1901	-
Parallelism	n/a	-
Carry over	No carry-over was observed	-
Method performance in study RAD1901-116: A Phase 1, Randomized, Open-label, Single-dose, Crossover Study to Evaluate the Bioequivalence of the Elacestrant Commercial Tablet Compared to the Elacestrant Clinical Tablet, Including an Assessment of the Food-Effect on the Commercial Tablet, in Healthy Men and Postmenopausal Women M5>5312> rad1901-116		
Assay passing rate	100% (42 out of 42 analytical runs)	
Standard curve performance	● Cumulative bias range: -1.3 to 1.3% ● Cumulative precision: ≤ 3.1% CV	
QC performance	● Cumulative bias range: 3.8 to 4.9 % ● Cumulative precision: ≤ 3.3% CV ● TE: Not Applicable	
Method reproducibility	Incurred sample reanalysis was performed in 7.5% of study samples and 98.4% of samples met the pre-specified criteria	
Study sample analysis/ stability	Standard/QC and study samples analysis performed within the stability range	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in Table 2 below.

Table 2b. Summary of method [(b) (4)0604] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink	RDU2022A-2022AX-C: Validation and Cross-Validation of a Method for the Determination of RAD1901 in Human K3-EDTA Plasma Samples by LC-MS/MS (Triple Quad 6500) Assay Method Code: (b) (4)0185 and (b) (4)0604 M5>5314>study-rdu2022a-2022a	
Changes in method	Cross-validation methods numbers: (b) (4)0185 and (b) (4)0604	
New validated assay range if any	0.0500 to 50.0 ng/mL (b) (4)0185) and 0.300 to 300 ng/mL (b) (4)0604)	
Validation parameters	**Cross-validation performance**	**Source location (hyperlinked)**

Standard calibration curve performance during accuracy & precision	(b) (4) 0185: Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-2.2 to 7.0%	Table 23 of report rdu2022a-2022ax-c M5>5314>study-rdu2022a-2022a
	(b) (4) 0604: Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-3.3 to 6.3%	Table 24 of report rdu2022a-2022ax-c M5>5314>study-rdu2022a-2022a
	Cumulative precision (%CV) from LLOQ to ULOQ	Not Applicable (n/a)	-
QCs performance during accuracy & precision	(b) (4) 0185: Cumulative accuracy (%bias) in 3 QCs levels	-3.1 to 0.0%	Table 26 of report rdu2022a-2022ax-c M5>5314>study-rdu2022a-2022a
	(b) (4) 0604: Cumulative accuracy (%bias) in 4 QCs levels (cross-validation between K2-EDTA and K3-EDTA)	-13.8 to -7.1%	Table 28 of report rdu2022a-2022ax-c M5>5314>study-rdu2022a-2022a
	(b) (4) 0185: Inter-batch %CV	≤ 4.0%	Table 26 of report rdu2022a-2022ax-c M5>5314>study-rdu2022a-2022a
	(b) (4) 0604: Inter-batch %CV (cross-validation between K2-EDTA and K3-EDTA)	≤ 4.5%	Table 28 of report rdu2022a-2022ax-c M5>5314>study-rdu2022a-2022a
	Percent total error (TE)	n/a	-
Cross-validation	Numbers of spiked or incurred samples analyzed and result	24 spiked samples	Table 29 of report

		Absolute relative difference : ≤10.9	rdu2022a-2022ax-c M5>5314>study-rdu2022a-2022a
List other parameters	-	-	-

Table 3a. Summary life cycle information of bioanalytical method used in submission of NDA 217639 to measure analyte Elacestrant (RAD-1901) in human plasma

	Method validation #1 RDU724UL-157247-B	Clinical Study RAD1901-109	Clinical Study RAD1901-110	Clinical Study RAD1901-112	Clinical Study RAD1901-113	Clinical Study RAD1901-114	Clinical Study RAD1901-115	Clinical Study RAD1901-116	Clinical Study RAD1901-117	Clinical Study RAD1901-308
Analyte	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)
Validation type	Full	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
• CTD ref #	5.3.1.4	5.3.1.1	5.3.3.4	5.3.1.2	5.3.3.4	5.3.3.4	5.3.3.4	5.3.1.2	5.3.3.3	5.3.5.1
• method ID • BA site	(b) (4)									
• Matrix	Plasma									
	LC/MS									

• Platform • Format	Not Applicable									
Stock reference & lot (expiry)	RAD-1901, lot 16-04202-01 / 02RAD08A-03-66-RS (Exp. Date 07 Oct 2018)	RAD-1901, lot 02RAD08A-03-66-RS (Exp. Date 30 Set 2020)	RAD-1901, lot 02RAD08A-03-66-RS (Exp. Date 30 Set 2020)	RAD-1901, lot 02RAD08A-03-66-RS (Exp. Date 30 Set 2020)	RAD-1901, lot 02RAD08A-03-66-RS (Exp. Date 30 Set 2020)	RAD-1901, lot 02RAD08A-03-66-RS (Exp. Date 30 Set 2020)	RAD-1901, lot 02RAD08A-03-66-RS (Exp. Date 30 Set 2020)	RAD-1901, lot RAD-19-2689 (Exp. Date 03 Apr 2022)	RAD-1901, lot RAD-19-2689 (Exp. Date 03 Apr 2022)	RAD-1901, lot#1 02RAD08A-03-66-RS (Retest Date May 2021) lot#2 RAD-19-2689 (Exp. Date 03 Apr 2022)
Calibration range (LLOQ - ULOQ) and levels validated	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)	0.0500 to 50 ng/mL (0.0500, 0.100, 0.250, 1.00, 2.50, 10.0, 25.0, 40.0, 50.0 ng/mL)
Matrix/ study population	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects and hepatic impaired patients	Plasma/ ER+/HER2-advanced breast cancer patients

Relevant reference and applicable report amendment (s) and links - Amendment 1 - Amendment 2	M5>5314>rdu724ul-157247-b Amendment 1, M5>5314>rdu724ul-157247-b Amendment 2, M5>5314>rdu185ec-143123-b	M5>5311>rad1901-109	M5>5334>rad1901-110	M5>5312>rad1901-112	M5>5334>rad1901-113	M5>5334>rad1901-114	M5>5334>rad1901-115	M5>5312>rad1901-116	M5>5333>rad1901-117	M5>5314>rdu138ul-181387-a
Amendment history	Amendment 1 Issue Date 17 Nov 2020 Amendment 2 Issue Date 18 Feb 2022	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable

Table 3b. Summary life cycle information of bioanalytical method used in submission of NDA 217639 to measure analyte Elacestrant (RAD-1901) in human plasma

	Method validation #1 RDU2022A-2022AX-B	Method validation #2 RDU2022A-2022AX-B	Clinical Study RAD1901-116	Clinical Studies y-z
Analyte	Elacestrant (RAD-1901)	Elacestrant (RAD-1901)	RAD-1901	Not Applicable
Validation type	Full	Cross-validation	NA	Not Applicable
● CTD ref #	5.3.1.4	5.3.1.4	5.3.1.2	Not Applicable
● method ID	(b) (4)			Not Applicable
● BA site				Not Applicable
● Matrix	Plasma			
● Platform	LC/MS			
● Format	Not Applicable			
Stock reference & lot (expiry)	RAD-1901, lot RAD-19-2689 (Exp. Date 03 Apr 2022)	RAD-1901, lot RAD-19-2689 (Exp. Date 03 Apr 2022)	RAD-1901, lot RAD-19-2689 (Exp. Date 03 Apr 2022)	Not Applicable
Calibration range (LLOQ -ULOQ) and levels validated	0.300 to 300 ng/mL (0.300, 0.600, 1.50, 6.00, 15.0, 60.0, 150, 240 and 300 ng/mL)	0.300 to 300 ng/mL (0.300, 0.600, 1.50, 6.00, 15.0, 60.0, 150, 240 and 300 ng/mL)	0.300 to 300 ng/mL (0.300, 0.600, 1.50, 6.00, 15.0, 60.0, 150, 240 and 300 ng/mL)	Not Applicable
Matrix/ study population	Plasma/healthy subjects	Plasma/healthy subjects	Plasma/healthy subjects	Not Applicable
Relevant reference and applicable report amendment (s) and links	M5>5314>rdu185ec-143123-e	M5>5314>rdu185ec-143123-e	M5>5312> rad1901-116	Not Applicable

-Amendment 1 -Amendment 2				
Amendment history	Not Applicable	Not Applicable	Not Applicable	Not Applicable

The FDA's Assessment:

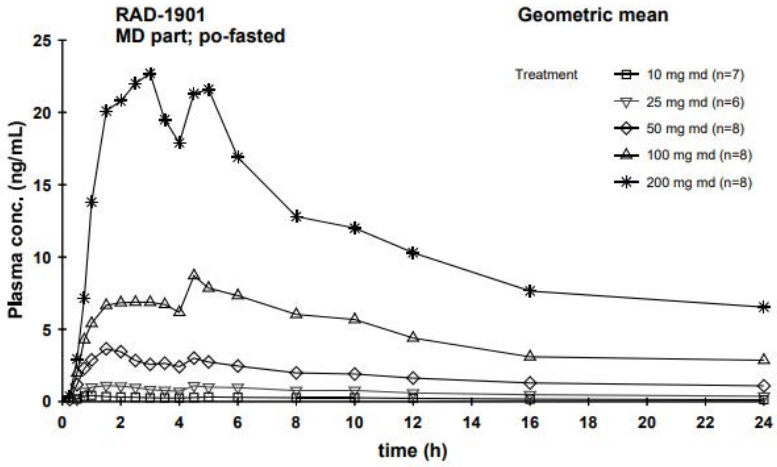
FDA agrees with the Applicant's position.

19.4.2. Clinical PK

Elacestrant PK following single and multiple dose administration was explored in healthy post-menopausal women in Study RAD1901-001. The explored dose range was 1 mg – 173 mg (SAD part) and 10 mg-173 mg (MAD part).

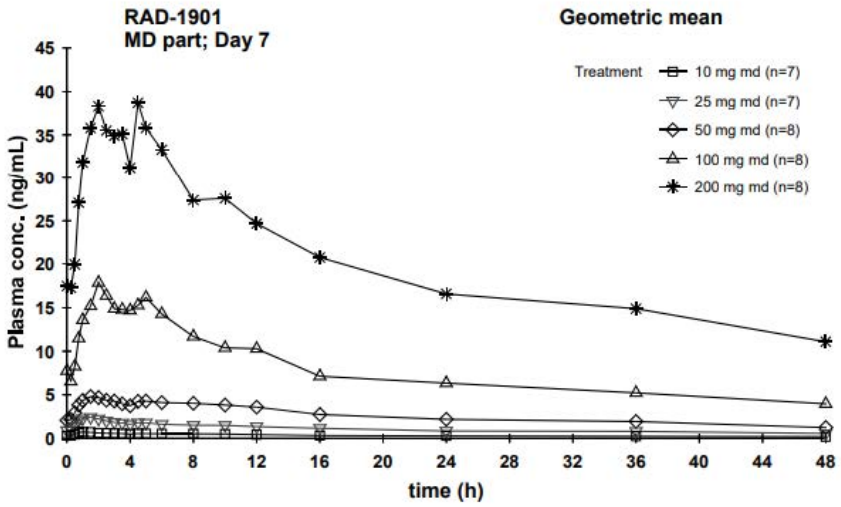
Geometric mean plasma concentration-time data of elacestrant in the MAD part after single dose (Day 1) and multiple doses (Day 7) are shown in Figure 19 and Figure 20, respectively. The summary statistics of PK parameters of elacestrant on Day 1 and Day 7 in the MAD part are presented in Table 33.

Figure 19: Geometric Mean Plasma Concentration Versus Time Profiles of elacestrant, MAD Part (Day 1)



(Source: Figure 5 in Applicant's Study Report RAD1901-001)

Figure 20: Geometric Mean Plasma Concentration Versus Time Profiles of RAD-1901, MAD Part (Day 7)



(Source: Figure 6 in Applicant's Study Report RAD1901-001)

Table 33: Summary Statistics of the Pharmacokinetic Parameters of elacestrant in Plasma, SAD Part

			arithmetic mean (SD) by parameter						
treatment With RAD-1901	day	N	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}last}$ (ng.h/mL)	$AUC_{0\text{-}inf}$ (ng.h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
1 mg sd	1	2*	0.0645 (0.0176)	2.63 (2.65)	--	--	--	--	--
1 mg sd-IV	1	5	69.8 (30.7)	0.0433 (0.0224)	23.9 (3.63)	28.0 (5.19)	33.4 (6.17)	36.8 (7.64)*	1730 (155)^
	1	5							1130 (120)+
10 mg sd	1	6	0.687 (0.377)	1.92 (1.28)	13.1 (9.41)	16.8 (11.7)	31.9 (8.14)	760 (323)	33700 (13800)
25 mg sd	1	6	1.79 (0.471)	1.64 (1.42)	32.2 (15.7)	40.6 (21.6)	32.5 (5.99)	786 (419)	34500 (13300)
50 mg sd-fasted	1	6	3.41 (0.711)	1.92 (2.03)	61.3 (11.7)	73.3 (13.2)	29.1 (3.41)	702 (134)	29800 (8910)
50 mg sd-fed	1	6	7.02 (1.45)	4.17 (1.33)	96.8 (20.0)	116 (26.9)	28.8 (2.69)	451 (111)	18500 (3050)
100 mg sd	1	6	11.8 (1.99)	2.58 (1.72)	247 (71.9)	294 (80.8)	28.4 (3.87)	361 (92.0)	14900 (4920)
200 mg sd	1	6	31.5 (5.64)	3.25 (1.57)	649 (183)	774 (239)	27.4 (3.74)	281 (90.1)	10800 (2860)

-- no result
* CL (L/h)
^ V_z (L)
+ V_{ss} (L)

sd single dose
IV intravenous
h hour
N no. of subjects with PK result

* Subject 8 excluded from descriptive statistics, due to emesis at 1.17 h after dosing

(Source: Table 9 in Applicant's Study Report RAD1901-001)

Table 34: Summary Statistics of the Pharmacokinetic Parameters of elacestrant in Plasma, MAD Part

			arithmetic mean (SD) by parameter						
treatment with RAD-1901	day	N	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0-\tau}$ (ng.h/mL)	R_{ac}	$t_{1/2}$ (h)	CL_{ss}/F (L/h)	V_z/F (L)
10 mg md	1	7	0.504 (0.130)	2.25 (2.24)	5.63 (1.95)				
	7	7	0.817 (0.215)	0.967 (0.273)	10.8 (3.69)	1.95 (0.291)	37.9 (4.70)	1020 (347)	54600 (15100)
25 mg md	1	6*	1.46 (0.470)	2.92 (3.50)	16.0 (4.05)				
	7	7	2.64 (0.751)	1.29 (0.466)	35.3 (13.9)	2.20 (0.675)	41.1 (12.7)	799 (281)	47100 (21100)
50 mg md	1	8	4.46 (0.996)	1.72 (0.839)	45.2 (12.8)				
	7	8	5.65 (1.16)	2.78 (2.47)	82.1 (17.3)	1.86 (0.269)	31.1 (6.80)	634 (139)	28300 (7750)
100 mg md	1	8	10.4 (2.83)	3.93 (3.01)	122 (55.6)				
	7	8	20.5 (7.66)	2.50 (1.10)	265 (118)	2.18 (0.373)	35.5 (8.23)	437 (166)	22500 (10100)
200 mg md	1	8	27.3 (6.79)	2.94 (1.47)	284 (64.8)				
	7	8	43.5 (10.8)	3.31 (1.58)	627 (164)	2.22 (0.272)	47.3 (24.9)	339 (90.4)	23200 (13200)

Md multiple dose
h hour
N no. of subjects with PK result

(Source: Table 10 in Applicant's Study Report RAD1901-001)

The arithmetic mean Tmax after single dosing with elacestrant under fasted conditions was between 1.64 and 3.93 h post-dose and was similar to Tmax after multiple dosing on Day 7 (between 0.97 – 3.31 h).

After 7 days of dosing with 10 to 173 mg elacestrant, accumulation was observed, with accumulation Rac values ranging between 1.86 and 2.22 across the dose range studied. After single dosing with elacestrant, the half-life ranged between 27.4 and 32.5 h and tended to increase after multiple dosing, ranging between 31.1 and 47.3 h.

