ELACESTRANT **M**ONOTHERAPY VS. STANDARD OF CARE FOR THE TREATMENT OF PATIENTS WITH **ER**+/HER2- **A**DVANCED BREAST CANCER FO**L**LOWING C**D**K4/6 INHIBITOR THERAPY: A PHASE 3 RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED, MULTICENTER TRIAL

(EMERALD)

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PROCEDURES IN CASE OF EMERGENCY

Emergency contact information can be found on the subject identification card.

1. SYNOPSIS

Name of Sponsor/Company:

Radius Pharmaceuticals, Inc. (RADIUS)

Name of Investigational Product:

Elacestrant (RAD1901)

Name of Active Ingredient:

Elacestrant

Title of Study:

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

Study Center(s):

Approximately 230 sites worldwide, including, but not limited to, Europe, North America, Middle East, Asia-Pacific, and South America

Objectives:

Primary Objective:

To demonstrate that elacestrant compared with the standard of care (SOC) options of either fulvestrant or an aromatase inhibitor (AI) is superior in prolonging progression-free survival (PFS) based on a blinded Imaging Review Committee (IRC) assessment in post-menopausal women and men with estrogen receptor positive (ER+)/human epidermal growth factor receptor 2 negative (HER2-) advanced/metastatic breast cancer (mBC), either in subjects with mutations of the estrogen receptor 1 (ESR1) gene (ESR1-mut subjects) or in all subjects which includes subjects without detectable ESR1 mutations (ESR1-mut-nd)

Key Secondary Objectives:

- To compare overall survival (OS) between treatment groups in ESR1-mut subjects
- To compare OS between treatment groups in all subjects (ESR1-mut and ESR1-mut-nd)

Other Secondary Objectives:

The following secondary objectives will be 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 will be assessed for ESR1-mut subjects, ESR1-mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd):

- To compare PFS based on local Investigator assessment between treatment groups
- To compare objective response rate (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 clinical benefit rate (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 secondary objectives will be assessed for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd):

- To compare the safety and tolerability between treatment groups
- To assess the pharmacokinetics (PK) of elacestrant
- To describe the changes in Patient Reported Outcomes (PROs) and Health-Related Quality of Life (HRQOL) and the changes in PROs/HRQOL between treatment groups

Exploratory Objectives:

The following exploratory objectives will be assessed in ESR1-mut subjects, ESR1-mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd):

- To determine the difference in the time to chemotherapy (TTC) between treatment groups
- To evaluate alterations in circulating tumor deoxyribonucleic acid (ctDNA) relevant to ER+ breast cancer and the cyclin-dependent kinase (CDK) 4/6 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 tissue and to explore the relationship between these findings and clinical response

Endpoints:

Primary Endpoints:

The primary endpoints of this study are as follows:

- IRC-assessed PFS in ESR1-mut subjects
- IRC-assessed PFS in all subjects (ESR1-mut and ESR1-mut-nd)

Key Secondary Endpoints:

The key secondary endpoints are as follows:

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

Other Secondary Endpoints:

The following endpoints will be analyzed for ESR1-mut-nd subjects:

- IRC-assessed PFS
- OS

The following endpoints will be analyzed for ESR1-mut, ESR1-mut-nd, and all subjects (ESR1-mut and ESR1-mut-nd):

- Local Investigator-assessed PFS
- IRC-assessed ORR
- IRC-assessed DoR
- IRC-assessed CBR
- Local Investigator-assessed ORR
- Local Investigator-assessed DoR
- Local Investigator-assessed CBR

The following endpoints will be assessed for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd):

- Safety and tolerability, assessed by adverse events (AEs), serious adverse events (SAEs), dose modifications, clinical laboratory parameters (ie, hematology, chemistry, and coagulation), electrocardiograms (ECGs), performance status, and vital signs
- PK, assessed by evaluation of elacestrant concentrations at pre-dose (pre-treatment) and 4 hours post-dose on Cycle 1 Day 1 (C1D1), pre-dose (trough concentration [C_{trough}]) and 4 hours post-dose on C1D15, and pre-dose (C_{trough}) on C2D1
- PRO endpoints, assessed using the HRQOL scales, EuroQoL 5 Dimension 5 Level (EQ-5D-5L), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), and Patient Reported Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Exploratory Endpoints:

The following exploratory endpoints will be assessed in ESR1-mut subjects, ESR1 mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd):

- TTC
- Alterations in ctDNA relevant to ER+ breast cancer and the CDK4/6 pathway and the relationship between these findings and clinical response
- Alterations in tumor-specific genes, proteins, and RNAs related to oncogenic pathways and proliferation and cell cycle markers in tumor tissue and the relationship between these findings and clinical response

Methodology:

This is an international, multicenter, randomized, open-label, active-controlled, event-driven, Phase 3 clinical study comparing the efficacy and safety of elacestrant to the SOC options of fulvestrant or an AI in post-menopausal women and men with ER+/HER2- mBC whose disease has relapsed or progressed on at least 1 and no more than 2 prior lines of endocrine therapy for advanced or metastatic disease, which must have included progression on prior CDK4/6 inhibitor therapy in combination with fulvestrant or an AI. Endocrine monotherapy with 1 of the SOC drugs (fulvestrant, anastrozole, letrozole, exemestane) must be an appropriate treatment option for subjects enrolled in this study.

Subjects will be randomized in a 1:1 ratio to receive either elacestrant or the Investigator's choice of endocrine monotherapy with 1 of the following SOC drugs: fulvestrant, anastrozole, letrozole, or exemestane.

Note: During SOC treatment, the Investigator will follow any warnings or precautions for use as detailed in each Product Insert (PI) or Summary of Product Characteristics (SmPC).

Randomization will be stratified based on the following criteria:

- ESR1 mutation(s) detected in ctDNA (ESR1-mut vs ESR1-mut-nd)
- Prior treatment with fulvestrant (yes vs no)
- Presence of visceral metastases (yes vs no); visceral includes lung, liver, brain, pleural, and peritoneal involvement

The ctDNA ESR1 mutation status must be centrally determined during Screening prior to randomization.

Study Committees:

IRC

A blinded, independent IRC will review radiographic images and clinical information collected on study to determine the protocol-defined endpoints of disease response and progression. Further information on the independent review process will be provided in the IRC Charter.

Independent Data Monitoring Committee (IDMC)

An IDMC external to both RADIUS and the clinical research organization (CRO) will be responsible for ongoing monitoring of the safety and efficacy according to the IDMC Charter. The IDMC will meet on a regular basis and will make recommendations as to whether the trial should continue, be amended, or be discontinued based on ongoing reviews of safety and efficacy data.

Study Steering Committee (SSC)

A SSC composed of international physicians with expertise in management of ER+ mBC will be convened by RADIUS. The remit of the SSC is to provide guidance to RADIUS on protocol development and implementation, Investigator selection, and recruitment strategies. The SSC will also apprise RADIUS on advances in the field that could impact the trial. The SSC will not be provided with any efficacy or safety data during the trial.

Number of Subjects (planned):

This study is event-driven and is planned for a total of approximately 160 PFS events (objective disease progression assessed by the blinded IRC or death) among the ESR1-mut subjects and 340 PFS events among all subjects (ESR1-mut and ESR1-mut-nd). It is estimated that approximately 466 subjects (220 ESR1-mut; 246 ESR1-mut-nd) will need to be enrolled in the study in a 1:1 randomization at approximately 230 clinical study sites experienced in conducting oncology clinical trials in Europe, North America, Middle East, Asia-Pacific, and South America. Additional or fewer subjects and regions may be required to achieve the planned total number of events.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria

Subjects must meet all the following inclusion criteria:

1. Must have a 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
2. Must be appropriate candidates for endocrine monotherapy
3. Must have 1 of the following as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1:
    a. Measurable disease
    b. Bone only disease with evaluable lesions. Subjects must have at least 1 lytic or mixed lytic/blastic bone lesion; blastic lesions only are not evaluable and allowed. Subjects who have had prior radiation to bone must have at least 1 evaluable lesion in a nonirradiated area
4. Female or male ≥ 18 years of age
5. Female subjects must be post-menopausal women, defined by 1 of the following criteria:

a. Documented bilateral surgical oophorectomy
b. Age ≥ 60 years with amenorrhea ≥ 1 year since last menses
c. Age < 60 years with amenorrhea ≥ 1 year since last menses with no alternative pathological or physiological cause (including ongoing or recent chemotherapy, treatment with tamoxifen or toremifene, or a gonadotropin releasing hormone agonist), and serum estradiol and follicle stimulating hormone (FSH) levels within the laboratory reference range for post-menopausal women
d. Age < 60 years with tamoxifen or toremifene therapy within the last 12 months, with documentation of 12 months of amenorrhea prior to tamoxifen or toremifene therapy and serum estradiol and FSH levels within the laboratory reference range for post-menopausal women
e. Females with hormonally-induced menopause (ie, requiring ongoing hormone suppression) are not eligible

6. Male subjects must, even if surgically sterilized (ie, status post-vasectomy):

   a. Agree to practice highly effective barrier contraception (use condoms) during the entire study treatment period and through 120 days after the last dose of study drug. For subjects (who have not undergone vasectomy) with female partners of childbearing potential, the subject and his partner must, in addition to condoms, use highly effective contraceptive measures when engaging in sexual intercourse throughout the treatment period and for at least 120 days after the last dose of study drug (ie, oral contraceptive and condoms; intrauterine device and condoms; diaphragm with spermicide and condoms; other forms of contraception must be approved by the medical monitor)