According to the exploratory statistical analysis, the SAD part of the study indicated dose proportionality for AUC_{0-inf} and Cmax values at dose levels up to 50 mg and a more than dose proportional increase at dose levels of more than 50 mg. Data for AUC_{0-last} showed a more than dose proportional increase across the dose range studied (90% CI interval of the estimated slopes >1, Table 35). The MAD part of the study showed dose proportionality at dose levels up to 25 mg QD and a more than dose proportional increase at dose levels higher than 25 mg QD for both $AUC_{0-\tau}$ and Cmax (90% CI of the estimated slopes was >1, Table 36).

Table 35: Summary results of Exploratory Statistical Analysis of Dose Proportionality of SAD Part

dose range	parameter	Day	N	estimate slope	90% confidence interval	
					lower limit	upper limit
1-10 mg	$AUC_{0\text{-}inf}$	1	6^	--	--	--
	$AUC_{0\text{-}last}$	1	7^	1.64	1.11	2.16
	C_{max}	1	8^	0.99	0.68	1.30
1-25 mg	$AUC_{0\text{-}inf}$	1	12^	0.99	0.36	1.61
	$AUC_{0\text{-}last}$	1	13^	1.40	1.09	1.72
	C_{max}	1	14^	1.03	0.87	1.20
1-50 mg	$AUC_{0\text{-}inf}$	1	18^	0.99	0.72	1.27
	$AUC_{0\text{-}last}$	1	19^	1.28	1.08	1.48
	C_{max}	1	20^	1.03	0.92	1.14
1-100 mg	$AUC_{0\text{-}inf}$	1	24^	1.25	1.07	1.44
	$AUC_{0\text{-}last}$	1	25^	1.37	1.23	1.51
	C_{max}	1	26^	1.13	1.04	1.22
1-200 mg	$AUC_{0\text{-}inf}$	1	30^	1.34	1.21	1.47
	$AUC_{0\text{-}last}$	1	31^	1.40	1.30	1.50
	C_{max}	1	32^	1.21	1.13	1.28

^ Subject 8 excluded, due to emesis at 1.17 h after dosing

-- no result

Estimation of the slope of the logarithmically transformed parameter values vs logarithmically transformed dose values

Model: log(Y) = log(a) + b*log(X)

A slope (b) of 1 (i.e., a 95% confidence interval containing 1 means that no evidence of deviation from dose proportionality was found

(Source: Table 11 in Applicant's Study Report RAD1901-001)

Table 36: Summary results of Exploratory Statistical Analysis of Dose Proportionality of MAD Part

dose range	parameter	day	N	estimate slope	90% confidence interval	
					lower limit	upper limit
10-25 mg	$AUC_{0-\tau}$	1	13^	1.17	0.84	1.51
		7	14	1.28	0.90	1.65
	C_{max}	1	13^	1.15	0.85	1.45
		7	14	1.28	0.98	1.57
10-50 mg	$AUC_{0-\tau}$	1	21^	1.30	1.14	1.47
		7	22	1.28	1.11	1.45
	C_{max}	1	21^	1.35	1.21	1.50
		7	22	1.21	1.07	1.35
10-100 mg	$AUC_{0-\tau}$	1	29^	1.34	1.22	1.45
		7	30	1.37	1.24	1.49
	C_{max}	1	29^	1.34	1.24	1.43
		7	30	1.36	1.25	1.47
10-200 mg	$AUC_{0-\tau}$	1	37^	1.34	1.26	1.41
		7	38	1.38	1.29	1.46
	C_{max}	1	37^	1.34	1.28	1.41
		7	38	1.35	1.27	1.43

^ subject 48 excluded, due to emesis at 0.95 h after dosing

Estimation of the slope of the logarithmically transformed parameter values vs logarithmically transformed dose values

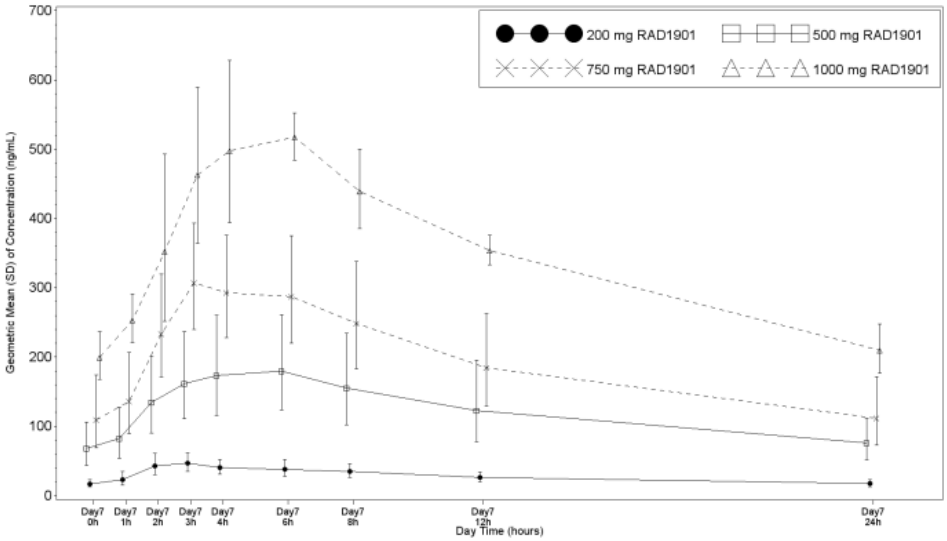
Model: log(Y) = log(a) + b*log(X)

A slope (b) of 1 (i.e., a 95% confidence interval containing 1 means that no evidence of deviation from dose proportionality was found

(Source: Table 12 in Applicant's Study Report RAD1901-001)

Elacestrant PK following multiple dose administration in healthy post-menopausal women was explored in the study RAD1901-004 in the dose range 173 mg- 863 mg. Geometric mean plasma concentration-time profiles of elacestrant are shown in Figure 21 and summary statistics of elacestrant PK parameters in plasma is reported in Table 37.

Figure 21: Geometric Mean Plasma Concentration-Time Profiles of elacestrant (Linear scale)



(Source: Figure 1 in Applicant's Study Report RAD1901-004)

Table 37: Summary Statistics of Pharmacokinetic Parameters for elacestrant in Plasma

Parameter	Statistic	200 mg (N=15)	500 mg (N=11)	750 mg (N=6)	1000 mg (N=3)
C_{max} (ng/mL)	Mean	51.6	209	328	543
	SD	14.5	72.7	68.6	60.5
	Geo-Mean	49.8	197	322	540
	Median	49.4	214	321	545
	Min, Max	30.6, 85.5	105, 316	248, 420	481, 602
	Q1-Q3	(42.3-56.4)	(135-266)	(279-380)	(481-602)
t_{max} (h)	Mean	3.41	4.46	3.33	4.33
	SD	1.18	1.57	0.516	1.53
	Median	3.00	4.00	3.00	4.00
	Min, Max	2.00, 6.00	2.00 - 6.02	3.00, 4.00	3.00, 6.00
	Q1-Q3	(3.00-4.00)	(3.00-6.00)	(3.00-4.00)	(3.00-6.00)
$AUC_{0\text{-}tau}$ (h*ng/mL)	Mean	695	3140	4810	8327
	SD	200	1195	1522	911
	Geo-Mean	670	2927	4614	8292
	Median	684	3439	4727	8753
	Min, Max	418, 1181	1562, 5460	3209, 7183	7281, 8947
	Q1-Q3	(533-812)	(1856-3878)	(3275-5738)	(7281-8947)
$t_{1/2}$ (h)	Mean	38.6	37.5	38.6	42.6
	SD	5.29	2.84	4.12	5.88
	Geo-Mean	38.3	37.5	38.4	42.3
	Median	38.3	37.4	38.0	39.7
	Min, Max	27.7, 51.4	33.8, 41.3	34.6, 46.4	38.7, 49.4
	Q1-Q3	(36.1-41.1)	(34.8-40.4)	(35.7-38.8)	(38.7-49.4)

Geo-Mean: geometric mean; Min: minimum; Max: maximum; Q1-Q3: interquartile range; SD: standard deviation.

(Source: Table 12 in Applicant's Study Report RAD1901-004)

Following multiple dosing with elacestrant at doses of 200 to 1000 mg administered once daily for 7 days, the median Tmax ranged between 3 and 4 h post-dose and was independent of dose

(Table 38). Geometric mean Cmax and $AUC_{0\text{-}tau}$ at steady state of elacestrant indicated that the systemic exposure increased with dose in a more than dose proportional manner over the dose range tested. These results are supported by the exploratory analysis of dose proportionality (slope of power model). For dose-normalized Cmax and $AUC_{0\text{-}tau}$, point estimates of 1.46 (90% CI: 1.32 - 1.59) and 1.53 (90% CI: 1.38 - 1.68), respectively, were calculated, and for both parameters the lower limit of the 90% CI stayed above the limit of 1.00 for dose proportionality (Table 38)

Table 38: Exploratory Analysis of Dose Proportionality

			90% Confidence Interval	
Parameter	**Slope**	**Standard Error**	**Lower Limit**	**Upper Limit**
$AUC_{0\text{-}tau}$	1.46	0.09	1.32	1.59
C_{max}	1.53	0.08	1.38	1.68

Using the power model: parameter = a*dose^b → log(parameter) = slope*log(dose)+intercept [+error]
Slope (b) and 90% confidence interval (CI) determined with the PROC REG procedure. A slope of 1 (i.e., a 90% CI containing 1.00) means that no evidence of a deviation from dose proportionality was found.

(Source: Table 13 in Applicant's Study Report RAD1901-004)

The FDA's Assessment:

FDA agrees with the Applicant's position.

19.4.3. Population PK Analysis

19.4.3.1. Executive Summary

The FDA's Assessment:

The Applicant submitted a population PK report entitled "Population Pharmacokinetic and Exposure Response Analysis for Elacestrant" to support the application of elacestrant for the treatment of women and men with mBC. The population PK model in this report was developed using data from multiple Phase I studies and one Phase 3 study (RAD1901-308). With derived exposures, exposure-response analyses were conducted to explore the relationships between elacestrant exposure and efficacy and safety.

The final PopPK model was a two-compartment model with linear elimination and first-order absorption (Ka) with a lag time (Tlag). The effect of dose on relative bioavailability (F1) was included as part of the structural model. Apart from the estimated allometric effect of baseline body weight on clearance and volume terms, CL/F was also found to decrease with age and Q/F to be higher for male subjects. None of those covariate effects suggests any dose adjustments are necessary. The final model was adequate to characterize the PK profile of elacestrant in healthy volunteers or patients with mBC. The Applicant's population PK analysis is acceptable.

19.4.3.2. PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		● To perform a PopPK analysis of elacestrant, pooling data from prior Phase 1 studies in healthy men and postmenopausal women and in women with mBC, and Phase 3 study RAD1901-308 in postmenopausal women and men with mBC: ● To develop an interim PopPK model to describe the PK of elacestrant using data from prior Phase 1 studies from both healthy men and postmenopausal women and subjects with mBC and explore intrinsic and extrinsic factors that are predictive of the PK variability; ● To evaluate the external predictability of the interim PopPK model by applying it to data in subjects with mBC from the Phase 3 Study RAD1901-308; ● To update and finalize the PopPK model, incorporating data from the Phase 3 Study RAD1901-308 and obtain measures of elacestrant exposure.
Study Included		RAD1901-004, RAD1901-109, RAD1901-110, RAD1901-112, RAD1901-113, RAD1901-114 and RAD1901-115, RAD1901-005 and RAD1901-308
Dose(s) Included		1, 10, 25, 50, 100, 200, 400, 500, 750, and 1000 mg
Population Included		Healthy postmenopausal women and men, women and men with metastatic breast cancer
Population Characteristics	General	Age: 59 yrs (24 - 89 yrs, 32% subj >=65 yrs, 9.6% subj >=75 yrs); Body weight: 72.4 kg (41.3 – 143 kg) Gender: male n = 86 (19%) Race: ● Caucasian = 353 (79%), ● Black n = 22 (5%), ● Asian n = 17 (4%), ● American Indian or Alaska Native n = 1 (0%), ● Multiple n = 6 (1%) ● Other n = 1 (0%) ● Missing n = 47 (11%)
	Organ Impairment	Albumin median : 43 g/L (range:29.9 – 54.0 g/L) Alkaline phosphatase median : 94.3 U/L (range: 18 – 663 U/L) Alanine aminotransferase median: 21.4 U/L (range: 7.00 – 295 U/L) Aspartate aminotransferase median: 24 U/L (range: 11.0 – 169 U/L) Bilirubin median: 0.460 mg/dL (range: 0.130 - 1.60 mg/dL) Creatinine median: 0.790 mg/dL (range 0.400 - 1.85 mg/dL) Creatinine clearance median: 92.9 mg/dL (28.5 – 430 mg/dL)
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ		22 (0.5%) of pre-/post-dose BLQ

Sampling Schedule	Rich Sampling	Study RAD1901-001: SAD part: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 h post-dose MAD part: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 h post-dose on Days 1 and 7; on Day 8 at 36 h and Day 9 at 48 h; trough samples pre-dose on Days 3, 4, 5 and 6. For the 86 and 173 mg QD, a final trough sample during the follow-up visit. Study RAD1901-004: Pre-dose at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 144 and 192 h post-dose on Day 7, and at follow-up. In addition, trough samples were obtained pre-dose on Days 5 and 6. Study RAD1901-109: Pre-dose and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 144, and 192 h after each single-dose administration for each period Study RAD1901-110: Pre-dose on Days 1 through 14. On Days 7 and 14: pre-dose, and at 1, 2, 3, 4, 6, 8, 12, and 24 h after dosing Study RAD1901-112: Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 96, 144, and 192 h after each single-dose administration for each period Study RAD1901-113: Pre-dose and at 1, 2, 3, 4, 4.5, 5, 6, 8, 12, 24, 48, 96, 144, and 192 h after each single-dose administration of elacestrant for each period Study RAD1901-114: Pre-dose and at 1, 2, 3, 4, 4.5, 5, 6, 8, 12, 24, 48, 96, 144, and 192 h after single-dose administration of elacestrant for Treatments A and C Study RAD1901-115: Pre-dose and at 1, 2, 3, 4, 4.5, 5, 6, 8, 12, 24, 48, 96, 144, and 192 h after single-dose administration of elacestrant for each period Study RAD1901-116: Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, 96, 144, and 192 h for each period
	In ITT Population	Study RAD1901-005: For capsule QD dosing, pre-dose and 4 h (± 30 min) post-dose on C1D8, pre-dose C1D28, then pre-dose every 28 days for 3 cycles. For tablet QD dosing, pre-dose and 4 h (± 30 min) post-dose on C1D8, 24 h (± 30 min) post C1D8 (pre-dose C1D9), pre-dose C1D28 then pre-dose every 28 days for 6 cycles Study RAD1901-106: Pre-dose and 4 h (± 30 min) post-dose on C1D1, and pre-dose on Days 14 (± 3 days) and 28 (± 3 days) of C1 and on Day 28 (± 3 days) of subsequent cycles. Study RAD1901-308: Pre-dose (pre-treatment) and 4 h post-dose on C1D1, pre-dose (C_{trough}) and 4 h post-dose on C1D15, and pre-dose (C_{trough}) on C2D1.
Covariates Evaluated	Static	Albumin, phosphatase alkaline, aspartate aminotransferase, total bilirubin, creatinine clearance, age, gender, highly plasma protein-bound drugs (HIBIND), and omeprazole or other stomach acid-reducing agents (ALTPH)
	Time-varying	Not applicable

<table>
<tr><th>Final Model</th><th>Summary</th></tr>
<tr><td>Software and Version</td><td>
NONMEM version 7.4.3 installed on a computer running under Windows 10 Professional (64 bit) with Intel Fortran Compiler (version 8) and run via PDx Pop (version 5.2.2) was used for the population PK analysis
Dataset creation, data manipulation, data presentation, construction of plots, Cox, parametric survival models and logistic regression analyses were carried out using R version 4.1.2 (the R Foundation for Statistical Computing).
</td></tr>
<tr><td>Model Structure</td><td>

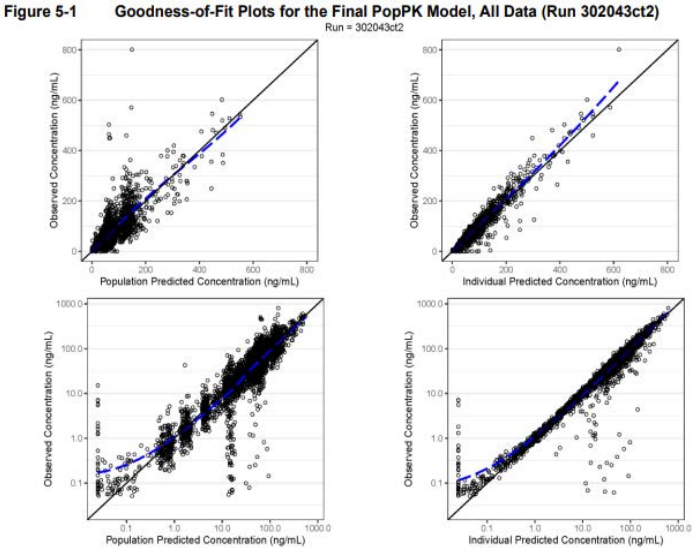
Two-compartment model with linear elimination, parameterized in terms of CL/F, Vc/F, Q/F, Vp/F, Ka, and Tlag.
An effect of dose on F1, an effect of baseline body weight on CL/F, Vc/F, Q/F and Vp/F were estimated.
The effects of age on CL/F and gender on Q/F were estimated.
IIV was estimated on all parameters and the Ω matrix had a form of 2 separate blocks: 4 x 4 for CL/F, Vc/F, Q/F and Vp/F) and 2 x 2 for Ka and Tlag.

Residual variability included a proportional and an additive term.
</td></tr>
<tr><td>Model Parameter Estimates</td><td>
Parameter Estimares of the Final PopPK model
<table>
<tr><th rowspan="2">Parameter (Units)</th><th colspan="4">NONMEM Estimates</th></tr>
<tr><th>Point Estimate</th><th>%RSE</th><th>95% CI</th><th>IIV CV%[a] [Shr]</th></tr>
<tr><td>CL/F (L/hr)</td><td>186</td><td>2.17</td><td>178 - 194</td><td>43.5 [2.29]</td></tr>
<tr><td>Vc/F (L)</td><td>422</td><td>17.9</td><td>297 - 599</td><td>87.5 [29.1]</td></tr>
<tr><td>Q/F (L/hr)</td><td>231</td><td>17.2</td><td>165 - 324</td><td>33.4 [14.1]</td></tr>
<tr><td>Vp/F (L)</td><td>5411</td><td>5.37</td><td>4871 - 6011</td><td>33.7 [9.81]</td></tr>
<tr><td>Ka (1/hr)</td><td>0.0997</td><td>14.4</td><td>0.0752 - 0.132</td><td>10.8 [62.2]</td></tr>
<tr><td>Tlag (hr)</td><td>0.812</td><td>3.36</td><td>0.760 - 0.867</td><td>33.9 [60.6]</td></tr>
<tr><td>pCLBWT[b]</td><td>0.390</td><td>28.6</td><td>0.172 - 0.609</td><td></td></tr>
<tr><td>pVcBWT[b]</td><td>0.493</td><td>70.6</td><td>-0.189 - 1.17</td><td></td></tr>
<tr><td>pQBWT[b]</td><td>1.16</td><td>15.6</td><td>0.803 - 1.51</td><td></td></tr>
<tr><td>pVpBWT[b]</td><td>1.03</td><td>12.9</td><td>0.770 - 1.29</td><td></td></tr>
<tr><td>pF1DOSE[c]</td><td>0.474</td><td>12.9</td><td>0.355 - 0.594</td><td></td></tr>
<tr><td>pCLAGE[d]</td><td>-0.411</td><td>20.5</td><td>-0.576 - -0.246</td><td></td></tr>
<tr><td>fQSEX[e]</td><td>1.28</td><td>4.95</td><td>1.16 - 1.41</td><td></td></tr>
<tr><td>Residual variability</td><td></td><td></td><td></td><td>CV% or SD</td></tr>
<tr><td>σ^2_{prop}</td><td>0.0409</td><td>5.84</td><td>0.0362-0.0455</td><td>20.2</td></tr>
<tr><td>σ^2_{add}</td><td>0.0139</td><td>25.3</td><td>0.00702-0.0208</td><td>0.118</td></tr>
<tr><td></td><td></td><td></td><td></td><td>covariance</td></tr>
<tr><td>ω^2_{CL}</td><td>0.173</td><td>7.80</td><td>0.147-0.200</td><td></td></tr>
<tr><td>Covariance $\omega^2_{CL} + \omega^2_{Vc}$</td><td>0.00307</td><td>995</td><td>-0.0568-0.0629</td><td>0.00978</td></tr>
<tr><td>ω^2_{Vc}</td><td>0.569</td><td>25.4</td><td>0.286-0.852</td><td></td></tr>
<tr><td>Covariance $\omega^2_{CL} + \omega^2_{Q}$</td><td>0.112</td><td>14.8</td><td>0.0797-0.145</td><td>0.807</td></tr>
<tr><td>Covariance $\omega^2_{Vc} + \omega^2_{Q}$</td><td>0.0319</td><td>216</td><td>-0.103-0.167</td><td>0.126</td></tr>
<tr><td>ω^2_{Q}</td><td>0.112</td><td>18.6</td><td>0.0711-0.152</td><td></td></tr>
<tr><td>Covariance $\omega^2_{CL} + \omega^2_{Vp}$</td><td>0.123</td><td>12.4</td><td>0.0933-0.153</td><td>0.879</td></tr>
<tr><td>Covariance $\omega^2_{Vc} + \omega^2_{Vp}$</td><td>0.00669</td><td>559</td><td>-0.0667-0.08</td><td>0.0263</td></tr>
<tr><td>Covariance $\omega^2_{Q} + \omega^2_{Vp}$</td><td>0.11</td><td>16.4</td><td>0.0749-0.146</td><td>0.979</td></tr>
<tr><td>ω^2_{Vp}</td><td>0.114</td><td>14.9</td><td>0.0804-0.147</td><td></td></tr>
<tr><td>ω^2_{Ka}</td><td>0.0116</td><td>56.3</td><td>-0.00119-0.0244</td><td></td></tr>
<tr><td>Covariance $\omega^2_{Ka} + \omega^2_{Tlag}$</td><td>0.0111</td><td>83.4</td><td>-0.00705-0.0293</td><td>0.305</td></tr>
<tr><td>ω^2_{Tlag}</td><td>0.115</td><td>21.4</td><td>0.0667-0.163</td><td></td></tr>
</table>
Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate*100, 95% CI= 95% confidence interval on the parameter, CV = Coefficient of variation of proportional error (=[σ²prop]^0.5*100), SD = standard deviation of additive error (=[σ²add]^0.5), σ²prop = proportional component of the residual error model, σ²add = additive component of the residual error model.

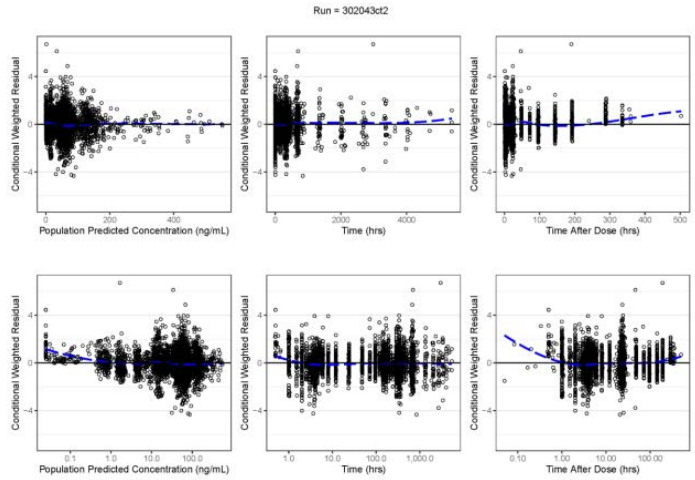
(Source: Table 5-7 in Applicant's Study Report 3882-0012)
</td></tr>
<tr><td>Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)</td><td>Not applicable</td></tr>
<tr><td>BLQ for Parameter Accuracy</td><td>BLQ PK data were disregarded</td></tr>
</table>

GOF, VPC	The GOF plots indicate that the model provided a satisfactory description of the overall elacestrant concentration data following single and multiple administration for doses ranging from 200 to 1000 mg across formulations, for both healthy subjects and patients with mBC.

Figure 5-1 Goodness-of-Fit Plots for the Final PopPK Model, All Data (Run 302043ct2)



Top: Linear xy axis; Bottom: Logarithmic xy axis. Concentration of 0 set to ½ LLOQ.
Black solid line: Identity line; Blue dashed line: Local regression (Loess) smoothing line;
Source: 302043ct2.tab, GoF Diagnostics & Eta 302043ct2_v1.R



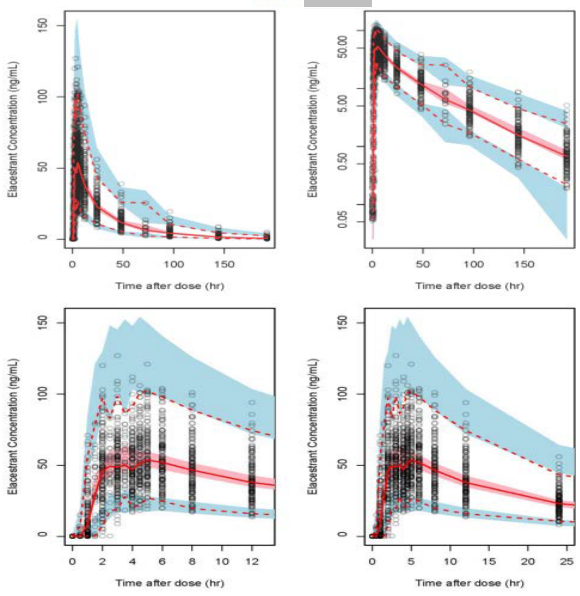
Top: Linear xy axis; Bottom: Logarithmic x axis.
Blue dashed line: Local regression (Loess) smoothing line;
Source: 302043ct2.tab, GoF Diagnostics & Eta 302043ct2_v1.R,

(Source: Figure 5-1 in Applicant's Study Report 3882-0012)

The final model was also evaluated by performing a VPC. VPC plots for the final model stratified by regimen (single and multiple dose) and by health status (healthy subjects / patients with mBC) confirm that the final model provided a satisfactory description of elacestrant concentrations. No substantial systematic bias with respect to either nominal time or elacestrant concentration level was apparent. Also, the 2.5th and 97.5th percentiles of observed concentrations mostly lie within the 95% prediction intervals for the 2.5th and 97.5th percentiles for the predicted concentrations, supporting the conclusion that the final model adequately described both the central tendency and the variability of the observed data.

Figure 5-2 Visual Predictive Check – Healthy Subjects Single 400 mg Dose

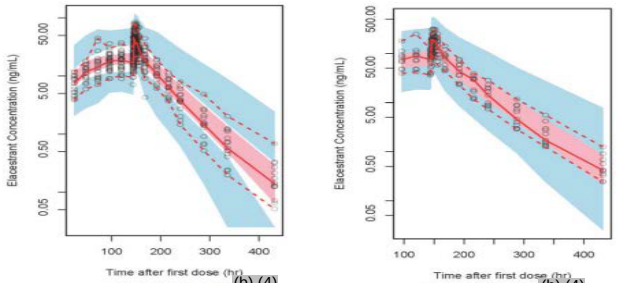
Tablets (b) (4)



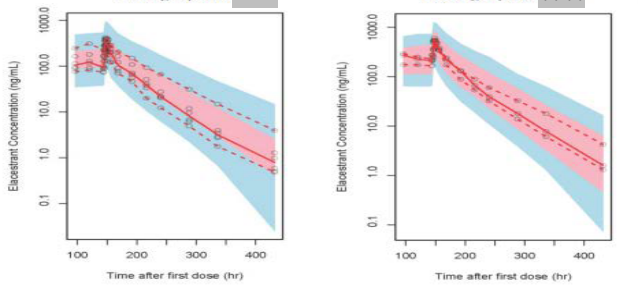
Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations.
Source: 302043ct2vpc.tab; CI-VPC_302043ct2_hv_v1.R; CI-302043ct2_hv_v1.pdf

Figure 5-3 Visual Predictive Check – Healthy Subjects Multiple QD Doses

200 mg capsules (b) (4) and tablets (b) (4) 500 mg capsules (b) (4)

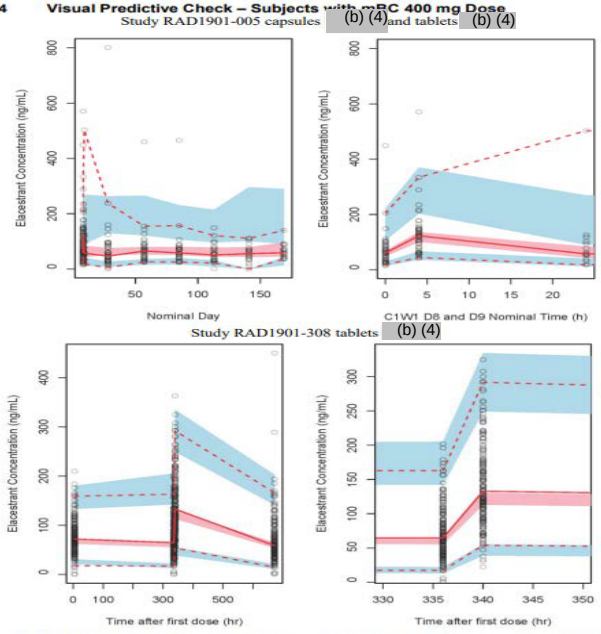


750 mg capsules (b) (4) 1000 mg capsules (b) (4)



Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations.
Source: 302043ct2vpc.tab; CI-VPC_302043ct2_hv_v1.R; CI-302043ct2_hv_v1.pdf

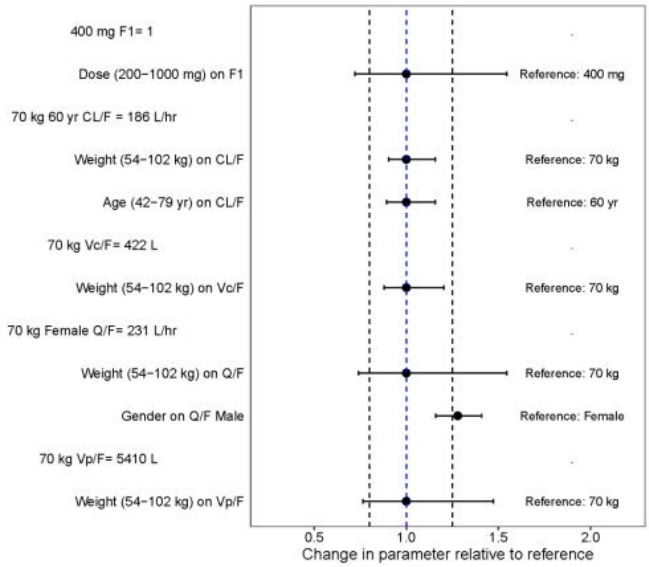
Figure 5-4 **Visual Predictive Check – Subjects with mBC 400 mg Dose**



Solid Line: Median of Observed Concentrations; Dashed Lines: 2.5th and 97.5th percentile of observed Concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 2.5th and 97.5th percentiles of Predicted Concentrations.

Source: 302043ct2vpc.tab; CI-VPC_302043ct2_005.R; CI-302043ct2_005.pdf; CI-VPC_302043ct2_308.R; CI-302043ct2_308.pdf

(Source: Figure 5-3, 5-3, 5-4 in Applicant's Study Report 3882-0012)

Significant Covariates and Clinical Relevance	The effect of dose on F1 using a power model was included as part of the structural model. Effects of baseline body weight on CL/F, Vc/F, Q/F and Vp/F were also included, with the additional effect of age on CL/F and gender on Q/F. Forest plot for covariates effects for the final PopPK model shows that most of the changes in PK parameters due to covariate effects are within the 0.80 to 1.25 range of clinical insignificance. **Figure 5-5 Forest Plot for Covariate Effects in the Final PopPK Model (302043ct2)**  Dashed black lines at 0.80 and 1.25 Source: 302043ct2.cnv, RAD1901_forestplot_43ct2_v1.R, Forestplot_302043ct2_v1.pdf *(Source: Figure 5-5 in Applicant's Study Report 3882-0012)* In addition, box plots of nominal AUCss for quartiles of baseline body weight, for different age groups and gender indicate that there are no clinically significant differences in exposures among the different groups (see Section 6.2.2).
Analysis Based on Simulation (optional)	None

Labeling Language	Description
	There were no clinically significant differences in the pharmacokinetics of elacestrant based on age (24 to 89 years), sex, and body weight (41 to 143 kg).