      OR

      Agree to practice true abstinence during the entire study treatment period and through 120 days after the last dose of study drug

      Note: Abstinence should only be used as a contraceptive method if it is in line with the subject's usual and preferred lifestyle. Periodic abstinence (calendar symptothermal, post-ovulation methods) is not an acceptable method of contraception.

   b. Agree not to donate sperm during the course of treatment period of this study or within 120 days after receiving the last dose of the study drug

7. Must have ER+ and HER2- tumor status confirmed per local laboratory testing. Status may be confirmed on original diagnosis tissue samples or post-treatment samples (most recent biopsy preferred, if testing available). ER and HER2 testing must be performed in the following manner:

   a. Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry (IHC) as defined in the 2010 American Society for Clinical Oncology (ASCO) recommendations for ER testing (Hammond et al, 2010), with or without progesterone receptor (PGR) positivity

AND

b. Documentation of HER2- tumor with an IHC result of 0 or 1+ for cellular membrane protein expression or an in situ hybridization negative result as defined in the 2013 or 2018 ASCO recommendations for HER2 testing (Wolff et al, 2013; Wolff et al, 2018)

8. 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 (eg, PI3K inhibitor), for mBC
    a. Must have progressed during or within 28 days of completion of each line of endocrine therapy; ie, if a subject was discontinued due to toxicity without progression, this would not count as a line of prior therapy
    b. For subjects who progress during or within 12 months of adjuvant endocrine therapy, this will count as 1 line of endocrine therapy for mBC. In the absence of such progression, adjuvant therapy does not count as 1 of the required lines of endocrine therapy
9. 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
    a. Prior treatment with a CDK4/6 inhibitor not in combination with fulvestrant or an AI will not fulfill this criterion
    b. Discontinuation of prior CDK4/6 inhibitor due to toxicity, in the absence of progression, will not fulfill this criterion
10. Must have received no more than 1 line of cytotoxic chemotherapy in the advanced/metastatic setting
    a. Cytotoxic chemotherapy does not include: CDK4/6 inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, phosphoinositide 3-kinase (PI3K) inhibitors, or immunotherapy. There are no restrictions on prior use of these agents
    b. There is no requirement for documentation of progressive disease to prior chemotherapy
    c. Chemotherapy given in combination with endocrine therapy counts as both a line of endocrine therapy and a line of chemotherapy
    d. Chemotherapy administered for less than 1 cycle will not be counted as a prior line of chemotherapy
    e. For subjects who progress within 12 months of neoadjuvant or adjuvant chemotherapy, this will count as 1 prior line of therapy for advanced/metastatic disease
11. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
12. Resolution of all toxic effects of prior therapies or surgical procedures to Grade $\leq$ 1 (except alopecia and peripheral neuropathy)
13. Adequate organ function as defined below:

a. Hematologic function (in the absence of transfusion of red blood cells or platelets or the use of growth factors within the preceding 4 weeks)
   - Absolute neutrophil count ≥ 1.0 x 10^9/L
   - Platelet count ≥ 75 x 10^9/L
   - Hemoglobin ≥ 9.0 g/dL

b. Renal function
   - Estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 or creatinine clearance calculated by Cockcroft-Gault equation ≥ 30 mL/min (Appendix 4)

c. Hepatic function
   - Alanine aminotransferase (ALT) ≤ 3x upper limit of normal (ULN)
   - Aspartate aminotransferase (AST) ≤ 3x ULN
   - Total bilirubin ≤ ULN or total bilirubin ≤ 1.5x ULN with direct bilirubin ≤ ULN of the laboratory in subjects with documented Gilbert's Syndrome

d. Chemistry
   - Potassium, sodium, calcium (corrected for albumin), magnesium, and phosphorus National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 Grade ≤ 1. If Screening assessments are abnormal, chemistry assessments may be repeated up to 2 times; subjects may receive appropriate supplementation or treatment (eg, for hypercalcemia) prior to re-assessment

e. Coagulation
   - International normalized ratio (INR) ≤ 1.5

   Note: Subjects who are receiving anticoagulation treatment which is monitored by international normalized ratio (INR) (eg, warfarin) may be allowed to participate if they have a stable INR (ie, within therapeutic range) for at least 28 days prior to the first dose of study drug, in the absence of any exclusionary medical conditions, and provided that an AI would be appropriate therapy for the subject

14. Ability to understand the protocol and provide informed consent

Exclusion Criteria

Subjects must meet none of the following exclusion criteria:

1. Prior treatment with elacestrant or investigational selective estrogen receptor degrader (SERD) or ER antagonist (eg, D-0502, GDC-0810, GDC-0927, GDC-9545, G1T-48, LSZ102, AZD9496, SAR439859, ZN-c5, H3B-6545, bazedoxifene, lasofoxifene)
2. Prior anti-cancer or investigational drug treatment within the following windows:

a. Fulvestrant treatment (last injection) < 42 days before first dose of study drug
b. Any other endocrine therapy < 14 days before first dose of study drug
c. Chemotherapy or other anti-cancer therapy < 21 days before first dose of study drug
d. Any investigational anti-cancer drug therapy < 28 days or 5 half-lives (whichever is shorter) before the first dose of study drug. Enrollment of subjects whose most recent therapy was an investigational agent should be discussed with RADIUS
e. Bisphosphonates or RANKL inhibitors initiated or dose changed < 3 months prior to first dose of study drug

3. Radiation therapy within 14 days (28 days for brain lesions per Exclusion Criterion 4) before the first dose of study drug
4. Presence of symptomatic metastatic visceral disease, including but not limited to, extensive hepatic involvement, untreated or progressive central nervous system (CNS) metastases, or symptomatic pulmonary lymphangitic spread. Subjects with discrete pulmonary parenchymal metastases are eligible provided their respiratory function is not significantly compromised as a result of disease in the opinion of the Investigator. Subjects with previously treated CNS metastases are eligible provided that all known lesions were previously treated, they have completed radiotherapy at least 28 days prior to first dose of study drug, and are clinically stable. If anticonvulsant medication is required, subjects must be stable on a non-enzyme inducing anticonvulsant regimen
5. Intact uterus with a history of endometrial intraepithelial neoplasia (atypical endometrial hyperplasia or higher-grade lesion)
6. Diagnosis of any other malignancy within 5 years before enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or second primary breast cancer
7. Any of the following within 6 months before enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE v5.0 Grade ≥ 2, prolonged QTcF ≥ Grade 2 (ie, > 480 msec), uncontrolled atrial fibrillation of any grade, coronary/peripheral artery bypass graft, heart failure ≥ Class II as defined by the New York Heart Association guidelines, or cerebrovascular accident including transient ischemic attack
8. Child-Pugh Score greater than Class A (ie, score >6)
9. Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism. However, subjects with the following conditions will be allowed to participate:
    a. Adequately treated catheter-related venous thrombosis occurring >28 days prior to the first dose of study drug
    b. Treatment with an anticoagulant, eg, warfarin or heparin, for a thrombotic event occurring > 6 months before enrollment, or for an otherwise stable and allowed medical condition (eg, well controlled atrial fibrillation), provided dose and coagulation parameters (as defined by local standard of care) are stable for at least

28 days prior to the first dose of study drug and provided that an AI would be an appropriate therapy for the subject

10. Known bleeding disorder which, in the opinion of the Investigator, would prohibit administration of fulvestrant if that would be SOC choice for the subject
11. Known difficulty in tolerating oral medications or conditions which would impair absorption of oral medications such as: uncontrolled nausea or vomiting (ie, CTCAE ≥ Grade 3 despite antiemetic therapy), ongoing gastrointestinal obstruction/motility disorder, malabsorption syndrome, or prior gastric bypass
12. Unable or unwilling to avoid prescription medications, over-the-counter medications, dietary/herbal supplements (eg, St. John's wort), and/or foods (eg, grapefruit, pomelos, star fruit, Seville oranges and their juices) that are moderate/strong inhibitors or inducers of CYP3A4 activity. Participation will be allowed if the medication, supplements, and/or foods are discontinued for at least 5 half-lives or 14 days (whichever is longer) prior to study entry and for the duration of the study
13. Major surgery < 28 days before the first dose of study drug
14. Any concurrent severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with compliance with study procedures or the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study
15. Known hypersensitivity reaction to drugs chemically related to elacestrant or their excipients
16. Known hypersensitivity to fulvestrant, anastrozole, letrozole, or exemestane (or to any of their excipients), unless treatment with 1 of the other 3 of these 4 treatment options would be appropriate therapy
17. Subjects who meet any contraindication, according to the respective PI or SmPC, for any SOC drug that the Investigator would choose for that subject should the subject be randomized to the SOC group

Investigational Product, Dosage and Mode of Administration:

Elacestrant will be provided as 100 mg and/or 400 mg tablets to be taken orally once per day on a continuous dosing schedule. Protocol-defined dose reductions will be permitted.