12.3 PK	Pharmacokinetics The elacestrant oral bioavailability is approximately 10%. Steady state is reached by Day 6 following once daily dosing. C_{max} and AUC increase slightly more than proportional to dose for doses ≥ 50 mg (salt form). <u>Absorption</u> Following oral administration, elacestrant was rapidly absorbed, reaching t_{max} within 1-4 hours. *Effect of Food* Administration of elacestrant 345mg tablet with a heavy meal increased C_{max} by 42% and increased $AUC_{0-\infty}$ by 22%, respectively, compared to fasted administration. (b) (4) <u>Distribution</u> The estimated volume of distribution was 422 L for central volume (Vc/F) and 5411 L for peripheral volume (Vp/F). Plasma protein binding of elacestrant is >99% and independent of concentration and hepatic impairment status. Elacestrant penetrates the blood brain barrier in a dose-dependent manner. <u>Elimination</u> The half-life of elacestrant is predicted to be approximately 30 hours. The mean (% CV) clearance of elacestrant is predicted to be 186 L/hr (43.5%). *Metabolism* Elacestrant is primarily metabolized by CYP3A4 with a potential small contribution by CYP2A6 and CYP2C9. Elacestrant exposure in plasma represented only 2%-3% of plasma total radioactivity, suggesting the presence of circulating metabolites. Only 1 metabolite (4 [2 (ethylamino)ethyl] benzoic acid glucuronide) represented > 10% of radiolabeled components in plasma. *Excretion* Following a single oral dose of 345 mg radiolabeled elacestrant, 81.5% (majority as unchanged) was recovered in feces and 7.53% (trace as unchanged) was recovered in urine. Elacestrant renal clearance is very low (≤ 2.3 mL/min) and it was eliminated by oxidative metabolism and fecal excretion. <u>Specific Populations</u> No clinically significant differences in the pharmacokinetics of elacestrant were predicted based on age (24 to 89 years), sex, and body weight (41 to 143 kg). The population PK analysis confirmed the negligible contribution of renal excretion on elacestrant elimination. *Hepatically Impaired* The C_{max} and AUC values were similar between subjects in the mild hepatic impairment group (Child-Pugh A) and the normal hepatic function group. There were significant increases in AUC_{0-t} (76%) and AUC_{0-inf}(83%) in the moderate hepatic impairment group (Child-Pugh B) compared to the normal hepatic function group. The C_{max} values were similar between the normal and moderate impairment groups. The geometric mean $t_{1/2}$ tended to increase with increasing severity of hepatic impairment. Elacestrant has not been studied in subjects with severe hepatic impairment (Child-Pugh C). In physiologically-based pharmacokinetic modeling, elacestrant exposure in subjects with severe hepatic impairment (Child-Pugh C) exhibited a 3.02-fold increase in AUC and a 1.88-fold increase in C_{max} than subjects with normal hepatic function. No dose adjustment is required for patients with mild hepatic impairment whereas elacestrant dose should be reduced to 258 (b) (4) mg QD in patients

	with moderate (b) (4) hepatic impairmen (b) (4) Drug Interaction Studies *Effect of Strong CYP3A4 Inhibitors on Elacestrant (Clinical Study):* Coadministration of ORSERDU with a strong CYP3A4 inhibitor (e.g., itraconazole) increases elacestrant total plasma exposure by 5.27-fold. *Effect of Moderate or Weak CYP3A4 Inhibitors on Elacestrant (Model-Based-Approach):* Coadministration of elacestrant (single dose 345 mg) with the following CYP3A4 inhibitors predicted the following effects: Moderate inhibitors (i.e., fluconazole and erythromycin) will increase elacestrant AUC between 2- and 5-fold; Weak inhibitors (i.e., cimetidine), will increase elacestrant AUC < 2-fold. *Effect of Strong CYP3A4 Inducers on Elacestrant (Clinical Study):* Coadministration of ORSERDU with a strong CYP3A4 inducer (e.g., rifampin) decreases elacestrant total plasma exposure by 86%. *Effect of Moderate CYP3A4 Inducers on Elacestrant (Model-Based Approach):* Coadministration of elacestrant (single dose 345 mg) with moderate CYP3A4 inducer, efavirenz (600 mg QD) is predicted to decrease elacestrant AUC between 50% and 80%. *Effect of Gastric Acid Reducing Agents on Elacestrant (Clinical Study):* Use of omeprazole and other commonly used acid-reducing agents had no effect on elacestrant PK. *Effect of Highly Protein-Bound Drugs on Elacestrant (Clinical Study):* Use of warfarin and other commonly used drugs had no impact on elacestrant PK. *P-gp and BCRP Substrates (Clinical Study):* Use of elacestrant with digoxin slightly increases digoxin exposure by 27% for C_{max} and 13% for AUC. Use of elacestrant with rosuvastatin slightly increases rosuvastatin exposure by 45% for C_{max} and 23% for AUC. *Effect of Elacestrant on CYP Enzymes (in vitro Studies):* Elacestrant does not induce cytochromes P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP3A in human hepatocytes. Elacestrant does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A at therapeutic plasma concentrations. Elacestrant is not a substrate of efflux transporters (e.g., P-gp), but it is potentially a relevant inhibitor of P-gp and BCRP. Elacestrant is not a substrate or clinically relevant inhibitor of the renal transporters OAT1, OAT3, OCT2, MATE1, and MATE2-K, or the hepatic transporters OCT1, OATP1B1, and OATP1B3. Elacestrant is a substrate for OATP2B1, but it does not inhibit this transporter.

The FDA's Assessment:

The Applicant's population PK analysis is acceptable. Overall, the final population PK model appeared adequate to characterize the PK profile of elacestrant as indicated in the Applicant's goodness-of-fit plots and VPC plots. The reviewer was able to repeat and verify the Applicant's analysis with no significant discordance identified. The reviewer agrees with the sponsor's conclusions regarding the effect of covariates on elacestrant exposure. No formulations effect was found to be statistically significant on elacestrant PK. FDA accepted the labeling language in 12.3 related to PK parameters and effect of covariates (age, sex, and body weight) estimated by population PK analysis.

19.4.4. Exposure-Response Analysis

19.4.4.1. ER (Efficacy) Executive Summary

The FDA's Assessment:

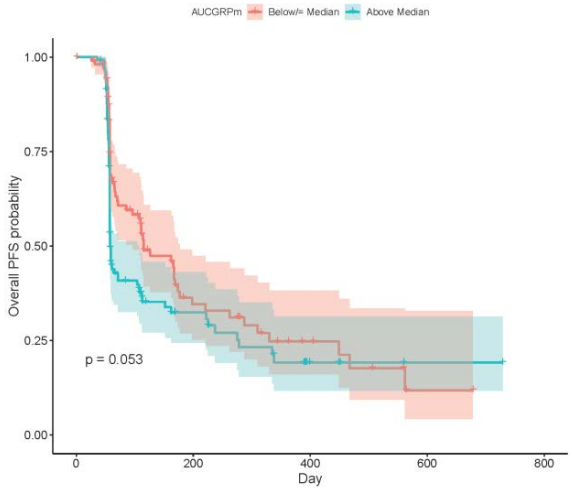
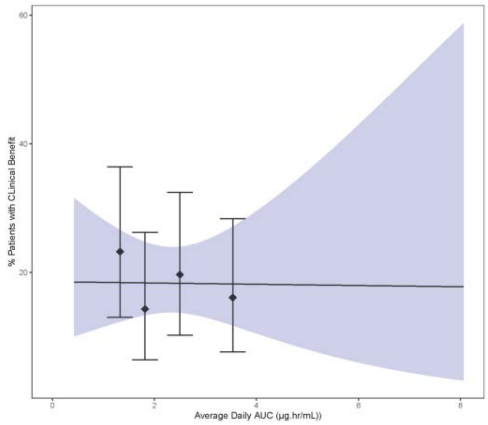
FDA deemed the ER analysis for efficacy was limited due to the narrow exposure from one dose in the pivotal study. The Applicant conducted exposure-response analysis for efficacy and safety using data from Study RAD1901-308. No significant relationships between elacestrant exposure and PFS and clinical benefit rate were identified. However, the results of this analysis should be interpreted with caution. The E-R relationship for efficacy was not fully characterized as the analysis was limited by the range of therapeutic exposure. Only one dose 345 mg was tested in the pivotal study RAD1901-308. Dose modifications could also confound the results of these ER analyses.

19.4.4.2. ER (Efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		To perform E-R analyses of the efficacy endpoints of Progression Free Survival (PFS) and Clinical Benefit (CB) rate from Study RAD1901-308.
Study Included		Study RAD1901-308
Endpoint		Primary: PFS Secondary: Clinical Benefit (CB)
No. of Patients (total, and with individual PK)		Total: 232 PFS: 232 CB: 224
Population Characteristics (Table XX)	General	Age: median: 63 yrs (range 24 – 89 yrs) Weight: median: 70 kg (42 – 135 kg) Gender: male n = 5 (2%) Race: Caucasian: n = 163 (70%) ● Black: n = 5 (2%) ● Asian: n = 16 (7%) ● Other: n = 1 (0%) ● Missing: n = 47 (20%)
	Pediatrics (if any)	Not applicable
Dose(s) Included		345 mg QD
Exposure Metrics Explored (range)		AUCss (µg*hr/mL): median = 2.19 (range: 0.461-8.47) AUCav (µg*hr/mL): median = 2.06 (range: 0.429-8.07) AUCav PFS (µg*hr/mL): median = 2.03 (range: 0.00-8.07) *AUCss: nominal steady-state daily AUC (Dose/CL/F); AUCav: average daily AUC derived from cumulative AUC until the last dose; AUCav PFS: average daily AUC derived from cumulative AUC until PFS*
Covariates Evaluated		Visceral disease; *ESR1* mutational status; Prior fulvestrant; Prior aromatase inhibitors; Lines of therapy.

Model Structure	Kaplan-Meier plots of PFS, stratified by average daily AUC group (≤ median, > median) Based on the logistic regression analyses, the predicted probabilities of CB versus AUCav
Model Parameter Estimates	**Table 5-9 Summary of Non-Parametric Survival Analyses with Average Daily AUC** Variable / Models / Estimate / SE / P-value / Hazard Ratio / L95% / U95% *Categorical AUCav* *PFS ~AUCav* Above Median 0.337 0.170 0.047 1.401 1.005 1.953 *PFS ~AUCav* 1stQ-2ndQ 0.192 0.255 0.453 1.211 0.734 1.998 2ndQ-3rdQ 0.373 0.251 0.137 1.453 0.889 2.375 Above 3rdQ 0.506 0.247 0.041 1.658 1.022 2.692 *Continuous AUCav* *PFS ~AUCav* AUCav 0.112 0.076 0.138 1.119 0.964 1.298 *PFS* *~AUCav* AUCav 0.144 0.083 0.081 1.155 0.982 1.359 *+ECOG* Score 1 -0.200 0.186 0.283 0.819 0.568 1.180 *+VISC* Yes 0.387 0.191 0.042 1.473 1.013 2.140 *+ESRSTATN* ESR1-mut -0.308 0.174 0.076 0.735 0.523 1.033 *+PRFULVFL* Yes 0.164 0.263 0.532 1.178 0.704 1.972 *+PRAIFL* Yes 0.176 0.282 0.534 1.192 0.685 2.073 *+ETCHLINE* 2 Lines 0.213 0.196 0.278 1.237 0.842 1.817 *+ETCHLINE* 3 Lines 0.816 0.293 0.005 2.262 1.275 4.014 VISC=Prior Visceral Disease; ESRSTATN= ESR1 mutational status; PRFULVFL: prior fulvestrant; PRAIFL= prior aromatase inhibitors; ETCHLINE= Lines of therapy; SE=standard error, CI=confidence interval Source: RAD1901-308 Survival_43v2t_v3n.R; Regression results PFS v3.xlsx **Table 5-10 Summary of Parametric Survival Analyses with Average Daily AUC** Variable / Models / Estimate / SE / P-value / Hazard Ratio / L95% / U95% *PFS ~AUCav* Intercept 5.575 0.188 <2e-16 AUCav -0.117 0.071 0.100 1.133 0.975 1.318 *PFS ~AUCav* Intercept 5.972 0.329 <2e-16 AUCav -0.145 0.073 0.047 1.181 1.001 1.392 *+ECOG* Score 1 0.267 0.162 0.099 0.737 0.512 1.061 *+VISC* Yes -0.341 0.167 0.041 1.476 1.017 2.143 *+ESRSTATN* ESR1-mut 0.361 0.152 0.017 0.663 0.471 0.931 *+PRFULVFL* Yes -0.106 0.232 0.649 1.128 0.672 1.895 *+PRAIFL* Yes -0.271 0.240 0.258 1.363 0.796 2.335 *+ETCHLINE* 2 Lines -0.203 0.176 0.249 1.261 0.850 1.871 *+ETCHLINE* 3 Lines -0.646 0.256 0.012 2.091 1.172 3.730 VISC=Prior Visceral Disease; ESRSTATN= ESR1 mutational status; PRFULVFL: prior fulvestrant; PRAIFL= prior aromatase inhibitors; ETCHLINE= Lines of therapy; SE=standard error, CI=confidence interval, AIC= Akaike Information Criterion. Source: RAD1901-308_ERdataset_43v2t.csv; RAD1901-308 Survival_43v2t_v3n.R; Regression results PFS_v3.xlsx **Table 5-12 Odds Ratio for Clinical Benefit - Model for Average Daily AUC** Model / Variable / Estimate / SE / P-value / Odds Ratio / Lower 95% CI / Upper 95% CI / AIC *Clinical Benefit~AUCav* Intercept -1.480 0.425 0.0005 0.228 0.099 0.523 217.23 AUCav -0.007 0.166 0.968 0.993 0.718 1.374 *Clinical Benefit ~AUCav* Intercept -0.775 0.790 0.327 0.461 0.098 2.168 216.11 AUCav -0.013 0.167 0.939 0.987 0.712 1.370 *+ECOG* Score 1 0.029 0.372 0.938 1.030 0.496 2.135 *+VISC* Yes -0.966 0.372 0.009 0.381 0.184 0.789 *+ESRSTATN* ESR1-mut 0.715 0.373 0.055 2.045 0.985 4.244 *+PRFULVFL* Yes 0.050 0.568 0.930 1.051 0.345 3.199 *+PRAIFL* Yes -0.167 0.598 0.781 0.846 0.262 2.735 *+ETCHLINE* 2 Lines -0.732 0.409 0.073 0.481 0.216 1.072 *+ETCHLINE* 3 Lines -0.808 0.816 0.322 0.446 0.090 2.206 VISC=Prior Visceral Disease; ESRSTATN= ESR1 mutational status; PRFULVFL: prior fulvestrant; PRAIFL= prior aromatase inhibitors; ETCHLINE= Lines of therapy; SE=standard error, CI=confidence interval, AIC= Akaike Information Criterion. Source: RAD1901-308_ERdataset_43v2t.csv; RAD1901-308 Clinical Benefit_43v2t.R; Regression results PFS CB NAUS_v1.xlsx *(Source: Table 5-9, Table 5-10, and Table 5-12 in Applicant's Study Report 3882-0012)*
Model Evaluation	For non-parametric survival model plots of residuals were evaluated as GOF for homoscedasticity and curvature to assess potential model misspecification. For parametric survival model, box plots of deviance residuals from the null model were assessed as GOF. No trends were identified for both analyses.
Covariates and Clinical Relevance	Although some trends of survival were shown for some covariates, no statistically significant (p>0.001) differences were observed for both parametric and non-parametric models in response to treatment among subpopulations (e.g. visceral metastasis, *ESR1* mutational status, prior lines of therapy).

Simulation for Specific Population	Not applicable
Visualization of E-R Relationships	**Figure 5-7 Kaplan-Mayer Plot of PFS stratified by Average Daily AUC Group**  **Figure 5-9 Percentage of Subjects with Clinical Benefit vs. Average Daily AUC**  Source: 302043ER_43v2t.tab; RAD1901-308 Clinical Benefit_43v2t.R; RAD1901-308 CLBEN_43v2t_1.pdf *(Source: Figure 5-7 and Figure 5-9 in Applicant's Study Report 3882-0012)*
Overall Clinical Relevance for E-R	The variability in elacestrant exposure (average daily AUC) had no significant effect on the PFS hazard ratio. Average daily AUC was not a predictor of CB.

19.4.4.3. ER (Safety) Executive Summary

The FDA's Assessment:

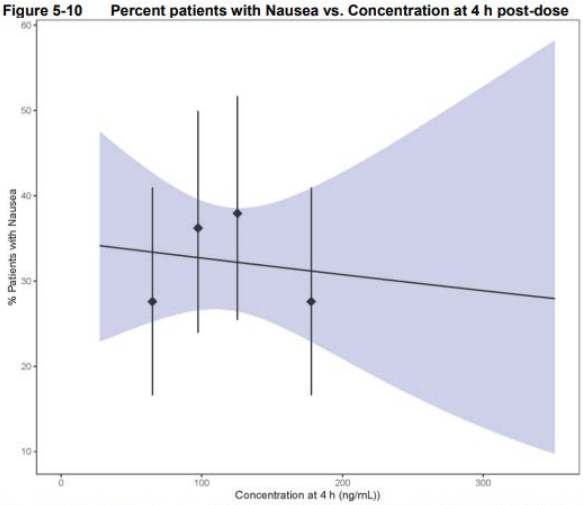
The Applicant explored the relationship between elacestrant exposure and AE of interest (Nausea) using data from pivotal study RAD1901-308. No relationship between predicted elacestrant concentrations at 4 h post-dose and first occurrence of nausea was evident. While the analysis is reasonable, the conclusion should be explained with caution, as the data only included one study and one dose level. To reach a more reliable conclusion, full analyses should be conducted with multiple studies and multiple dose levels.

19.4.4.4. ER (Safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		To perform E-R analyses of the safety endpoint AE of interest (nausea), from Study RAD1901-308.
Study Included		Study RAD1901-308
Population Included		Not applicable
Endpoint		Nausea occurrences
No. of Patients (total, and with individual PK)		Total: 232
Population Characteristics (Table XX)	General	Age: median: 63 yrs (range 24 – 89 yrs) Weight: median: 70 kg (42 – 135 kg) Gender: male n = 5 (2%) Race: ● Caucasian: n = 163 (70%) ● Black: n = 5 (2%) ● Asian: n = 16 (7%) ● Other: n = 1 (0%) ● Missing: n = 47 (20%)
	Organ impairment	Not applicable
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	Not applicable
Dose(s) Included		345 mg QD
Exposure Metrics Explored (range)		Conc4h (ng/mL): median = 108 (range: 27.5-351)
Covariates Evaluated		Not applicable
Final Model Parameters		Summary
Model Structure		Based on the logistic regression analyses, the predicted probabilities of nausea versus Conc4h.
Model Parameter Estimates		**Table 5-14 Odds Ratio for Nausea - Models for Concentration at 4 h post-dose and Covariates** Conc4h: Concentrations at 4h; VISC=Prior Visceral Disease; ESRSTATN= ESR1 mutational status; PRFULVFL: prior fulvestrant; PRAIFL= prior aromatase inhibitors; ETCHLINE= Lines of therapy; SE=standard error, CI=confidence interval, AIC= Akaike Information Criterion. Source: RAD1901-308_ERdataset_43v2t.csv; RAD1901-308 AE_43v2t.R; Regression results PFS CB NAUS_v1.xlsx *(Source: Table 5-14 in Applicant's Study Report 3882-0012)*
Model Evaluation		Not applicable
Covariates and Clinical Relevance		*ESR1* mutation, prior visceral disease, ECOG score, prior treatment with fulvestrant or aromatase inhibitors and lines of anti-estrogen therapy and chemotherapy did not appear to be predictors of the frequency of nausea occurrence.
Simulation for Specific Population		Not applicable

Model	Variable	Estimate	SE	P-value	Odds Ratio	Lower 95% CI	Upper 95% CI	AIC
Nausea~Conc4h	Intercept	-0.632	0.352	0.072	0.531	0.267	1.058	295.89
	Conc4h	-0.001	0.003	0.742	0.999	0.994	1.004	
Nausea~Conc4h	Intercept	-0.841	0.648	0.194	0.431	0.121	1.536	302.97
	Conc4h	-0.001	0.003	0.627	0.993	0.999	1.004	
+ECOG	Score 1	0.146	0.295	0.622	1.157	0.649	2.063	
+VISC	Yes	-0.009	0.310	0.978	0.991	0.540	1.820	
+ESRSTATN	ESR1-mut	-0.185	0.293	0.528	0.831	0.468	1.476	
+PRFULVFL	Yes	-0.066	0.421	0.876	0.936	0.411	2.135	
+PRAIFL	Yes	-0.067	0.462	0.884	0.935	0.378	2.312	
+ETCHLINE	2 Lines	0.719	0.321	0.025	2.052	1.094	3.849	
+ETCHLINE	3 Lines	0.119	0.552	0.829	1.127	0.382	3.322	

Visualization of E-R relationships	Figure 5-10 Percent patients with Nausea vs. Concentration at 4 h post-dose  Source: RAD1901-308_ERdataset_43v2t.csv; RAD1901-308 AE_43v2t.R; RAD1901-308 NAUSEA_43v2t_1.pdf *(Source: Figure 5-10 in Applicant's Study Report 3882-0012)*
Overall Clinical Relevance for ER	No relationship between predicted elacestrant concentrations at 4 h post-dose and first occurrence of nausea was evident.
Labeling Language	None
12.2 Pharmacodynamics	See Section 19.4.4.2

The FDA's Assessment:

The ER analysis for safety was limited. Please see ER (Safety) Executive Summary (19.4.4.3)

19.4.4.5. ER Review Issues

Please see ER (Efficacy) Executive Summary (19.4.4.1), ER (Safety) Executive Summary (19.4.4.3)

19.4.4.6. Overall Benefit-risk Evaluation

The Applicant's Position:

Elacestrant is proposed for the treatment of postmenopausal women and men with ER+/HER2- advanced or mBC who have progressed following at least 1 line of endocrine therapy. Based on the mechanism of action, nonclinical safety profile, and the experience in clinical trials to date, elacestrant may provide a significant new treatment option to address an unmet medical need for patients with ER+/HER2- mBC after progression on hormonal therapy in combination with a CDK4/6 inhibitor.

The PFS benefit was statistically significant in all subjects and in subjects with *ESR1*-mut and was supported by statistically significant results from all sensitivity analyses. In addition, the landmark analysis at different time points for both PFS and OS showed clear differences in favor of elacestrant.

All subjects:

- The IRC-assessed PFS estimates at 3, 6, 12, and 18 months were 49.75% versus 39.29%, 34.32 versus 20.38%, 22.32% versus 9.42% and 16.82% versus 0%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308 Table 14.2.1.1.2).
- Overall survival estimates at 3, 6, 12, and 18 months were 98.72% versus 94.61%, 93.01% versus 85.23%, 79.27% versus 73.34%, and 65.24% versus 55.62%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308, Table 14.2.2.1.2).

ESR-mut group:

- The IRC-assessed PFS estimates at 3, 6, 12, and 18 months were 55.93% versus 39.55%, 40.76% versus 19.14%, 26.76% versus 8.19% and 24.33% versus 0%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308 Table 14.2.1.1.1).
- Overall survival estimates at 3, 6, 12, and 18 months were 98.24% versus 98.09%, 92.79% versus 94.36%, 82.64% versus 73.58%, and 67.81% versus 49.36%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308, Table 14.2.2.1.1).

The results of all subgroup analyses were also supportive and consistent with the overall results.

Of special interest is the post hoc exploratory analysis of elacestrant versus fulvestrant, where the results were consistent with the results of the main analysis for PFS and OS in terms of median values, hazard ratios, and landmark estimates. This analysis is especially important given that fulvestrant is the most commonly used hormonal monotherapy after failure of therapy with the combination of a CDK4/6 inhibitor and AI. The efficacy advantage of elacestrant versus fulvestrant was observed despite the fact that both drugs share a common mechanism of action, ER degradation.

Another post hoc exploratory subgroup analysis, based on one of the stratification factors (prior fulvestrant therapy in the advanced/metastatic setting) showed that PFS estimates of elacestrant against SOC, irrespective of prior use of fuvlesrant) were consistent with the results in all subjects. This is important for patients who receive fulvestrant, either as monotherapy or in combination with a CDK4/6 inhibitor as a first- or second-line therapy, as elacestrant, if approved, will be a more tolerable alternative to combination therapy (everolimus USPI; alpelisib USPI) or chemotherapy.

In addition to the clear and consistent efficacy benefit in favor of elacestrant in all subjects and in subjects with *ESR1*-mut, the oral route of administration is more convenient and acceptable relative to the IM administration of fulvestrant.

Although the trial was not powered to detect a statistically significant difference in the *ESR1*-mut-nd group, the efficacy benefit was also observed to a smaller extent in this group, both in terms of PFS HR and, more clearly, in terms of landmark analysis.

- IRC-assessed PFS estimates at 3, 6, 12, and 18 months were 44.30% versus 38.92%, 28.58% versus 21.85%, 18.16% versus 11.22%, and 9.08% versus 0%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308, Table 14.2.1.1.3).

- Overall survival estimates at 3, 6, 12, and 18 months were 99.16% versus 91.54%, 93.23% versus 86.18%, 76.37% versus 73.29%, and 62.67% versus 59.52%, in the elacestrant and SOC arms, respectively (CSR RAD1901-308, Table 14.2.2.1.3).

Despite a smaller efficacy benefit compared to SOC, the convenience of the oral route of administration compared to the IM administration of fulvestrant constitutes an additional benefit for these patients.

The safety profile of elacestrant, relative to SOC, was almost identical in all 3 groups. That main adverse drug reactions were nausea and other gastrointestinal (GI) adverse reactions but grade 3/4 treatment related GI side effects were limited (1.7% and 0.4% for nausea and voimiting, respectively), with no grade 4 reported.

The incidence of elacestrant-related AEs leading to treatment interruption and dose reduction was low (6.3% and 2.5, respectivley). Similarly, the incidence of treatment-related AEs leading to discontinuation of elacestrant was low (3.4%). The incidence of treatment-related serious adverse events was low (1.3%) and no treatment-related fatal adverse events were observed.

To date, no important identified or potential risks have been determined for elacestrant in the target population. Of note, elacestrant was not associated with cardiac safety issues, and hematological AEs were rare.

The favorable benefits of PFS and OS profiles of elacestrant versus SOC, added to the convenience of an oral administration, outweigh the risks in the proposed patient population in all subjects, including both subjects with *ESR1*-mut and subjects with *ESR1*-mut-nd. These results are clinically relevant for the patient population under study.

In conclusion, the benefit-risk assessment for elacestrant for the treatment of postmenopausal women and men with ER+/HER2- advanced or metastatic breast cancer who have progressed following at least 1 line of endocrine therapy is positive in all subjects, irrespective of the *ESR1* mutation status.

The FDA's Assessment:

The Applicant's position is stated in Section 8.4. See FDA's Assessment in Section 1 and Section 8.4.

19.4.5. Physiologically-based Pharmacokinetic Modeling

19.4.5.1 The Applicant's Position:

A physiologically based pharmacokinetic (PBPK) model based on in vitro and in vivo information on the metabolism and pharmacokinetics (PK) of elacestrant was constructed. The model was developed to simulate plasma concentration-time profiles of elacestrant following single dose and repeat dosing in healthy subjects and to evaluate the likely impact of administration of strong/moderate/weak cytochrome P450 (CYP) 3A4 inhibitors and strong/moderate CYP3A4 inducers on the PK of elacestrant.

A combination of in vitro data and clinical PK data of single ascending doses (i.e., 1 mg intravenous dose, 9, 22, 43, 86, and 173 mg oral doses) of elacestrant in healthy subjects was used to develop the PBPK model. The contribution of CYP3A4 in metabolism (fraction metabolised, fmCYP3A4 = 87%) was determined using an itraconazole clinical drug-drug interaction (DDI) study. Elacestrant exhibited non-linear PK across 9 mg to 863 mg oral doses in clinical studies. The area under the curve from time zero to infinity (AUC0-inf) and maximal drug concentration (Cmax) of elacestrant increased more than dose proportionally above 50 mg following single doses. Supra-proportional increases were also manifested in elacestrant AUC0-tau and Cmax above 25 mg following once-daily (QD) multiple doses.

Simulated PK profiles, elacestrant exposures following single intravenous or oral doses (1 mg to 173 mg) and repeat oral doses (9 mg to 863 mg) to healthy subjects were in reasonable agreement with observed data (all AUC0-last, AUC0-inf and Cmax within 1.5-fold; Clinical Studies RAD-1901-001 and RAD-1901-004). The AUC0-tau ratios (AUCR) and Cmax ratios (CmaxR) following repeated administration of elacestrant in the presence and absence of itraconazole were consistent with the observed values from Clinical Study RAD1901-110 (observed vs. simulated AUCR = 5.27 vs. 5.23 and CmaxR = 4.37 vs. 3.87). The AUC0-last and Cmax geometric mean ratios (GMRs) following a single dose of elacestrant in the presence and absence of rifampicin were consistent with the observed values from Clinical Study RAD1901-113 (observed vs. simulated AUC0-last GMR = 0.142 vs. 0.168 and Cmax GMR = 0.270 vs. 0.301).

Prospective use of the model to predict the likely outcomes of interaction of elacestrant with itraconazole (strong CYP3A4 inhibitor; 173 mg QD), fluconazole (moderate CYP3A4 inhibitor; 173 mg QD), erythromycin (CYP3A4 mechanism-based inhibitor (MBI); 500 mg four times daily (QID)), and cimetidine (weak CYP3A4 inhibitor; 400 mg twice daily (BID)) following single 173 mg and 345 mg doses of elacestrant in healthy subjects indicated increases in elacestrant exposure, as summarised in Table 39. In addition, prospective prediction of interaction of elacestrant with efavirenz (moderate CYP3A4 inducer; 600 mg QD) following single 345 mg and 800 mg doses of elacestrant in healthy subjects indicated decreases in elacestrant exposure, also included in Table 39.

Table 39: Summary of simulated geometric mean AUC0-336h and Cmax ratios for elacestrant in the presence and absence of CYP3A4 inhibitors and inducers in healthy subjects following single oral dosing of 173, 345 and 690 mg elacestrant.

Perpetrator	Single 200 mg dose		Single 400 mg dose	
	$AUC_{0\text{-}336h}$ GMR	C_{max} GMR	$AUC_{0\text{-}336h}$ GMR	C_{max} GMR
Itraconazole	6.27	2.42	5.39	2.15
Fluconazole	2.53	1.70	2.34	1.59
Erythromycin	4.15	2.13	3.61	1.92
Cimetidine	1.13	1.15	1.11	1.13
	Single 400 mg dose		Single 800 mg dose	
	$AUC_{0\text{-}336h}$ GMR	C_{max} GMR	$AUC_{0\text{-}336h}$ GMR	C_{max} GMR
Efavirenz	0.452	0.561	0.458	0.565

In conclusion, simulations with itraconazole predicted strong inhibition (AUC GMR ≥ 5), simulations with fluconazole and erythromycin predicted moderate inhibition (AUC GMR ≥ 2

and < 5), whereas simulations with cimetidine predicted weak inhibition (AUC GMR < 2). Finally, simulations with efavirenz predicted moderate induction (AUC decrease ≥ 50% and < 80%).

19.4.3.2 PBPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PBPK Analysis	The aim of this modelling was to develop a PBPK model for elacestrant based on the available in vitro and clinical PK data to assess the DDI liability of elacestrant as a victim of CYP3A4-mediated metabolism in healthy subjects.	
Studies Included	RAD1901-111, RAD1901-109, RAD1901-001, RAD1901-110, RAD1901-004 and RAD1901-113	
Dose(s) Included	1 mg, 9 mg, 22 mg, 43 mg, 86 mg, 173 mg, 345 mg, 431 mg, 647 mg and 863 mg	
Population Included	Healthy postmenopausal women and men	
Final Model	Summary	Acceptability [FDA's comments]
Software and Version	Version 20 of the Simcyp Population-Based Simulator (www.simcyp.com) was used for all PBPK modelling and simulation.	

Model Structure	A PBPK model including a simple first-order absorption model was developed. The fraction of elacestrant absorbed (fa) was estimated from mass balance data (human absorption, metabolism and excretion (AME) study, RAD1901-111) and was of approximately 50% after a light meal. The fasted fa was estimated using the relative bioavailability (fasted vs. low-fat fed) reported in the food effect study (RAD1901-109). Distribution was described using a minimal PBPK model, which considers liver and intestinal metabolism. Observed clearance (CL) (31.75 L/h, corrected for MW from salt to free base) obtained from healthy female subjects following a single intravenous dose of 1 mg elacestrant (RAD1901-001) was used to calculate CYP3A4 intrinsic clearance (CLint) using a retrograde model. The relative contribution of CYP3A4 in elacestrant CL (fraction metabolised, fmCYP3A4) was determined using itraconazole DDI data (RAD1901-110). A CLR of 0.134 L/h was calculated using the total cumulative amount of elacestrant excreted in urine and AUC0-inf (RAD1901-111). While maintaining the CYP3A4 CLint, CYP3A4 maximum metabolic rate (Vmax) and Michaelis-Menten constant (KM) were optimised to recover the observed elacestrant plasma concentration-time profiles following single ascending oral doses from 9 to 173 mg (Clinical Study RAD1901-001). The process of refining fmCYP3A4 and CYP3A4 Vmax and KM continued until a set of values was found able to recover itraconazole DDI data and single ascending dose data simultaneously. Elacestrant enzyme competitive inhibition constant (Ki) values for enzymes and transporters were not incorporated into the PBPK model.	