Reference Therapy, Dosage and Mode of Administration:

SOC monotherapy of either fulvestrant or an AI (letrozole, anastrozole, exemestane) is to be administered as follows: fulvestrant 500 mg administered intramuscularly (IM) into the buttocks as 2 - 5 mL injections on C1D1, C1D15 and C2D1, and Day 1 of every subsequent 28-day cycle or an AI taken orally on a continuous dosing schedule (anastrozole 1 mg/day; letrozole 2.5 mg/day; or exemestane 25 mg/day).

Duration of Treatment:

Subjects will continue to receive treatment until disease progression, clinically significant AE, significant study noncompliance, unable to receive study treatment for > 14 consecutive days, treatment discontinuation in the best interest of the subject, or subject refuses treatment. Based on median duration of treatment of 3.8 months in Study RAD1901-005 for all subjects treated with 400 mg elacestrant, subjects randomized to elacestrant are expected to remain on treatment for approximately 4 months. Subjects exhibiting a response would be expected to have longer treatment duration.

Criteria for Evaluation:

Efficacy:

Efficacy analyses will be performed using tumor assessments made by the blinded IRC as the primary data source. Analyses of endpoints based on local Investigator assessment will also be performed as supportive analyses.

Safety:

Assessment of safety and tolerability will be based on incidence of AEs, SAEs, dose modifications, review of clinical laboratory data (ie, hematology, chemistry, and coagulation), ECG monitoring, physical examinations, performance status, and vital signs.

Statistical Methods:

Sample Size Assumptions:

Among the ESR1-mut subjects, the study requires approximately 160 PFS events to have a power of 80% to detect a hazard ratio of 0.610 at the 2-sided alpha level of 2.5%. Assuming a median PFS of 5.3 months for the SOC treatment group, this treatment effect represents a median PFS of 8.7 months for the elacestrant treatment group, an increase of approximately 3.4 months among the ESR1-mut subjects.

Among all subjects (ESR1-mut and ESR1-mut-nd), a total of approximately 340 PFS events will have 92% power to detect a hazard ratio of 0.667 at the 2-sided alpha level of 2.5%.

The 2-sided alpha level of 2.5% for the sample size calculation was selected to ensure that at least 1 of the 2 primary endpoints will pass the Hochberg procedure to control the overall alpha level at 5.0%.

The study will need to randomize approximately 220 ESR1-mut subjects (110/treatment group) and a total of approximately 466 subjects of both types (ESR1-mut and ESR1-mut-nd; 233/treatment group) in a 1:1 ratio to the 2 treatment groups. To prevent exceeding the target recruitment by more than 10% (ie, 512 subjects total), if a total of 292 ESR1-mut-nd subjects is reached before 220 ESR1-mut subjects are enrolled, further enrollment will be restricted to ESR1-mut subjects only until the target of 220 is achieved.

Final analysis of the primary endpoints will be performed at approximately 160 PFS events among the ESR1-mut subjects and 340 PFS events among all subjects (ESR1-mut and ESR1-mut-nd), estimated to occur 30-33 months after the first subject is randomized.

Analysis Populations:

The following populations will be defined and used for analysis:

- The Intention-to-Treat (ITT) Population consists of all randomized subjects. This is the primary population for PFS and OS analyses. Subjects will be analyzed according to their randomized treatment assignments.
- The Safety Population consists of all subjects who received at least 1 dose of study medication. All safety analyses will be performed using the Safety population. Subjects will be analyzed according to the treatments they actually received in Cycle 1.
- The Response Evaluable (RE) population includes all ITT subjects who had measurable disease (ie, at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion. The RE population is used for the analyses of best overall response and ORR.
- The Clinical Benefit Evaluable (CBE) population includes all ITT subjects who had measurable and/or evaluable disease (ie, target and/or non-target lesions) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion. The CBE population is used for the analyses of CBR.
- The PK population consists of all subjects who received at least 1 dose of elacestrant and have PK concentration data for at least 1 scheduled time point. PK analyses will be performed using the PK population.
- The Biomarker population consists of all subjects in the Safety population for whom adequate quality and volume of biomarker samples are available for analysis. The exploratory biomarker analysis will be performed using the Biomarker population.

Subject Characteristics:

Subject characteristics will be summarized by treatment group using the ITT population for 2 sets of study subjects: ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd). Standard descriptive statistics for continuous and categorical variables will be provided for subject demographics, baseline disease characteristics, prior anti-cancer therapies, and other baseline characteristics. No hypothesis testing will be conducted.

Efficacy Analysis

Type I Error Control

The 2 primary endpoints will be evaluated using the Hochberg procedure in order to maintain the overall alpha level at 2-sided 5.0%:

- 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 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 the 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 for either of the 2 primary endpoints

Primary Endpoints

Analyses of IRC-assessed PFS in ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd) will be performed using the ITT population for the ESR1-mut subjects and the entire ITT population, respectively. PFS will be analyzed 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 will be 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 log-rank test will be performed as a sensitivity analysis. The Cox regression model, including treatment and the stratification factors as above, will be used to estimate the hazard ratio and 95% CI.

Key Secondary Endpoints

Analyses of OS in ESR1-mut subjects and in all subjects (ESR1-mut and ESR1-mut-nd) will be 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 will be analyzed at the following 2 time points:

- At the time of the final PFS analysis (when approximately 160 and 340 PFS events are observed among the ESR1-mut and all subjects [ESR1-mut and ESR1-mut-nd], respectively)
- At the time of the final OS analysis (when 50% of the subjects have died)

At each time point, OS for the treatment groups will be analyzed using KM methods and displayed graphically, with median event times and 95% CIs displayed only for analysis at the final OS time. The Cox regression model that includes treatment and stratification factors (as in the primary analyses of the primary endpoints) will be used to estimate the hazard ratio and 95% CI. In addition, the difference between treatment groups will be analyzed using the stratified log-rank test at the final OS time. A 2-sided alpha level of 0.01% will be 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.

Other Secondary Endpoints

Analyses of IRC-assessed PFS in ESR1-mut-nd subjects will be performed using the ITT population for ESR1-mut-nd subjects in the same manner as the analyses of the primary endpoints.

Analyses of OS in ESR1-mut-nd subjects will be performed using the ITT population for the ESR1-mut-nd subjects in the same manner as the analyses of OS in ESR1-mut subjects and in all subjects (ESR1-mut and ESR1-mut-nd).

Local Investigator-assessed PFS will be analyzed in the same manner as IRC-assessed PFS.

ORR and CBR will be summarized as binomial response rates and compared between treatment groups using stratified Fisher's exact test.

DoR will be summarized for subjects who achieve either a confirmed complete response or partial response using the KM method. Estimated median values of DoR along with 95% CI will be provided.

Results of the efficacy analyses in the 3 sets of study subjects, ESR1-mut subjects, ESR1-mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd) will be presented using Forest plots.

Subgroup analyses of PFS, OS, ORR, and CBR based on prior treatment with fulvestrant and presence of visceral metastases will be performed in the same manner as the analyses in the overall populations.

Safety Analyses

Safety analyses will be performed using the Safety population for 2 sets of study subjects: ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd).

For each set of study subjects, safety analyses will be performed by treatment group and include summaries of the following:

- AEs, including NCI CTCAE v5.0 severity grade and relationship to study drug
- Deaths, SAEs, and AEs leading to study drug withdrawal
- Dose interruptions and reductions due to AEs
- Laboratory values over time and shifts in laboratory measurements by NCI CTCAE v5.0 grade
- ECG values over time and change from baseline
- ECOG performance status over time and shifts in ECOG performance status
- Vital sign values over time and incidence of potentially clinically significant values

Interim Analysis

An interim futility analysis will be performed at about 70% enrollment. Recommendations for further enrollment in the study will be made by the IDMC.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AI	Aromatase inhibitor
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BP	Blood pressure
BUN	Blood urea nitrogen
C1D1……. CxDx	Cycle 1 Day 1…… Cycle x Day x
CBE	Clinical Benefit Evaluable
CBR	Clinical benefit rate
CDK	Cyclin-dependent kinase
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor
CI	Confidence intervals
CNS	Central nervous system
CR	Complete response
CRA	Clinical research associate
CRF	Case Report Form
CRO	Clinical Research Organization
CSF	Cerebrospinal fluid
CT	Computed tomography
ctDNA	Circulating tumor deoxyribonucleic acid
C_{trough}	Trough concentration
CV	Coefficient of variation
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ER	Estrogen receptor
ERα	Estrogen receptor-alpha
ER+	Estrogen receptor positive
EOT	End of treatment
ESR1	Estrogen receptor 1 gene

Abbreviation	Definition
ESR1-mut	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)
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FES	16a-^{18}F-fluoro-17β-estradiol
FES-PET	Fluoroestradiol-positron emission tomography
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin releasing hormone
HDPE	High density polyethylene
HER2	Human epidermal growth factor receptor 2
HER2+	Human epidermal growth factor receptor 2 positive
HER2-	Human epidermal growth factor receptor 2 negative
HR	Heart rate
HRQOL	Health-Related Quality of Life
HV	Healthy volunteer
IB	Investigator's Brochure
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IM	Intramuscular(ly)
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Imaging Review Committee
IRT	Interactive randomization technology
ITT	Intention-to-treat
KM	Kaplan-Meier
LBD	Ligand-binding domain
LH	Luteinizing hormone
mBC	Advanced/metastatic breast cancer
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease

Abbreviation	Definition
PDX	Patient-derived xenograft
PET	Positron emission tomography
PFS	Progression-free survival
PGR	Progesterone receptor
PI	Product Insert
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcomes
PRO-CTCAE	Patient Reported Outcome-Common Terminology Criteria for Adverse Events
PT	Prothrombin time
PTx	Post-treatment
Q1	1st quartile
Q3	3rd quartile
QD	Once daily
QTcF	QT corrected by Fridericia's formula
RNA	Ribonucleic acid
RP2D	recommended Phase 2 dose
RADIUS	Radius Pharmaceuticals, Inc
RE	Response Evaluable
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SERD	Selective estrogen receptor degrader
SERM	Selective estrogen receptor modulator
SmPC	Summary of Product Characteristics
SOC	Standard of care
SSC	Study Steering Committee
$t_{½}$	Half-life
TEAE	Treatment emergent adverse event
t_{max}	Time to maximum concentration
TTC	Time to chemotherapy
ULN	Upper limit of normal
U.S.	United States
WT	Wild-type

2. INTRODUCTION

2.1. Breast Cancer

Breast cancer is the leading type of cancer in women and the second leading cause of all new cancers worldwide when genders are combined (Ferlay et al, 2015). In women, it is the fifth leading cause of death (Ferlay et al, 2015) and the leading cause of cancer-related deaths (DeSantis et al, 2015). For European women, there were ~464,000 new cases and, concurrently, ~131,000 deaths from breast cancer in 2012 (Ferlay et al, 2015). In the United States (U.S.), approximately 330,000 (~ 266,120 invasive and ~63,960 non-invasive or in situ) new cases are expected for 2018 while an estimated 40,920 American women will die from the disease during this same period (breastcancer.org). 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 there will be 2,550 new cases of invasive breast cancer in men and nearly 500 men will die from breast cancer in 2018 (breastcancer.org).

In the U.S. and Europe, improved treatments for many breast cancer patients are prolonging survival and improving quality of life, but the death rate for breast cancer is second only to lung cancer for women in the U.S. Furthermore, preventive methods are not abolishing new cases; breast cancers account for ~30% of all newly diagnosed cancers among U.S. women and the incidence rate of male breast cancer has not changed over the last 30 years (breastcancer.org). Thus, even in developed regions of the world, there is an unmet medical need for improving the care and treatment of patients diagnosed with this disease.

Breast cancer is subdivided into categories based on tumor receptor status and is considered hormone receptor positive (+) if the tumor expresses the estrogen receptor (ER) or the progesterone receptor (PGR) and human epidermal growth factor receptor 2 positive (HER2+) if the tumor expresses the HER2 receptor. Alternatively, a tumor may not express any of these receptors and is considered receptor negative (-). Approximately 60-75% of breast cancers express the ER at the time of diagnosis (Hawkins, 1987). Given that the ER drives the growth and survival of these hormone-positive tumors, the National Comprehensive Cancer Network (NCCN, 2018) guidelines recommend endocrine treatment for estrogen receptor positive (ER+) breast cancer patients. Available endocrine treatments act as antiestrogens either by 1) decreasing ligand levels (ovarian ablation, gonadotropin releasing hormone (GnRH) agonists, aromatase inhibitors [AIs]) or 2) antagonizing the receptor (selective estrogen receptor modulators [SERMs]; eg, tamoxifen, toremifene), or 3) acting as selective estrogen receptor degraders (SERDs; eg, fulvestrant).

While ER+ status has proven to be a positive prognostic factor and adjuvant endocrine therapy for primary ER+ disease can lead to long-term clinical benefit, there is currently no cure for advanced or metastatic ER+ breast cancer. Interestingly, even after treatment progression on multiple endocrine therapies, ER expression is often maintained in the metastatic setting, allowing physicians to cycle through available endocrine therapies in an attempt to control disease progression and reduce or delay the need for chemotherapeutic intervention (McDonnell and Wardell, 2010; Oesterreich and Davidson, 2013). Despite the availability of several approved endocrine therapies, there remains a large unmet need for improved treatment options, particularly in the setting of recurrent metastatic disease (Glück, 2014).

Fulvestrant (Faslodex® AstraZeneca) is currently the only approved SERD for the treatment of patients who have ER+ advanced or metastatic breast cancer (mBC). Fulvestrant effectively degrades the ER and has demonstrated clinical benefit in ER+ mBC patients. In the first-line metastatic setting, fulvestrant was associated with a median progression-free survival (PFS) of 6.5 months at 500 mg monthly dose in patients with ER+ metastatic or locally advanced breast cancer who failed previous hormonal therapy (DiLeo et al, 2010). While fulvestrant has demonstrated clinical benefit and is currently the only approved SERD for use in breast cancer patients, it has been described as being limited by its pharmacokinetic (PK) properties and its intramuscular (IM) route of administration, underscoring the need for novel ER antagonists (Wardell et al, 2015; Bihani et al, 2017).

A sizable proportion of ER+ patients are de novo resistant to first-line endocrine therapy in the metastatic setting and the majority of those who initially respond ultimately become resistant to all available endocrine agents (Osborne and Schiff, 2011). These treatment failures have fueled the development of novel endocrine agents or targeted therapies that can be combined with endocrine therapies to increase clinical efficacy. The combination of cyclin-dependent kinase 4/6 inhibitors (CDK 4/6i) with AIs or fulvestrant in the first and second-line metastatic setting, respectively, has resulted in significant increases in PFS (Cristofanilli et al, 2016; Finn, et al 2016). However, patients receiving combination regimens that include a CDK4/6 inhibitor are rarely cancer free and unfortunately, the disease will inevitably progress. For patients who have disease progression on first- and second-line monotherapy and combination hormonal therapies, there is a need for well-tolerated and efficacious therapeutic options.

Point mutations in the ligand-binding domain (LBD) of ER have been described as a potential mechanism of treatment resistance and as a poor prognostic factor in metastatic ER+ disease (Chandarlapaty et al, 2016; Fanning et al, 2016). Two of the most frequently found estrogen receptor 1 gene (ESR1) mutations in patients, Y537S and D538G, have been shown to result in estradiol-independence and constitutive activation of ER in nonclinical models (Li et al, 2013; Toy et al, 2013; Jeselsohn et al, 2014). Furthermore, nonclinical studies have suggested that mutations in ER can cause decreased binding of ER antagonists to the receptor and a corresponding decrease in activity (Fanning et al, 2016). Recent clinical reports have demonstrated that some patients who have received AI therapy had detectable point mutations in ER (Chandarlapaty et al, 2016; Fribbens et al, 2016). While the detection of ESR1-mut post-AI has been demonstrated clinically, the efficacy of AIs or fulvestrant in tumors harboring ESR1-mut has not been evaluated in a prospective clinical study where patients were stratified based on ESR1 status. The limited available clinical data are based on retrospective study designs with relatively small data sets, making it difficult to accurately predict hormonal agent activity against specific ESR1-mut or against tumors that harbor multiple ESR1-mut. Prospective studies stratified by ESR1-mut status will be critical in identifying the optimal therapeutic approach for subjects with tumors bearing ESR1-mut.

Next-generation, orally-bioavailable SERDs with improved PK properties have garnered significant interest as potential therapies for metastatic ER+ breast cancer in an effort to produce more durable clinical responses with a more favorable route of administration (Bentzon et al, 2008; McDonnell and Wardell, 2010; Osborne and Schiff, 2011; Glück, 2014). Herein, the rationale for the proposed evaluation of elacestrant, a novel,

orally-bioavailable SERD for the treatment of ER+ breast cancer in a post-endocrine, post-CDK4/6 inhibitor setting, including patients who have tumors harboring ESR1 mutations, is described.

2.2. Elacestrant

Elacestrant is a tetrahydronaphthalene compound with a favorable tissue selective ER profile. Elacestrant is intended for once daily (QD) oral administration in tablet form. Elacestrant acts as a SERD at higher doses and, therefore, is being developed for the treatment of ER+ mBC. At lower doses, elacestrant was evaluated as a treatment for menopause-related vasomotor symptoms in women experiencing natural or surgically-induced menopause.