PBPK Results	*Results of model development* ● The simulated profile of elacestrant was comparable to the clinical data (SAD part of RAD1901-001; 1 (IV), 9, 22, 43, 86 and 173 mg (oral)). The simulated geometric mean of AUC0-last and Cmax values for elacestrant administered to healthy postmenopausal females were within 0.794 – 1.39-fold of the observed values. ● The simulated profiles of elacestrant before and after co-administration with itraconazole were comparable to the clinical data (RAD1901-110). The simulated geometric mean AUC0-tau, Cmax, and AUC0-tau and Cmax ratios for elacestrant administered to healthy subjects were within 0.885 – 1.13-fold of the observed values. *Results of model verification* ● The simulated profile of elacestrant was comparable to the clinical data (MAD part, RAD1901-001; 9, 22, 43, 86 and 173 mg QD). The simulated geometric mean AUC0-tau, Cmax, and Rac for elacestrant administered to healthy subjects were within 0.826 – 1.21-fold of the observed values. ● The simulated profile of elacestrant was comparable to the clinical data (RAD1901-004; 173, 431, 647 and 863 mg QD). The simulated geometric mean AUC0-tau and Cmax for elacestrant administered to healthy subjects were within 0.784 – 1.19-fold of the observed values. *Results of model application* The model was then used prospectively to predict the likely outcome of DDI with CYP3A4 inhibitors, including itraconazole (strong CYP3A4 inhibitor; 173 mg QD), fluconazole (moderate CYP3A4 inhibitor; 173 mg QD), erythromycin (moderate CYP3A4 MBI; 500 mg QID) and cimetidine (weak	

	CYP3A4 inhibitor, 400 mg BID), following single doses of elacestrant 173 or 345 mg. At 173 mg, the model predicted increases in elacestrant exposure with GMRs for AUC0-336h of 6.27, 2.53, 4.15, and 1.13, respectively. Prospective use of the model to predict the likely outcomes of interaction with efavirenz indicated decreases in elacestrant exposure with GMRs for AUC0-336h and Cmax of 0.452 and 0.561 at 345 mg, respectively, and 0.458 and 0.565 at 690 mg, respectively.	

19.4.5.2 The FDA's Assessment:

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK reports to support the intended uses.

- Radi-2b: Development of a PBPK model for elacestrant with the Simcyp population-based simulator and subsequent evaluation of DDI liability as a victim of CYP3A4
- Radi-2b ad-hoc: Additional hepatic impairment simulations associated with PBPK report Radi-2b

The Division of Pharmacometrics has reviewed the PBPK reports and supporting modeling files to conclude the following:

- The elacestrant PBPK model is adequate to predict the PK of elacestrant following a single intravenous administration (1 mg), a single oral dose administration (10, 25, 50, 100 and 200 mg), or multiple oral dose administration (10, 25, 50, 100 and 200 mg QD) in healthy subjects.
- The elacestrant PBPK model is adequate to predict the effect of itraconazole (a strong CYP3A inhibitor) on elacestrant PK following multiple dose administration of elacestrant (400 mg QD) in healthy subjects. The model predicted elacestrant exposure increased around 5-fold when coadministered with itraconazole following multiple dose administration of elacestrant (400 mg QD) in healthy subjects.
- The elacestrant PBPK model is adequate to predict the effect of fluconazole and erythromycin (moderate CYP3A inhibitors) on elacestrant PK following multiple dose administration of elacestrant (400 mg QD) in healthy subjects. The model predicted elacestrant exposure increased about 2.5-fold or 3.5-fold when coadministered with fluconazole or erythromycin, respectively, following multiple dose administration of elacestrant (400 mg QD) in healthy subjects.
- The elacestrant PBPK model is adequate to predict the effect of cimetidine (a weak CYP3A inhibitor) on elacestrant PK following multiple dose administration of elacestrant (400 mg QD) in healthy subjects. The model predicted elacestrant exposure increased about 10%

when coadministered with cimetidine following multiple dose administration of elacestrant (400 mg QD) in healthy subjects.

- The elacestrant PBPK model is inadequate to predict the effect of efavirenz (a moderate CYP3A inducer) on elacestrant PK following multiple dose administration of elacestrant (400 mg QD) in healthy subjects. However, the modeling analysis provided supporting information that the elacestrant exposure would likely be reduced about 55 to 80% when administered with efavirenz following multiple dose administration of elacestrant (400 mg QD) in healthy subjects.
- The elacestrant PBPK model, validated using clinical PK data in patients with mild and moderate hepatic impairment (HI), and healthy subjects following a single dose administration of elacestrant (200 mg) was considered to be acceptable for simulating the steady-state PK of elacestrant in patients with mild and moderate HI. The total AUC ratios of elacestrant were 1.35 and 1.51 in mild and moderate HI patients following multiple dose administration of 400 mg QD and 300 mg QD elacestrant, respectively, when compared to the total AUC value in healthy subjects following multiple dose administration of 400 mg QD elacestrant.
- The elacestrant PBPK model is inadequate to predict the effects of severe HI on the PK of elacestrant since no clinical PK data were available for HI model validation.

Applicant's PBPK Modeling Effort

PBPK software

Simcyp V20 (Simcyp Ltd, UK) was used to develop the PBPK models and predict the effects of itraconazole, fluconazole, erythromycin, cimetidine and efavirenz on the PK of elacestrant in healthy subjects.

Part A: DDI Assessment

Model development

Absorption was described using a first order absorption model. The fraction absorbed (fa=0.429) was estimated based on mass balance study (light meal) (Study RAD1901-111) and relative bioavailability study (fasted vs. low-fat meal) (Study RAD1901-109). The absorption rate constant (ka) of 0.22 h^{-1} was optimized based on clinical data in Study RAD1901-001.

A minimal PBPK model was used to simulate the distribution phase of elacestrant PK profiles. The volume of distribution at steady state (Vss) (17.17 L/kg) and single adjusting compartment parameter values (kin=5.65 h^{-1}, kout=0.14 h^{-1} and Vsac=16.84 L/kg) were optimized to recover the elacestrant distribution profile following intravenous administration of 1 mg elacestrant in Study RAD 1901-001. The fraction unbound in plasma (f_u) and blood and plasma ratio were 0.01 and 0.69, respectively.

Elacestrant was primarily metabolized by CYP3A4 based on in vitro phenotyping study (study 7801-109). Total intrinsic clearance (CLint) and fraction metabolized by CYP3A4 (fmCYP3A4) were refined based on the total clearance (CL/F=31.75 L/h) reported in the clinical PK study RAD1901-001 and clinical DDI study results with itraconazole (Study RAD1901-110), respectively. For the

CYP3A4 kinetics parameter value, Km (=0.255 mM) was optimized based on elacestrant PK data in Study RAD 1901-001, and Vmax (=0.517 pmol/min/pmol) was calculated based on CLint, Km and fraction unbound in liver microsomes (fumic). CYP3A4 CLint was calculated using retrograde approach based on total clearance and fmCYP3A4. The fumic value was predicted using Simcyp. Following oral administration, the unchanged parent drug accounted for 0.0487% and 34.5% of the dose administered in urine (7.53% of total administered radioactivity) and feces (81.5% of total administered radioactivity), respectively. The absolute bioavailability was approximately 10% following oral administration of 100 mg elacestrant. The first pass metabolism of elacestrant (Fg*Fh) was estimated to be 0.23 which was calculated using the fraction absorbed (0.429) and the absolute bioavailability (0.10). Renal clearance of 0.134 L/h was obtained from the clinical PK study RAD1901-111.

Elacestrant exposure (AUC and Cmax) increased with increasing oral dose in a greater than proportional manner following a single or multiple dose administration over a dose range of 10 mg to 1000 mg (Study RAD1901-001).

Based on in vitro study results, no significant impact of elacestrant at clinically relevant concentration is expected on CYP enzymes (Summary of Clinical Pharmacology). Although elacestrant mediated inhibition toward P-gp and BCRP in the intestine was expected according to the in vitro study results, the clinical DDI study showed less than 20% increase in the exposure of digoxin (a P-gp substrate) and rosuvastatin (a BCRP substrate) with and without elacestrant (Summary of Clinical Pharmacology). Therefore, elacestrant enzyme competitive inhibition constant (Ki) values for enzymes and transporters were not incorporated into the PBPK model.

Victim drug models

The default PBPK models of itraconazole, fluconazole, erythromycin, cimetidine and efavirenz in Simcyp (V20) were used for DDI predictions.

FDA's assessment

1. Simcyp V20 was used in the Applicant's model prediction, while Simcyp V21 was used in the FDA reviewer's analysis. The reviewer's analysis showed a less than 5% difference in predicted Cmax and AUCinf values using Simcyp V21 compared to those simulated values using Simcyp V20.
2. Elacestrant exhibited nonlinear PK in which larger than dose-proportional increases in concentrations were observed in the single and multiple ascending dose study (Study RAD1901-001). The dose normalized Cmax and AUC increased by approximately 8 and 5-fold, respectively, over a dose range of 10 mg to 1000 mg following a single dose administration. Comparable half-lives in ascending dose PK along with the information that elacestrant is not a substrate of efflux transporters (Study RAD-1901) may suggest a

saturable first pass metabolism of elacestrant. It appears reasonable to describe the elacestrant nonlinear PK by incorporating the saturable metabolism by CYP3A in the model.

3. It appears that the Applicant's model over-predicted the induction effect of rifampin on the PK of elacestrant following a single dose administration of elacestrant (400 mg) (Table 1).

(b) (4)

The reviewer noticed that the fraction unbound in the enterocytes (fuGut) for rifampin (default Simcyp model) was assigned (b) (4) Therefore, the rifampin mediated induction effect in intestine was likely overpredicted for elacestrant (b) (4) The reviewer exploratory analysis showed that the model captured well the observed DDI data with rifampin by assigning a lower fuGut value (e.g.,0.02) for rifampin (Table 1).

Table 1 Observed and simulated Cmax and AUC ratios with rifampin with different Indmax and fuGut values following multiple dose

	Predicted CmaxR	Predicted AUCR	Observed CmaxR	Observed AUCR
(b) (4)			0.27	0.142
Indmax=16, fuGut=0.02	0.26[b]	0.16[b]		

Sources: a: PBPK report RADI-2b, Table 13; b: reviewer's analysis; observed data were from study RAD1901-113.

Model application

The developed PBPK model was used to simulate the DDI for elacestrant in the following scenarios:

- To predict the effect of itraconazole (a strong CYP3A inhibitor) on the PK of elacestrant following oral administration of elacestrant (200 mg SD, 400 mg SD and 400 QD) in healthy subjects.

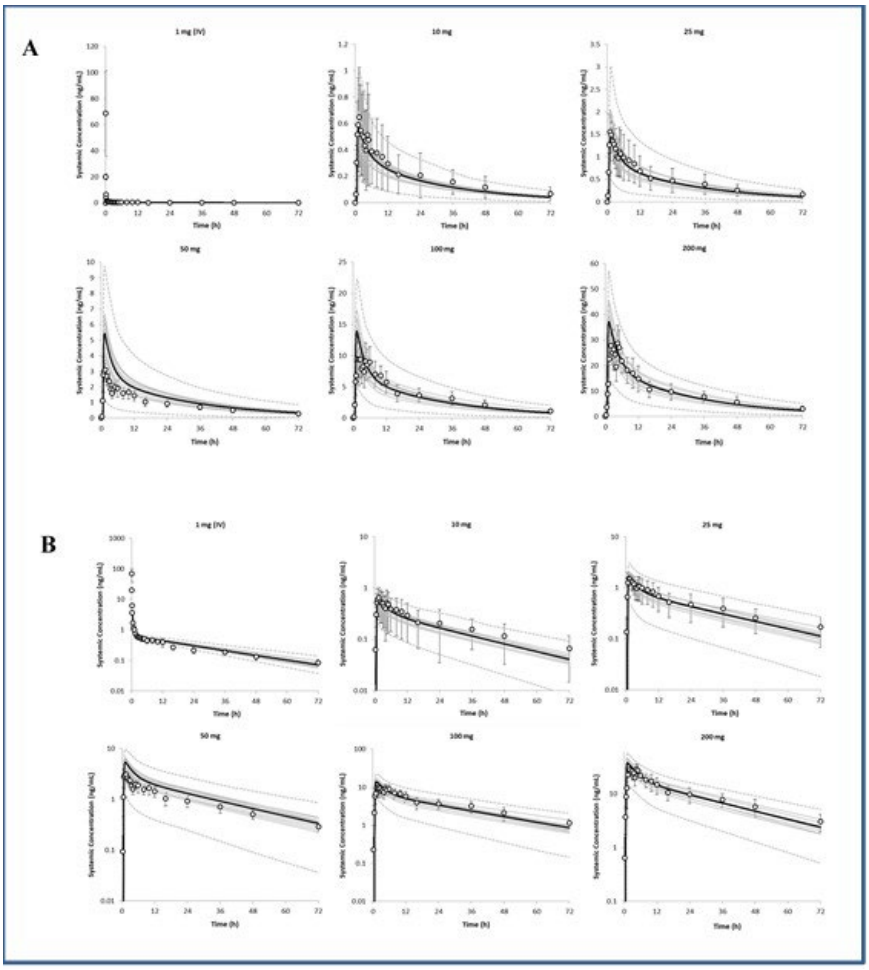
- To predict the effect of fluconazole (a moderate CYP3A4 inhibitor) and erythromycin (a moderate CYP3A inhibitor) on the PK of elacestrant following oral administration of elacestrant (200 mg SD, 400 mg SD and 400 mg QD) in healthy subjects.
- To predict the effect of cimetidine (a weak CYP3A inhibitor) on the PK of elacestrant following oral administration of elacestrant (200 mg SD, 400 mg SD and 400 mg QD) in healthy subjects.
- To predict the effect of efavirenz (a moderate CYP3A4 inducer) on the PK of elacestrant following oral administration of elacestrant (200 mg SD, 400 mg SD and 400 mg QD) in healthy subjects.

Results

1. Can elacestrant PBPK model describe the elacestrant PK in healthy subjects?

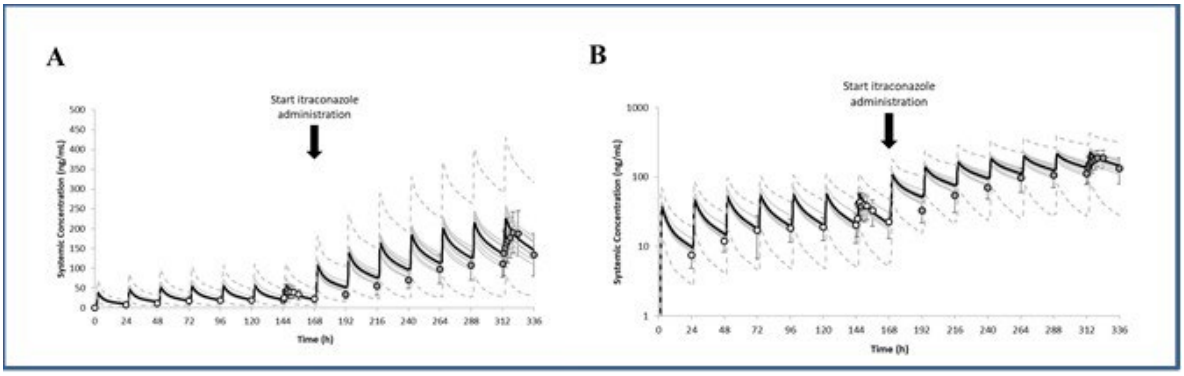
Yes. The elacestrant model was able to capture the observed elacestrant PK profiles following a single intravenous administration (1 mg), a single oral dose administration (10, 25, 50, 100 and 200 mg), or multiple oral dose administration (10, 25, 50, 100 and 200 mg QD) in healthy subjects (Figure 1, Figure 2, Figure 3, Figure 4 and Table 2). The nonlinear PK profiles observed in the single and multiple ascending dose study were well captured.