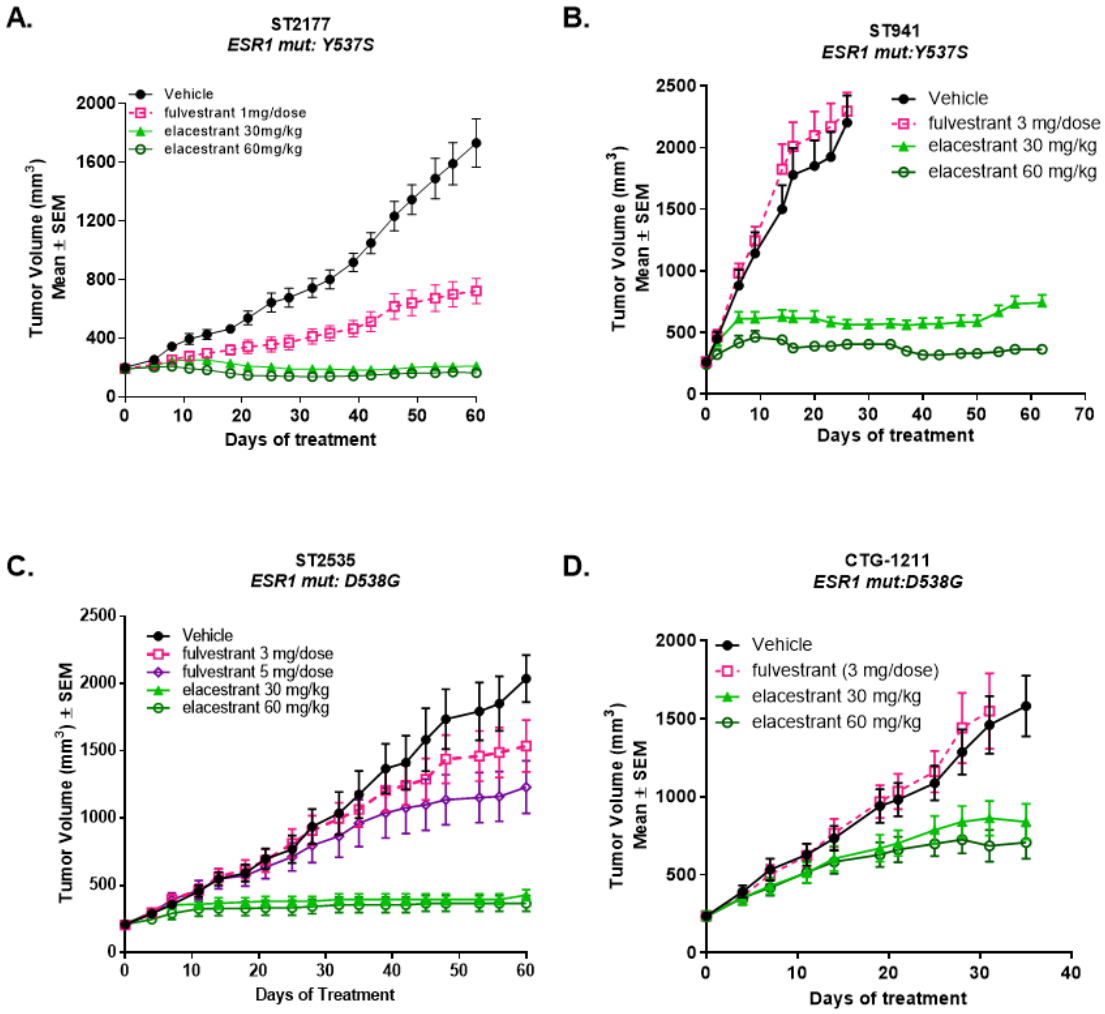
2.2.1. Nonclinical Studies

Elacestrant has been evaluated in a series of general pharmacology and toxicology studies. Data relevant to this protocol are described below with additional details provided in the Investigator's Brochure (IB).

Elacestrant binds with high affinity and selectivity for estrogen receptor-alpha (ERα) in vitro, causes a dose-dependent degradation of the ER, and has good oral bioavailability. Elacestrant has a low risk for adverse cardiac safety events and no effect on mortality in rats and monkeys. Slight increases in clotting time were observed, but clotting times were less than those observed in warfarin-treated rats. No adverse effects were observed on the respiratory system, the central nervous system, wound healing, or animal behavior and social interactions. To date, nonclinical studies of elacestrant in rats have shown no evidence of uterine stimulation (a known risk factor for endometrial cancer) or an increase in bone loss. Elacestrant showed a favorable profile when assessed for genetic toxicology and did not demonstrate mutagenic, clastogenic, aneuploidy, or genotoxic effects. Fertility, reproductive, and developmental toxicity studies have not been performed. Nonclinical data suggest elacestrant also has a favorable tissue selectivity profile, with an antagonist effect on ER in the breast and uterine tissue, while having agonist effects on bone (Garner et al, 2015).

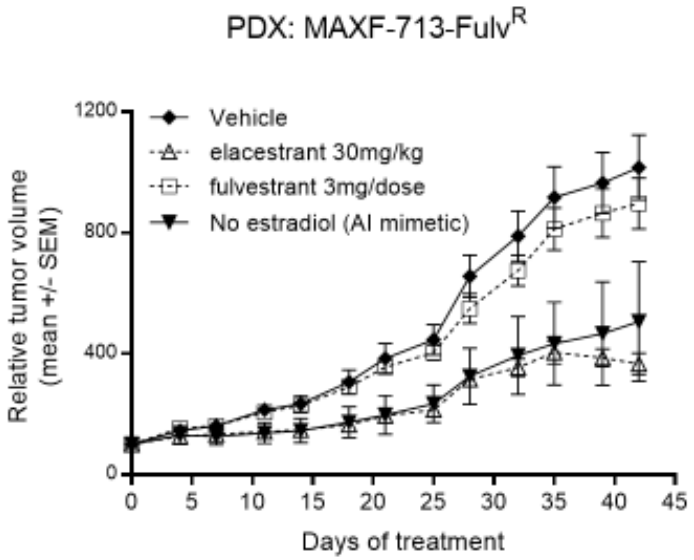
Studies using in vivo xenografts and in vitro cancer cell lines have been used to demonstrate elacestrant-induced growth inhibition of a variety of breast cancer models. In the presence of estradiol, elacestrant showed dose-dependent antagonism of estradiol-mediated proliferation of MCF-7 and T47D breast cancer cells. In the in vivo setting, elacestrant also inhibited the estrogen-dependent growth of MCF-7 breast cancer tumors. Furthermore, elacestrant has anti-tumor activity in multiple patient-derived xenograft (PDX) models of ER+ breast cancer, including those that are estrogen-independent, insensitive to fulvestrant, and/or harbor mutations in the ESR1 gene (Figure 1, Figure 2, and Figure 3). Anti-tumor activity of elacestrant was demonstrated in PDX models harboring either Y537S or D538G mutations in the ER, 2 of which came from patients treated with AIs, tamoxifen, and fulvestrant (Figure 1 and Figure 2). Additionally, 1 of these PDX models, WHIM43, was also resistant to the CDK4/6 inhibitor, palbociclib. In that model, elacestrant treatment resulted in significant growth inhibition compared to vehicle-treated tumors. Fulvestrant produced some growth inhibition; however, this effect was not statistically significantly different from vehicle-treated tumors (Figure 3).

Figure 1: Elacestrant Inhibits the Tumor Growth of PDX Models that Harbor Frequently Detected ESR1 Mutations, Y537S and D538G



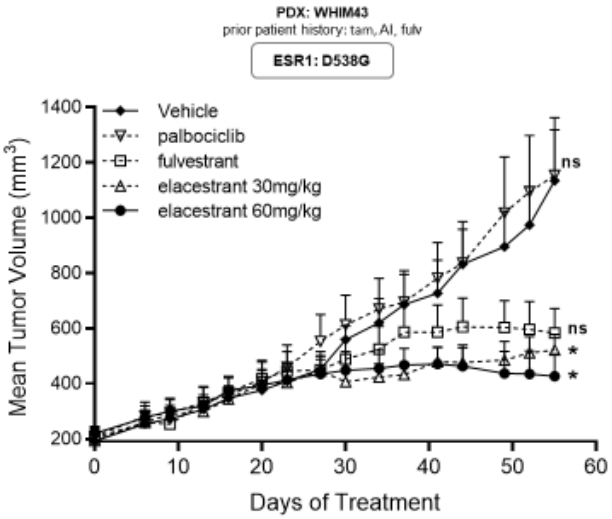
ESR1 mut = estrogen receptor 1 gene mutation.

Figure 2: Anti-Tumor Activity of Elacestrant in a Post-Fulvestrant Setting



Fulvestrant resistance was generated in the MAXF-713 PDX model by exposing mice to 4 rounds of fulvestrant treatment. This derivative model was supplemented with estradiol and treated with a vehicle control, fulvestrant (subcutaneous, weekly), or elacestrant (oral, daily) as shown and tumor growth measured. Tumor growth was also evaluated in this model in the absence of estradiol supplementation as a method of mimicking aromatase inhibitor treatment.
AI = aromatase inhibitor; PDX = patient-derived xenograft; SEM = standard error of the mean.

Figure 3: Elacestrant Anti-Tumor Activity in a Palbociclib-Resistant PDX Model (WHIM43)



WHIM43 is a PDX model derived from a patient previously treated with multiple endocrine therapies (tamoxifen, fulvestrant, AIs). The WHIM43 model harbors a D538G mutation in the ESR1 gene and demonstrates treatment resistance to CDK4/6 inhibitor palbociclib. PDX models are derived from patients that have received hormonal therapies. PDX mice were treated with vehicle, elacestrant (oral, daily), palbociclib (oral, daily) or fulvestrant (subcutaneous, weekly).
AI = aromatase inhibitor; ESR1 = estrogen receptor gene 1; fulv = fulvestrant; PDX = patient-derived xenograft; tam = tamoxifen.

2.2.2. Clinical Studies

As of 27 December 2019, a total of 585 subjects have been enrolled in the elacestrant development program, with 451 subjects having received elacestrant: 431 post-menopausal women and 20 men. The clinical development program includes 9 clinical studies: 2 dose-finding studies in healthy volunteers, 2 Phase 2 safety and efficacy studies in post-menopausal women with vasomotor symptoms, 2 Phase 1 clinical pharmacology studies in healthy volunteers, 2 Phase 1 studies and the ongoing Phase 3 study in post-menopausal women (and men in study RAD1901-308) with mBC (Table 1). Safety data from these studies is provided in more detail in Section 2.2.2.5.4 and in the IB.

Table 1: Summary of Elacestrant Clinical Studies

Study Number	Phase	Population	N	Primary Objective	Elacestrant Doses/formulations	Status
RAD1901-001	1	Postmenopausal women HVs	80 (62 elacestrant capsule[a] /18 placebo)	Safety, tolerability, single and multiple dose PK of elacestrant, bioavailability and food effect	1, 10, 25, 50, 100, 200 mg QD capsule and 1 mg IV	Completed
RAD1901-002	2	Postmenopausal women with vasomotor symptoms	100 (81 elacestrant capsule/ 19 placebo)	Safety and efficacy of elacestrant on vasomotor symptoms	10, 25, 50, 100 mg QD; capsule	Completed
RAD1901-004	1	Postmenopausal women HVs	52 (44 elacestrant / 8 placebo	Safety, tolerability, and PK of elacestrant	200, 500, 750, 1000 mg QD; capsule	Completed
RAD1901-005	1	Postmenopausal women with mBC	57 (33 capsule and 27 tablet[b])	Safety, PK, and MTD and/or RP2D of elacestrant	200, 400, 600 mg QD; capsule and tablet	Enrollment completed
RAD1901-106	1	Postmenopausal women with mBC	16 (16 capsule and 2 tablet[c])	Effect of elacestrant on the availability of ER binding sites using FES-PET imaging	200 mg QD x 14 days then escalated to 400 mg QD; and 400 mg QD; capsule and tablet	Completed
RAD1901-109	1	Postmenopausal women and men HVs	18 elacestrant (9F and 9M)	Effect of food on elacestrant PK	400 mg QD; tablet	Enrollment completed
RAD1901-110	1	Postmenopausal women and men HVs	18 elacestrant (9F and 9M)	Effect of strong CYP3A4 inhibitor itraconazole on elacestrant PK	200 mg QD; tablet	Enrollment completed
VMRAD1901-203	2	Postmenopausal women with vasomotor symptoms	139 (101 elacestrant/ 38 placebo)	Safety and efficacy of elacestrant on vasomotor symptoms	5, 10, 20 mg QD; capsule	Completed
RAD1901-308	3	Postmenopausal women and men with mBC	466 (planned)	Efficacy (PFS) of elacestrant vs active comparators[d]	400 mg QD; tablet	Enrollment ongoing

F = female; FES-PET = 16α-^{18}F-fluoro-17β-estradiol positron emission tomography; HV = health volunteer; IV = intravenous; M = male; mBC = advanced/metastatic breast cancer; MTD = maximum-tolerated dose; PFS = progression-free survival; PK = pharmacokinetics; RP2D = recommended Phase 2 dose; QD = once daily

[a]Five subjects in Study RAD1901-001 received both IV and capsules.

[b]Three subjects in Study RAD1901-005 received both capsules and tablets.

[c]Two subjects in Study RAD1901-106 received both capsules and tablets.

[d]Active comparators includes Standard of Care - Fulvestrant, Anastrozole, Letrozole, Exemestane.

2.2.2.1. Pharmacokinetic Data

PK data have been evaluated in all of the clinical studies, including studies in healthy post-menopausal women, post-menopausal women with vasomotor symptoms, and women with mBC. Key PK findings are as follows:

- Following oral administration, elacestrant is absorbed rapidly, reaching maximum plasma concentrations (t_{max}) within approximately 1 to 4 hours after multiple daily ascending doses (10 to 1000 mg for 7 days). Steady-state plasma concentrations of elacestrant were reached at approximately Day 6 following QD dosing, which is consistent with the observed half-life ($t_{1/2}$) of approximately 30 to 50 hours. Human plasma protein binding was high (essentially 100%).
- Exposure to elacestrant increased in a dose-dependent manner.
- Preliminary results from the food-effect study with elacestrant tablets (study RAD1901-109) indicate that administration with a light, low-fat meal or a heavy, high-fat meal increased the geometric mean elacestrant C_{max} by 32% and 36%, respectively, and increased the geometric mean elacestrant $AUC_{0-\infty}$ by 16% and 26%, respectively.
- The PK of elacestrant is similar between healthy post-menopausal women and post-menopausal women with ER+/HER2- mBC.
- In vitro studies indicate that elacestrant is a CYP3A4 substrate. The preliminary results from the drug-drug interaction study RAD1901-110 indicate that coadministration of the potent CYP3A4 inhibitor, itraconazole 200 mg QD, with elacestrant 200 mg QD increased the geometric mean elacestrant C_{max} by 4.37-fold (from 45.6 ng/mL to 199.3 ng/mL) and increased the geometric mean elacestrant $AUC_{0-\infty}$ by 5.27-fold (from 720 ng·h/mL to 3710 ng·h/mL). Therefore, elacestrant should not be coadministered with other drugs that alter (inhibit or induce) CYP3A4.
- Preliminary data from exposure-response analyses support the proposed elacestrant QD dose of 400 mg for treatment of ER+/HER2- mBC.

2.2.2.2. Safety and Tolerability in Healthy Volunteers Studies

Study RAD1901-001 is a Phase 1, randomized, double-blind, placebo-controlled study evaluating safety, tolerability, single and multiple dose PK, bioavailability and food effect in healthy volunteers. Overall, 80 subjects were enrolled, with 62 treated with elacestrant (capsule formulation) and 18 with placebo. Single oral doses ranged from 1 to 200 mg and multiple oral doses (QD for 7 days) ranged from 10 to 200 mg. This study showed food effects via differences in PK under fasting and fed conditions. There were no clinically-relevant changes in laboratory parameters, vital signs, physical examinations, or 12-lead electrocardiograms (ECGs). There were no deaths, no serious adverse events (SAEs), and no subject withdrawals due to adverse events (AEs). Overall, the drug was well-tolerated. The most frequently reported (>5%) AEs in subjects receiving elacestrant were headache, nausea, dyspepsia, myalgia, diarrhea, and dizziness; all were mild in intensity and transient. Tolerability was similar under fed and fasting conditions and the AE profiles were similar for both the single- and multiple-dose parts of the study. There were no clinically relevant changes in laboratory parameters, vital signs

(blood pressure [BP], pulse rate, body temperature), physical examination or ECG over the course of the study. ECG parameters (heart rate [HR], PR interval, QT interval, QTcB-interval) showed no changes of clinical relevance.

Study RAD1901-004 is a Phase 1, randomized, double-blind, placebo-controlled, multiple-ascending-dose study in healthy post-menopausal women. The study primarily evaluated safety, tolerability, and PK of elacestrant (capsule formulation) administered orally QD for 7 consecutive days at doses of 200 mg to 1000 mg QD. The secondary objectives were to determine the occupancy of ERα in peripheral tissues and to determine if elacestrant crossed the blood-brain barrier. Overall, 52 subjects were enrolled with 44 treated with elacestrant and 8 with placebo. Static positron emission tomography (PET) scans of the uterus showed a mean ERα occupancy of 83% in the 200 mg dose group and a mean ERα occupancy of 92% in the 500 mg dose group. Minimal levels of elacestrant were detected in cerebrospinal fluid (CSF; CSF/plasma concentration ratios <0.2%), suggesting a small amount of elacestrant penetrated the blood-brain barrier. Elacestrant was well tolerated by the majority of subjects. There were no deaths or SAEs reported. A total of 9 subjects were withdrawn from elacestrant treatment due to 1 or more AEs. The majority of AEs leading to withdrawal were gastrointestinal AEs. The maximum intensity of these AEs was Grade 3 for 3 of the 9 withdrawn subjects, Grade 2 for 5 of these subjects and Grade 1 for 1 subject. The most frequently reported AEs for elacestrant vs placebo were nausea (43% vs 25%, respectively), dyspepsia (36% vs 13%, respectively), headache (34% vs 25%, respectively), and vomiting (32% vs 0%, respectively).

2.2.2.3. Clinical Pharmacology in Healthy Volunteer Studies

Study RAD1901-109 is a Phase 1, randomized, open-label, 3-period, crossover food-effect study comparing the PK profile of elacestrant 400 mg tablets administered in the fasted, fed (light, low-fat meal), and fed (heavy, high-fat meal) states in 18 healthy men and post-menopausal women. Preliminary results indicate that administration of the elacestrant 400 mg tablet with a light, low-fat meal or a heavy, high-fat meal increased the geometric mean elacestrant C_{max} by 32% and 36%, respectively, and increased geometric mean elacestrant $AUC_{0-\infty}$ by 16% and 26%, respectively, compared to fasted administration. These effects were smaller than the food-effect observed with the original elacestrant capsule formulation that exhibited a 106% increase in elacestrant C_{max} and a 57% increase in elacestrant $AUC_{0-\infty}$ for administration with a heavy, high-fat meal. It is recommended to administer elacestrant after a light meal to improve the gastrointestinal tolerability effects associated with fasted administration.