Figure 1 Linear (A) and log-linear (B) simulated (lines) and observed (circles) plasma concentration-time profiles following a single intravenous dose of 1 mg and a single oral dose of 10, 25, 50, 100 and 200 mg elacestrant in healthy subjects



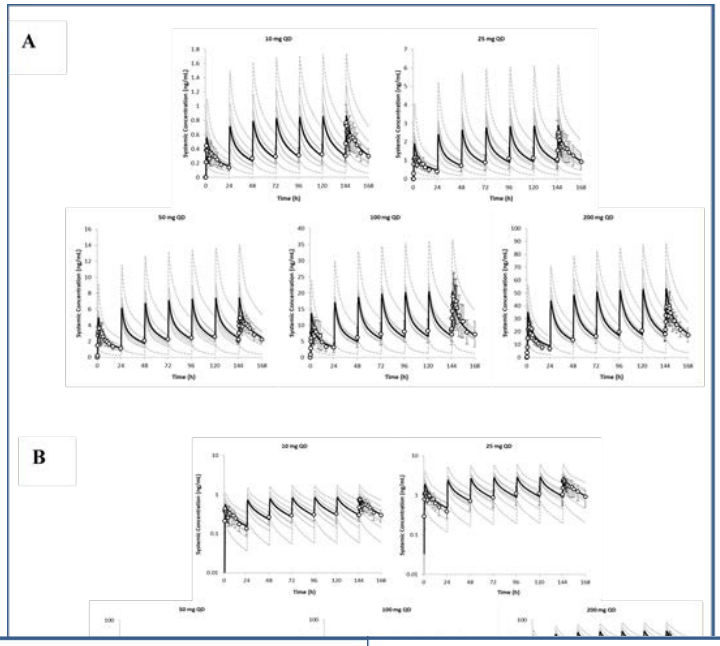
Sources: Simulated data were from PBPK report RADI-2b, Figure 4 and observed data were from Study RAD1901-001.

Figure 2 Linear (A) and log-linear (B) simulated (lines) and observed (dots) plasma concentration-time profiles of 200 mg elacestrant QD before and after co-administration with itraconazole in healthy subjects



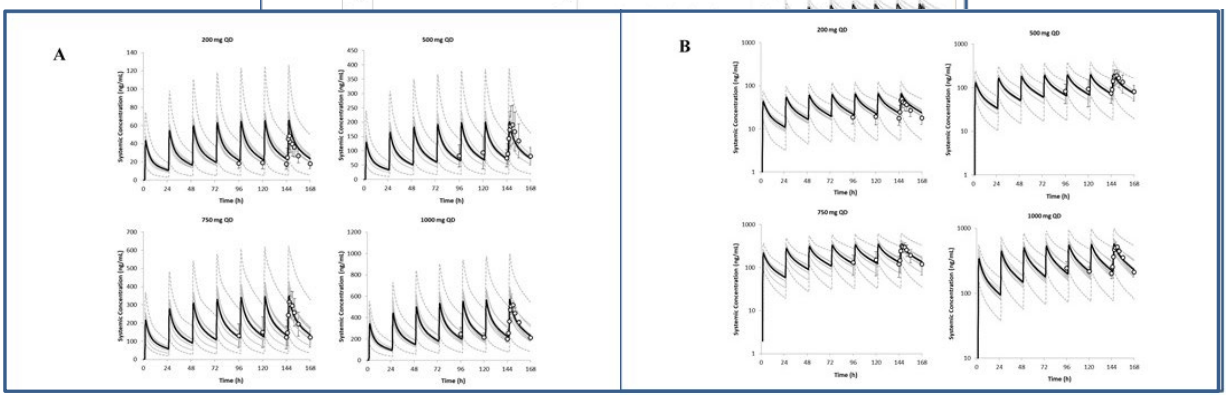
Sources: Simulated data were from PBPK report RADI-2b, Figure 5 and observed data were from Study RAD1901-110.

Figure 3 Linear (A) and log-linear (B) simulated (circles) and observed (dots) plasma concentration-time profiles following oral doses of 10, 25, 50, 100 and 200 mg QD elacestrant in healthy subjects



Sources: Simulated data were from PBPK report RADI-2b, Figure 6 and observed data were from Study RAD1901-001.

Figure 4 Linear (A) and log-linear (B) simulated (circles) and observed (lines) plasma concentration-time profiles following oral doses of 200, 500, 750 and 1000 mg QD elacestrant in healthy subjects



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Sources: Simulated data were from PBPK report RADI-2b, Figure 7 and observed data were from Study RAD1901-004.

Table 2 Simulated and observed geometric mean PK parameters for elacestrant following a single intravenous administration, a single oral dose administration or multiple oral dose administration of elacestrant in healthy subjects

Study	n	Dose mg	Prandial State		C_{max} CV (%) ng/mL	AUC_{blast} CV (%) ng*h/mL
RAD1901-001	5	1 (IV)	fasted	Simulated	--	24.0
					--	16.0
				Observed	125#	23.6
					61.0	15.0
				S/O	--	1.02
RAD1901-001	6	10	fasted	Simulated	0.512	9.41
					45.8	51.5
				Observed	0.619	11.2
					55.0	72.0
				S/O	0.827	0.840
RAD1901-001	6	25	fasted	Simulated	1.38	23.6
					50.2	58.3
				Observed	1.74	29.1
					26.0	49.0
				S/O	0.794	0.810
RAD1901-001	6	50	fasted	Simulated	4.66	71.5
					46.8	56.4
				Observed	3.35	60.3
					21.0	19.0
				S/O	1.39	1.19
RAD1901-001	6	100	fasted	Simulated	12.7	196
					39.0	53.0
				Observed	11.6	239
					17.0	29.0
				S/O	1.10	0.819
RAD1901-001	6	200	fasted	Simulated	34.9	578
					34.6	45.7
				Observed	31.1	627
					18.0	28.0
				S/O	1.12	0.921

Study	n	Dose mg	Prandial State	Day		C_{max} CV (%) ng/mL	AUC_{tau} CV (%) ng*h/mL	R_{ac}
RAD1901-004	15	200 QD	light meal	7	Simulated	59.3	742	1.88
						48.6	55.3	14.1
					Observed	49.8	670	--
						14.5	29.0	--
					S/O	1.19	1.11	--
RAD1901-004	11	500 QD	light meal	7	Simulated	180	2295	1.89
						48.9	54.7	14.5
					Observed	197	2927	--
						35.0	38.0	--
					S/O	0.913	0.784	--
RAD1901-004	6	750 QD	light meal	7	Simulated	317	4163	1.98
						46.0	54.4	17.0
					Observed	322	4614	--
						21.0	32.0	--
					S/O	0.984	0.902	--
RAD1901-004	3	1000 QD	light meal	7	Simulated	526	7020	
						43.7	54.3	
					Observed	540	8292	--
						11.0	11.0	--
					S/O	0.974	0.847	--

Study	n	Dose mg	Prandial State	Day		C_{max} CV (%) ng/mL	AUC_{tau} CV (%) ng*h/mL	R_{ac}
RAD1901-001	7	10 QD	fasted	1	Simulated	0.481	5.37	--
						52.1	54.7	--
					Observed	0.490	5.33	--
						26.0	35.0	--
					S/O	0.981	1.01	--
RAD1901-001	7	10 QD	fasted	7	Simulated	0.725	9.50	1.77
						56.5	62.3	12.0
					Observed	0.791	10.3	1.93
						26.0	34.0	15.0
					S/O	0.916	0.923	0.917
RAD1901-001	7	25 QD	fasted	1	Simulated	1.61	16.4	--
						55.3	57.5	--
					Observed	1.38	15.6	--
						31.0	23.0	--
					S/O	1.17	1.05	--
RAD1901-001	7	25 QD	fasted	7	Simulated	2.39	29.7	1.81
						59.7	66.5	11.6
					Observed	2.55	33.2	2.13
						28.0	39.0	31.0
					S/O	0.939	0.893	0.851
RAD1901-001	8	50 QD	fasted	1	Simulated	4.28	40.3	--
						48.9	54.9	--
					Observed	4.37	43.7	--
						22.0	28.0	--
					S/O	0.979	0.922	--
RAD1901-001	8	50 QD	fasted	7	Simulated	6.27	74.5	1.85
						53.8	62.7	13.6
					Observed	5.54	80.5	1.84
						21.0	21.0	14.0
					S/O	1.13	0.925	1.00
RAD1901-001	8	100 QD	fasted	1	Simulated	12.2	116	--
						44.1	52.5	--
					Observed	10.1	114	--
						27.0	46.0	--
					S/O	1.21	1.02	--
RAD1901-001	8	100 QD	fasted	7	Simulated	17.8	214	1.84
						51.9	63.7	12.1
					Observed	19.3	245	2.16
						37.0	44.0	17.0
					S/O	0.924	0.873	0.854
RAD1901-001	8	200 QD	fasted	1	Simulated	32.0	325	--
						39.3	45.0	--
					Observed	26.5	276	--
						25.0	23.0	--
					S/O	1.21	1.18	--
RAD1901-001	8	200 QD	fasted	7	Simulated	47.2	591	1.82
						46.3	55.2	11.9
					Observed	42.3	608	2.20
						25.0	26.0	12.0
					S/O	1.12	0.973	0.826

Sources: Simulated data were from PBPK report RADI-2b Table 9, 10, 11 and 12. Observed data were from clinical Studies shown in the Table.

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Study	n	Dose mg	Prandial State		C_{max} Geo CV (%) ng/mL	$C_{max,inh}$ Geo CV (%) ng/mL	C_{max} Ratio 90% CI	AUC_{tau} Geo CV (%) ng*h/mL	$AUC_{tau,inh}$ Geo CV (%) ng*h/mL	AUC_{tau} Ratio 90% CI
RAD1901-110	17	200 QD	light meal	Simulated	51.4	199	3.87	658	3438	5.23
					59.3	57.8	(3.75, 3.99)	68.2	76.6	(5.02, 5.45)
				Observed	45.6	199	4.37	720	3791	5.27
					38.3	30.4	(3.96, 4.83)	37.7	32.3	(4.69, 5.91)
				S/O	1.13	1.00	0.885	0.914	0.907	0.993

2. Can elacestrant PBPK model predict the effect of itraconazole (a strong CYP3A inhibitor) on the PK of elacestrant following a single dose administration (200 mg and 400 mg) or multiple dose administration of elacestrant (400 mg QD) in healthy subjects?

Yes. The elacestrant model validated using clinical DDI data between itraconazole and elacestrant (200 mg QD) was adequate to predict the effect of itraconazole on the PK of elacestrant following a single oral dose administration (200 mg and 400 mg) or multiple oral dose administration of elacestrant (400 mg QD) in healthy subjects. The model predicted elacestrant exposure increased greater than 5-fold when coadministered with itraconazole (Table 3).

Table 3 Simulated and observed geometric mean Cmax and AUC ratios for elacestrant in the presence and absence of CYP3A4 modulators following a single or multiple oral dose administration of elacestrant

		Elacestrant Dose (mg)	Predicted CmaxR	Predicted AUCR	Observed CmaxR	Observed AUCR
Model Validation	Itraconazole (200 mg QD)	200 mg QD	3.87	5.23	4.37[a]	5.27[a]
	Rifampin (600 mg QD)	400 mg SD	0.26	0.16	0.27[b]	0.14[b]
	Itraconazole (200 mg QD)	200 mg SD	2.42	6.27		

Model Application		400 mg SD	2.15	5.39		
		400 mg QD	3.79	5.10		
	Fluconazole (200 mg QD)	200 mg SD	1.70	2.53		
		400 mg SD	1.59	2.34		
		400 mg QD	2.14	2.55		
	Erythromycin (500 mg QID)	200 mg SD	2.13	4.15		
		400 mg SD	1.92	3.61		
		400 mg QD	2.78	3.55		
	Cimetidine (400 mg BID)	200 mg SD	1.15	1.13		
		400 mg SD	1.13	1.11		
		400 mg QD	1.14	1.12		
	Efavirenz (600 mg QD)	400 mg SD Indmax=9.9	0.37	0.27		
		400 mg SD Indmax=5.14	0.56	0.45		

Sources:

a. Simulated data following a single dose administration of elacestrant (200 mg or 400 mg) with or without all the CYP 3A4 modulators except for rifampin were from the PBPK report RADI-2b, Table 14.
b. Simulated data following a single dose administration of elacestrant (400 mg) with or without rifampin or following multiple dose administration of elacestrant (400 mg, QD) were from reviewer's analysis.
c. Observed data were from study RAD1901-110 (a) and RAD1901-113 (b).

3. Can elacestrant PBPK model predict the effect of fluconazole (a moderate CYP3A4 inhibitor) and erythromycin (a moderate CYP3A inhibitor) on the PK of elacestrant following a single dose administration (200 mg and 400 mg) or multiple dose administration (400 mg QD) of elacestrant in healthy subjects?

Yes. The elacestrant model validated using clinical DDI data between itraconazole and elacestrant (200 mg QD) was adequate to predict the effect of fluconazole or erythromycin on the PK of elacestrant following a single dose administration (200 mg and 400 mg) or multiple dose administration of elacestrant (400 mg QD) in healthy subjects. The model predicted elacestrant exposure increased about 2.5-fold or 3.5-fold when coadministered with fluconazole or erythromycin, respectively (Table 3).

4. Can elacestrant PBPK model predict the effect of cimetidine (a weak CYP3A4 inhibitor) on the PK of elacestrant following a single dose administration (200 mg and 400 mg) or multiple dose administration (400 mg QD) of elacestrant in healthy subjects?

Yes. The elacestrant model validated using clinical DDI data between itraconazole and elacestrant (200 mg QD) was adequate to predict the effect of cimetidine on the PK of elacestrant following

a single dose administration (200 mg and 400 mg) or multiple dose administration of elacestrant (400 mg QD) in healthy subjects. The model predicted elacestrant exposure increased about 10% when coadministered with cimetidine (Table 3).

5. **Can elacestrant PBPK model predict the effect of efavirenz (a moderate CYP3A4 inducer) on the PK of elacestrant following a single dose administration (200 mg and 400 mg) or multiple dose administration of elacestrant (400 mg QD) in healthy subjects?**

NO, but the Reviewer's additional analysis could provide supportive information. The Reviewer noted that the DDI predictive performance of efavirenz model needs to be validated using clinical DDI data with a substrate having high first pass metabolism before it can be used in the DDI prediction with elacestrant. (b) (4) The evaluation result showed that the default efavirenz model in Simcyp over predicted the effect of efavirenz on the PK of simvastatin (Table 4). (b) (4)

The reviewer analysis showed that the default efavirenz model still over-predicted the observed clinical DDI with simvastatin (b) (4) (Table 4). The over-predicted induction effect of efavirenz on simvastatin PK could be attributed to 1) the Indmax value assigned in the efavirenz model is too large; 2) the fmCYP3A4 value in simvastatin model is too high. Nonetheless, these assumptions need to be further verified with additional clinical DDI data of efavirenz with CYP3A substrates having high first pass metabolism, and simvastatin with strong CYP3A inhibitors.

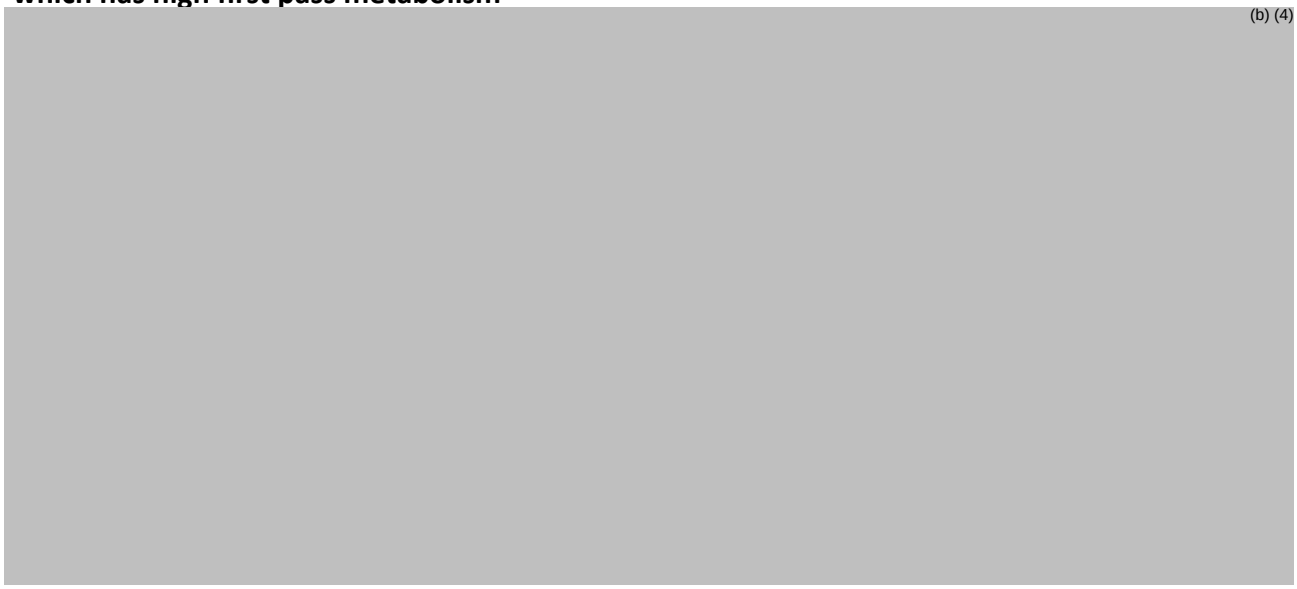
Based on the current assumptions #1 and #2, the reviewer conducted additional exploratory analysis to estimate a range of the potential effect of efavirenz on the PK of elacestrant.

a. If the over-predicted induction effect of efavirenz on simvastatin PK is due to the Indmax value assigned in the efavirenz model is too large, then the Indmax value needs to be reduced which is similar to the Applicant's analysis. As shown in Table 3, the model estimated about 55% decrease in the exposure of elacestrant with efavirenz.
b. If the over-predicted induction effect of efavirenz on simvastatin PK is due to the fmCYP3A4 value in simvastatin model is too high, then the default efavirenz model in Simcyp was used to predict the DDI for elacestrant with efavirenz. The model predicted about 73% decrease in the exposure of elacestrant with efavirenz, which was similar to the observed effect of rifampin on elacestrant (86% decrease) and was likely over-predicted.