Study RA1901-110 is a Phase 1, nonrandomized, open-label, drug-drug interaction study evaluating the effect of a potent CYP3A4 inhibitor, itraconazole, on the steady-state PK profile of elacestrant in 18 healthy men and post-menopausal women. Preliminary results indicate that coadministration of the potent CYP3A4 inhibitor, itraconazole 200 mg QD, with elacestrant 200 mg QD increased the geometric mean elacestrant C_{max} by 4.37-fold (from 45.6 ng/mL to 199.3 ng/mL) and increased the geometric mean elacestrant $AUC_{0-\infty}$ by 5.27-fold (from 720 ng·h/mL to 3710 ng·h/mL). Therefore, elacestrant should not be coadministered with other drugs that alter (inhibit or induce) CYP3A4.

2.2.2.4. Vasomotor Symptoms Studies

The efficacy of elacestrant in reducing the frequency or severity of vasomotor symptoms in post-menopausal women with moderate to severe vasomotor symptoms was studied in 2 Phase 2 clinical studies: RAD1901-002 and VMRAD1901-203. The efficacy of elacestrant in reducing vasomotor symptoms was not clearly demonstrated. No further trials in subjects with vasomotor symptoms are planned.

2.2.2.5. Metastatic Breast Cancer Studies

The safety, tolerability, and efficacy of elacestrant in post-menopausal women with ER+/HER2- mBC have been studied in 2 Phase 1 clinical studies: RAD1901-005 and RAD1901-106, and is currently being evaluated in the ongoing Phase 3 study RAD1901-308. Efficacy results for each of the Phase 1 studies is provided in Section 2.2.2.5.1 Section 2.2.2.5.1 , respectively. Safety data for subjects receiving 400 mg elacestrant QD from Studies RAD1901-005 and RAD1901-106 have been pooled and are shown separately for subjects receiving capsules or tablets in Section 2.2.2.5.4.

2.2.2.5.1. Study RAD1901-106

Study RAD1901-106 is a Phase 1b study in post-menopausal women with ER+/HER2- mBC to evaluate the effect of elacestrant on the availability of ER binding sites using fluoroestradiol-positron emission tomography (FES-PET) imaging. Overall, 16 subjects were enrolled; 8 received 200 mg QD of elacestrant which was increased to 400 mg QD after 14 days (200/400 mg group), and 8 subjects received 400 mg QD of elacestrant. The primary study endpoint was the percentage difference in FES uptake in tumor lesions (up to a maximum of 20 lesions) after 14 days of treatment with elacestrant compared with baseline.

At baseline, over half (56.3%) of the subjects had at least 1 ESR1 mutation based on circulating tumor deoxyribonucleic acid (ctDNA). Subjects had received a median of 3.0 lines of prior anticancer therapies (inclusive of all types of therapy, regardless of setting), and a median of 1.0 line of prior chemotherapy. Six (37.5%) subjects received prior therapy with fulvestrant and 6 (37.5%) subjects received prior therapy with an mechanistic target of rapamycin (mTOR) inhibitor; no subject received a prior CDK4/6 inhibitor.

Van Kruchten (2015) previously reported on the relationship between ER reduction and response to the SERD fulvestrant by using FES-PET imaging at baseline and after fulvestrant treatment. The study defined subjects with a <75% reduction in FES uptake as having “residual ER availability.” Based on this cut-off, 38% (6/16) of subjects had significant residual ER availability after 4 weeks of fulvestrant treatment and this residual ER availability was associated with early progression. In study RAD1901-106, elacestrant greatly reduced FES uptake from baseline to Day 14. All but 1 subject in the 400 mg cohort (7/8; 87.5%) and 57% of subjects (4/7) in the 200/400 mg cohort had a greater than 75% reduction in FES uptake. The overall median reduction in FES uptake was 88.0%. This reduction in FES uptake was similar in subjects with and without mutations in ESR1.

For subjects receiving the recommended Phase 2 dose (RP2D) of elacestrant of 400 mg QD, with or without a 14-day lead-in at 200 mg QD, and having Response Evaluation Criteria in Solid Tumors (RECIST) measurable disease at baseline and with at least 1 post-baseline measurement,

the objective response rate (ORR) was 11.1% (N=1/9), clinical benefit rate (CBR) at 24 weeks was 30.8% (N=4/13), duration of response (DoR) was 22.00 weeks, and median PFS was 5.3 months (Table 2). No significant correlation was found between FES uptake and best overall response, using Spearman's rank correlation coefficient.

Table 2: Study RAD1901-106 Summary Table of Efficacy Endpoints

	Elacestrant		
Parameter	**200/400 mg**	**400 mg**	**Overall**
ORR[a] % (n/N)	0 (0/4)	20.0 (1/5)	11.1 (1/9)
DoR (weeks)		22.00	22.0
Time to Response (weeks)		7.86	7.86
CBR[b] at 24 weeks % (n/N)	16.7 (1/6)	42.9 (3/7)	30.8 (4/13)
Median PFS (months)	3.6	6.9	5.3

DoR = Duration of Response; PFS = Progression Free Survival.
[a]ORR = Objective Response (CR+PR) Rate, CR = Complete Response, PR = Partial Response. The ORR is calculated as the proportion of RE subjects who had objective response. RE population: all ITT subjects who had target lesion at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion.
[b]The CBR at 24 weeks is calculated as the proportion of CBE subjects who had confirmed CR or PR any time during the study, or SD that lasts at least 24 weeks. CBE population: all ITT subjects who had measurable and/or evaluable disease (ie, target or non-target lesions) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion.
Database lock date for study RAD1901-106: November 27, 2018.
Source: Section 14.2, Table 14.2.1.2, Table 14.2.1.5, Table 14.2.1.3.1, Table 14.2.1.4

2.2.2.5.2. Study RAD1901-005

Study RAD1901-005 is a Phase 1 study to determine the safety, PK, and maximum tolerated dose and/or RP2D of elacestrant in post-menopausal women with ER+/HER2- mBC. The study consisted of 4 parts: dose escalation (Part A), safety expansion (Part B), tablet introduction (Part C), and dose expansion (Part D). Part A used a 3+3 design with planned escalating oral capsule QD doses of 200, 400, 600, 800, and 1000 mg. Part B enrolled subjects to further study 400 mg QD, the RP2D identified from Part A. Part C evaluated the safety, tolerability, and PK of the elacestrant tablet dosage formulation at 400 mg QD. Part D enrolled additional subjects to evaluate the safety and preliminary efficacy of elacestrant tablet 400 mg oral QD dose in a subject population with different eligibility requirements from Parts A, B, and C. Although the study planned to enroll 36 subjects in Part D, due to a change in corporate strategy, enrollment was terminated after only 10 subjects were enrolled, limiting the conclusions that can be drawn from this cohort of subjects.

At baseline 50.9% (29/57) of subjects had at least one ESR1 mutation based on ctDNA. Subjects received a median of 3.0 lines of prior anticancer therapies (inclusive of all types of therapies, regardless of setting); approximately half of the subjects had prior treatment with a CDK4/6 inhibitor and/or SERD; approximately one-third had prior treatment with an mTOR inhibitor. Subjects enrolled in Part D had to meet different eligibility criteria than subjects enrolled in

Parts A, B, and C and received a greater number of prior lines of therapy than subjects enrolled in other parts of the study (median of 4.0 vs 3.0); therefore, antitumor activity for subjects in Part D cannot be directly compared to activity in Parts A, B, and C.

Preliminary efficacy results are summarized in Table 3. Regardless of which study part they were enrolled in, all subjects treated at the RP2D of elacestrant 400 mg QD, the confirmed ORR with RECIST measurable disease at baseline and with at least 1 post-baseline measurement was 19.4% (N=6/31); CBR at 24 weeks was 42.6% (N=20/47), median DoR was 24.86 weeks, and median PFS was 4.5 months (Table 3).

Table 3: Study RAD1901-005 Summary Table of Efficacy Endpoints

	Elacestrant		
Parameter	**Part A+B+C 400 mg**	**Part D 400 mg**	**All 400 mg**
ORR[a] % (n/N)	27.3 (6/22)	0 (0/9)	19.4 (6/31)
Median DoR (weeks)	24.86		24.86
Median Time to Response (weeks)	8.21		8.21
CBR[b] at 24 weeks % (n/N)	47.4 (18/38)	22.2 (2/9)	42.6 (20/47)
Median PFS (months)	5.4	1.9	4.5

Part A = Dose Escalation, Part B = Safety Expansion, Part C = Tablet Introduction, and Part D = Dose Expansion.
DoR = Duration of Response; PFS = Progression Free Survival.
[a]ORR = Objective Response (CR+PR) Rate, CR = Complete Response, PR = Partial Response.
[a]The ORR is calculated as the proportion of RE subjects who had objective response. RE population: all ITT subjects who had measurable disease (ie, at least 1 target lesion at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion.
[b]The CBR at 24 weeks is calculated as the proportion of CBE subjects who had confirmed CR or PR any time during the study, or SD that lasts at least 24 weeks.
[b]CBE population: all ITT subjects who had measurable and/or evaluable disease (ie, target or non-target lesions) at baseline and at least 1post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion.
Database lock date for study RAD1901-005: December 20, 2019.
Source: Section 14.2, Table 14.2.1.1a, Table 14.2.1.4a, Table 14.2.1.2.1a, Table 14.2.1.3a

2.2.2.5.3. Exploration of Anti-Tumor Activity based on ESR1 Mutational Status in Studies RAD1901-106 and RAD1901-005

To understand potential biomarkers for identification of patient populations who may derive preferential benefit from elacestrant, ctDNA from subjects enrolled in studies RAD1901-005 and RAD1901-106 were analyzed to determine ESR1 mutational status at baseline. A subset analysis was then conducted to determine PFS for subjects by baseline ESR1 mutational status (Table 4). A trend showing increased PFS in the subjects whose tumors harbored ESR1 mutations was observed; median PFS for subjects with ESR1 mutations compared with subjects without ESR1 mutations was 7.4 and 2.8 months, respectively, in Study RAD1901-005 and 3.9 and 5.3 months, respectively, in Study RAD1901-106. Notably, in Study RAD1901-005, of the 6 subjects who achieved partial response (PR) by RECIST criteria, 5 had ESR1 mutations at baseline.