In summary, the modeling analysis indicated that the exposure of elacestrant would likely to be reduced about 55% to 73% when administered with efavirenz (Table 3).

Table 4 Efavirenz model predictive performance validation with clinical data of simvastatin which has high first pass metabolism

(b) (4)



Part B: Assessment of the effect of hepatic impairment on elacestrant steady-state exposure

Applicant's PBPK Modeling Effort

The Applicant has conducted a clinical PK study RAD1901-117 to evaluate the effect of mild and moderate HI on the PK of elacestrant following a single dose administration (200 mg). The observed total elacestrant AUC ratios in subjects with mild and moderate were 1.28 and 1.83, respectively, relative to the subjects with normal liver function. The fraction unbound of elacestrant in plasma were measured in all groups and no particular trends in fu were detected (RAD1901-117).

The PBPK model developed for elacestrant DDI evaluation was further refined based on the results of the Study RAD1901-117 and utilized to evaluate the effect of HI on the steady state PK of elacestrant.

PBPK software

Simcyp V20 (Simcyp Ltd, UK) was used to develop the elacestrant PBPK models in hepatic impaired populations and predict the effect of HI on the steady state PK of elacestrant.

Model development

The developed PBPK platform for DDI assessment was further refined to better capture the observed effects of mild and moderate HI on the single dose PK of elacestrant. Please refer to "Part A: DDI assessment" for the detailed information of the PBPK model developed for elacestrant DDI evaluation. The details of model refinement for HI evaluation were as follows:

1. CYP3A4 abundance in HI patients

The elacestrant PBPK model was previously developed and verified using Simcyp V20. For the elacestrant PK simulations in HI patients, the CYP abundances in HI patients in Simcyp V20 were adjusted according to the updated values in the newer version of the software (Simcyp V21) (Table 5).

Table 5 CYP3A4 abundance in Simcyp V20 and V21 for subjects with normal liver function (healthy), mild (CP-A), moderate (CP-B), and severe (CP-C) hepatic impairment

	Healthy	CP-A	CP-B	CP-C
V20 CYP3A4 (pmol/mg protein)	137	108	56.0	31.0
V21 CYP3A4 (pmol/mg protein)	137	107	70.2	42.8

Source: PBPK report RADI-2B Table 1. Note: Simcyp updated the hepatic impairment population files in V21 based on recently published literature data[3],[4] and HI model predictive performance

2. Elacestrant parameter values

The values for the distribution parameters related to the single-adjustment compartment (SAC) were adjusted in order to capture well the observed PK profiles of elacestrant in HI patients in Study RAD1901-117 (Table 6). The total Vss remained unchanged. All other parameter values remained the same as those in the model for DDI assessment with respect to the characterization of absorption, metabolism, and elimination processes.

Table 6 Single-adjustment compartment parameter value comparison in models for DDI assessment and simulations in HI patients

	kin (1/h)	kout (1/h)	Vsac (L/kg)
DDI assessment	5.65	0.14	16.84
Simulations in HI patients	3.99	0.16	16.33

Source: PBPK report RADI-2B, Table 2.

Model application

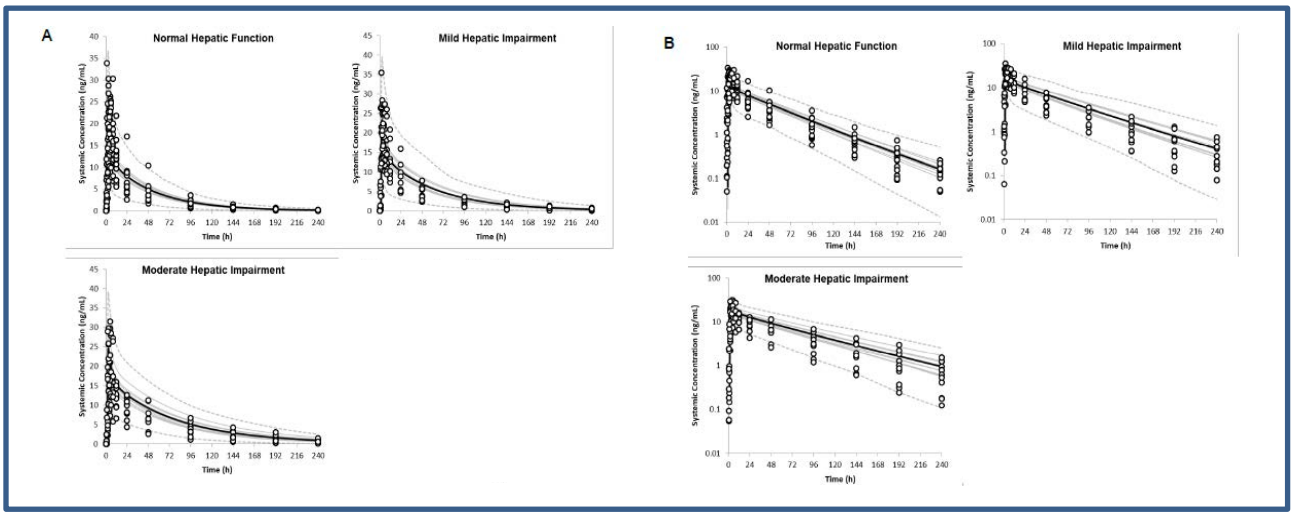
The refined model of elacestrant in HI populations was applied to predict the impact of HI on the PK of elacestrant following a single or multiple-dose administration of elacestrant. Simulations were performed with 100 subjects (10 trials with 10 subjects for each trial). Subjects in each virtual trial were age and sex matched to each group of clinical trials subjects in Study RAD1901-117.

Results

Model validation

The refined elacestrant model in HI populations was able to capture the observed elacestrant PK profiles in patients with mild and moderate HI following a single dose administration of 200 mg elacestrant (Figure 5). A comparison of predicted and observed total Cmax and AUCinf values and ratios for elacestrant in patients with mild and moderate HI and healthy subjects following a single oral dose of 200 mg are shown in Table 7.

Figure 5 Linear (A) and log-linear (B) simulated (lines) and observed (dots) elacestrant plasma concentration-time profiles in HI patients and healthy subjects following a single dose administration of 200 mg elacestrant



Sources: simulation data were from PBPK report RADI-2B AD-Hoc, Figure 1; observed data were from clinical study RAD-1901-117.

Table 7 Simulated and observed geometric mean PK parameters of elacestrant following a single dose of 200 mg in mild and moderate HI patients and healthy subjects

	Normal (Control)		Mild HI		Mild HI/Ctrl		Moderate HI		Moderate HI/Ctrl	
	AUC_{0-inf} ng*h/mL	C_{max} ng/mL	AUC_{0-inf} ng*h/mL	C_{max} ng/mL	AUCR	$C_{max}R$	AUC_{0-inf} ng*h/mL	C_{max} ng/mL	AUCR	$C_{max}R$
Simulated	588	18.3	819	21.3	1.39	1.16	1198	22.9	2.04	1.25
CV (%)	62.4	50.4	68.5	50.1			61.8	42.8		
Observed	565	19.1	687	22.4	1.28	1.11	942	20.3	1.83	1.14
CV (%)	40.5	33.4	40.3	27.5			46.4	39.2		
S/O	1.04	0.96	1.19	0.95	**1.09**	**1.05**	1.27	1.13	**1.11**	**1.10**

Sources: simulation data were from PBPK report RADI-2B AD-Hoc, Table3; observed data were from clinical study RAD-1901-117.

Model application

1. **Can elacestrant PBPK model predict the elacestrant PK in mild and moderate HI patients following multiple dose administration of elacestrant?**

Yes. Elacestrant clinical data did not indicate any time-dependent PK and PBPK modeling approach can be used to capture the dose dependent PK of elacestrant at steady state. Therefore, the model validated using clinical PK data in patients with mild and moderate HI and healthy subjects following a single dose administration of elacestrant (200 mg) was considered to be acceptable for simulating the steady-state PK of elacestrant in patients with mild and moderate HI.

As shown in Table 8, the total AUC ratios of elacestrant were 1.35 and 1.51 in mild and moderate HI patients following multiple dose administration of 400 mg QD and 300 mg QD elacestrant, respectively, when compared to the AUC value in healthy subjects following multiple dose administration of 400 mg QD elacestrant.

2. **Can elacestrant PBPK model predict the elacestrant PK in severe HI patients following multiple dose administration of elacestrant?**

No. The model predicted total AUC ratio of elacestrant was (b) (4) in severe HI patients following multiple dose administration of 200 mg QD elacestrant, when compared to the AUC value in healthy subjects following multiple dose administration of 400 mg elacestrant (Table 8). Since no clinical PK data are available for model validation regarding the effects of severe HI on the PK of elacestrant, the current modeling effort should be considered as an exploratory analysis and cannot serve as the basis to inform dosing recommendations in patients with severe HI without further substantiation.

Table 8 Summary of predicted elacestrant Cmax and AUC ratios following multiple dose administration of elacestrant (200, 300 and 400 mg QD) when compared to those in healthy subjects after multiple dosing of elacestrant (400 mg QD)

HI	Elacestrant dosing information		CmaxR	AUCtauR
Mild HI	200 mg QD	Mild HI/Healthy Subject 400mg QD	0.55	0.55

	300 mg QD		0.92	0.94
	400 mg QD		**1.31**	**1.35**
Moderate HI	200 mg QD	Moderate HI/Healthy Subject 400mg QD	0.84	0.92
	300 mg QD		**1.36**	**1.51**
	400 mg QD		1.92	2.14
Severe HI	**200 mg QD**	Severe HI/Healthy Subject 400mg QD	(b) (4)	
	300 mg QD		1.73	1.97
	400 mg QD		2.44	2.80

(b) (4)

[3] Murray M, Gillani TB, Ghassabian S, Edwards RJ, Rawling T (2018). Differential effects of hepatic cirrhosis on the intrinsic clearances of sorafenib and imatinib by CYPs in human liver. Eur J Pharm Sci 114:55-63.

[4] Prasad B, Bhatt DK, Johnson K, Chapa R, Chu X, Salphati L, Xiao G, Lee C, Hop CECA, Mathias A, Lai Y, Liao M, Humphreys WG, Kumer SC, Unadkat JD (2018). Abundance of Phase 1 and 2 Drug-Metabolizing Enzymes in Alcoholic and Hepatitis C Cirrhotic Livers: A Quantitative Targeted Proteomics Study. Drug Metab Dispos 46(7):943-952.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

NA

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Nikolett Biel, PhD	OOD/DHOT	Sections: 5	**Select one:** __x__Authored __x__Approved
	Signature: Nikolett M. Biel -S Digitally signed by Nikolett M. Biel -S Date: 2023.01.25 12:57:10 -05'00'			
Nonclinical Team Leader	Tiffany Ricks, PhD	OOD/DHOT	Sections: 5	**Select one:** __x__Authored __x__Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S Date: 2023.01.25 13:03:05 -05'00'			
Nonclinical Team Division Director N/A (NME only)	John Leighton, PhD	OOD/DHOT	Sections: 5	**Select one:** ____Authored __X__Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2023.01.25 13:39:08 -05'00'			
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	Signature: Wentao Fu -S Digitally signed by Wentao Fu -S Date: 2023.01.25 15:42:44 -05'00'			

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	Signature: Fang Li -S Digitally signed by Fang Li -S Date: 2023.01.26 10:11:19 -05'00'			
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	Signature: Jielin Sun -S Digitally signed by Jielin Sun -S Date: 2023.01.26 10:26:14 -05'00'			
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Clinical Pharmacology Team Leader	Salaheldin Hamed, PhD	OCP/DCP II	Sections: 6, 19.4	**Select one:** __X__Authored __X__Approved
	Signature: Salaheldin S. Hamed -S Digitally signed by Salaheldin S. Hamed -S Date: 2023.01.26 10:47:56 -05'00'			
Clinical Pharmacology Team Leader	Jerry (Jingyu) Yu, PhD	OCP/DPM	Sections: 6, 19.4	**Select one:** ____Authored __X__Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S Date: 2023.01.26 11:08:41 -05'00'			
Clinical Pharmacology Team Leader	Robert Schuck, PharmD, PhD	OCP/DTPM	Sections: 6	**Select one:** __X__Authored __X__Approved
	Signature: Robert Schuck -S Digitally signed by Robert Schuck -S Date: 2023.01.26 12:07:19 -05'00'			

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	Signature: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2023.01.26 12:54:03 -05'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	OCP/DCPII	Sections: 6, 19.4	**Select one:** ____Authored __x__Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2023.01.25 17:02:36 -05'00' *Stacy S. Shord, PharmD, signing on behalf of Nam Atiqur Rahman, PhD.*			
Clinical Reviewer	Danielle Krol, MD	DO1	Sections: 2, 3, 7, 8	**Select one:** ____Authored __X__Approved
	Signature: Danielle N. Krol -S Digitally signed by Danielle N. Krol -S Date: 2023.01.26 13:20:07 -05'00'			
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	Signature: Hima B. Lingam -S Digitally signed by Hima B. Lingam -S Date: 2023.01.26 14:20:43 -05'00'			
Clinical Team Leader	Mirat Shah, MD	DO1	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 11, 12, 13	**Select one:** __x__Authored __x__Approved
	Signature: Mirat Shah -S Digitally signed by Mirat Shah -S Date: 2023.01.25 17:35:56 -05'00'			
Statistical Reviewer	Haley Gittleman, PhD	OB/DBV	Sections: 8	**Select one:** __X__Authored ____Approved
	Signature: Haley R. Gittleman -S Digitally signed by Haley R. Gittleman -S Date: 2023.01.26 14:41:19 -05'00'			

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	Signature: Xin Gao -S Digitally signed by Xin Gao -S Date: 2023.01.26 15:09:37 -05'00'			
Statistical Team Leader	Mallorie Fiero, PhD	OB/DBV	Sections: 1,8	**Select one:** __X__ Authored __X__ Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S Date: 2023.01.26 15:25:20 -05'00'			
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Associate Director for Labeling (ADL)	William Pierce, PharmD, MPH, BCPS		Sections: 11	**Select one:** __X__ Authored __X__ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2023.01.25 16:42:52 -05'00' *Elizabeth Everhart, MSN, RN, ACNP, signing for William Pierce, PharmD, MPH, BCPS.*			
Associate Director Patient Outcomes (PRO)	Vishal Bhatnagar, MD		Sections: 8.1.1	**Select one:** __X__ Authored __X__ Approved
	Signature: Vishal Bhatnagar -S Digitally signed by Vishal Bhatnagar -S Date: 2023.01.26 15:46:42 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Mirat Shah, MD Mirat Shah -S Digitally signed by Mirat Shah -S Date: 2023.01.25 17:38:23 -05'00'		Sections: 1-19	**Select one:** ____ Authored __x__ Approved
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Division Director (Clinical)	Laleh Amiri-Kordestani, MD Laleh Amiri Kordestani -S Digitally signed by Laleh Amiri Kordestani -S Date: 2023.01.26 11:00:16 -05'00'		Sections: 1-19	**Select one:** ____ Authored __X__ Approved
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