PFS was also calculated for subjects who had previously been treated with CDK4/6 inhibitors in Study RAD1901-005 (Table 4). While the number of subjects is small, the trend toward an increased PFS in CDK4/6 pre-treated subjects whose tumors harbor ESR1 mutations persisted.

Table 4: Progression-Free Survival by ESR1 Mutational Status for All Subjects and for Subjects Previously Treated with CDK4/6 Inhibitors in Elacestrant Studies RAD1901-106 and RAD1901-005

	Median PFS (months)		
Prior Anti-Cancer Therapy	**ESR1-mut**	**ESR1-mut-nd**	**Overall**
RAD1901-005 + RAD1901-106			
All Prior Therapies	7.4 (n=34)	3.7 (n=32)	5.3 (n=66)
Prior CDK4/6 inhibitor	4.9 (n=13)	1.9 (n=13)	3.8 (n=26)
RAD1901-005			
All Prior Therapies	7.4 (n=25)	2.8 (n=25)	4.5 (n=50)
Prior CDK4/6 inhibitor	4.9 (n=13)	1.9 (n=13)	3.8 (n=26)
RAD1901-106			
All Prior Therapies	3.9 (n=9)	5.3 (n=7)	5.3 (n=16)
Prior CDK4/6 inhibitor	NA[a]	NA[a]	NA[a]

CDK = cyclin-depedent kinase; ESR1 = estrogen receptor gene; ESR1-mut = ESR1 mutation; ESR1-mut-nd = no ESR1 mutation detected (includes samples with no mutation detected and samples where ESR1 mutational status could not be determined).
Study RAD1901-106 ESR1 mutation status determined in ct-DNA samples at baseline using OncoBEAM™ (Sysmex Inostics) assay.
Study RAD1901-005 ESR1 mutation status determined in ct-DNA samples at baseline using Guardant360® assay unless subject had baseline Sysmex result but no baseline Guardant result, in which case Sysmex result was used in the analysis.
All prior therapies includes ITT subjects who received any prior anti-cancer therapies.
RAD1901-005 database lock date: December 20, 2019; RAD1901-106 database lock date: November 27, 2018.
N=16 subjects receiving 400 mg (with or without 14-day lead in at 200 mg) elacestrant QD for RAD1901-106 and N=50 subjects receiving 400 mg elacestrant QD for RAD1901-005.
[a]NA = Not available: no subject received prior CDK4/6 inhibitors in this study.

2.2.2.5.4. Combined Safety from Studies RAD1901-005 and RAD1901-106

Safety data were combined for subjects enrolled in the 2 Phase 1 studies of elacestrant in post-menopausal women with mBC and are presented in Table 5 and Table 6 for subjects treated at the RP2D of 400 mg QD. Data are presented separately for subjects treated with the capsule formulation and the tablet formulation. Two subjects in study RAD1901-106, and 3 subjects in study RAD1901-005, initially received capsules and were then switched to tablets; these 5 subjects are included in the capsule group in the capsule group in the tables below.

Most subjects receiving either formulation experienced TEAEs and treatment-related TEAEs (Table 5). The incidence of subjects experiencing TEAEs leading to dose interruption and Grade 3 or 4 TEAEs were similar between the 2 formulations, while the incidence of SAEs was higher in subjects with tablets as compared to those with capsules. There were no treatment-related deaths.

Table 5: Overall Summary of Adverse Events in Subjects with Breast Cancer using Combined Data from RAD1901-106 and RAD1901-005 (ITT Population)

Adverse Event Category	Elacestrant 400 mg capsules (N=42)[a] n (%)	Elacestrant 400 mg tablets (N=24) n (%)	Overall (N=66)[a] n (%)
TEAEs	42 (100)	22 (91.7)	64 (97.0)
Treatment-Related TEAEs	40 (95.2)	19 (79.2)	59 (89.4)
Serious TEAEs	8 (19.0)	8 (33.3)	16 (24.2)
Treatment-Related Serious TEAEs	2 (4.8)	1 (4.2)	3 (4.5)
TEAEs Leading to Dose Interruption	13 (31.0)	8 (33.3)	21 (31.8)
Treatment-Related TEAEs Leading to Dose Interruption	9 (21.4)	1 (4.2)	10 (15.2)
TEAEs at Grade 3 or 4[b]	16 (38.1)	10 (41.7)	26 (39.4)
Treatment-Related TEAEs at Grade 3 or 4	9 (21.4)	1 (4.2)	10 (15.2)
TEAEs Leading to Death	1 (2.4)	1 (4.2)	2 (3.0)
Treatment-Related TEAEs Leading to Death	0	0	0
TEAEs Leading to Study Medication Discontinuation	8 (19.0)	1 (4.2)	9 (13.6)
Treatment-Related TEAEs Leading to Study Medication Discontinuation	7 (16.7)	0	7 (10.6)

Treatment-Emergent Adverse Events (TEAEs) are those events which started on or after the first dose of study medication.
a Eight patients initiated treatment at 200 mg for 14 days.
b Severity grad based upon CTCAE version 5.0
Study RAD1901-106 database lock date: November 27, 2018.
Study RAD1901-005 database lock date: December 20, 2019.
Source: SRT Table 2.1

For both formulations, TEAEs occurred most frequently in the gastrointestinal disorders system organ class. The overall incidence of the most common (≥ 20%) TEAEs in subjects receiving capsules (N=42) were, in descending order, nausea, dyspepsia, fatigue, vomiting, and diarrhea. For subjects receiving tablets (N=24), TEAEs generally occurred with lower frequency (ie, nausea occurred in 66.7% of subjects receiving capsules vs 33.3% of subjects receiving tablets). For subjects receiving tablets, the most common (≥ 20%) TEAEs in descending order include nausea (33.3%), blood triglycerides increased (25.0%), blood phosphorus decreased (25.0%), as well as blood potassium decreased, urinary tract infection, constipation, dyspepsia, fatigue, and headache (all 20.8%; Table 6).

Table 6: Most Common (>10%) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Synonym[a] in Subjects with Breast Cancer using Combined Data from RAD1901-005 and RAD1901-106 (ITT Population)

Adverse Event	Elacestrant 400 mg capsules (N=42)[b] n (%)	Elacestrant 400 mg tablets (N=24) n (%)	Overall (N=66)* n (%)
Any TEAEs	42 (100)	22 (91.7)	64 (97.0)
Gastrointestinal disorders	38 (90.5)	19 (79.2)	57 (86.4)
Nausea	28 (66.7)	8 (33.3)	36 (54.5)
Dyspepsia	18 (42.9)	5 (20.8)	23 (34.8)
Vomiting	17 (40.5)	4 (16.7)	21 (31.8)
Diarrhoea	11 (26.2)	3 (12.5)	14 (21.2)
Constipation	6 (14.3)	5 (20.8)	11 (16.7)
Gastrooesophageal reflux disease	8 (19.0)	2 (8.3)	10 (15.2)
Dysphagia	7 (16.7)	1 (4.2)	8 (12.1)
Abdominal pain upper	5 (11.9)	2 (8.3)	7 (10.6)
Flatulence	6 (14.3)	1 (4.2)	7 (10.6)
Investigations	19 (45.2)	15 (62.5)	34 (51.5)
Aspartate aminotransferase increased	9 (21.4)	3 (12.5)	12 (18.2)
Blood triglycerides increased	6 (14.3)	6 (25.0)	12 (18.2)
Blood glucose increased	7 (16.7)	4 (16.7)	11 (16.7)
Blood phosphorus decreased	4 (9.5)	6 (25.0)	10 (15.2)
Alanine aminotransferase increased	6 (14.3)	3 (12.5)	9 (13.6)
Blood Pressure Increased	6 (14.3)	2 (8.3)	8 (12.1)
Blood cholesterol increased	4 (9.5)	4 (16.7)	8 (12.1)
Blood potassium decreased	2 (4.8)	5 (20.8)	7 (10.6)
General disorders and administration site conditions	23 (54.8)	10 (41.7)	33 (50.0)
Fatigue	17 (40.5)	5 (20.8)	22 (33.3)
Oedema peripheral	6 (14.3)	1 (4.2)	7 (10.6)
Musculoskeletal and connective tissue disorders	19 (45.2)	12 (50.0)	31 (47.0)
Arthralgia	7 (16.7)	4 (16.7)	11 (16.7)
Back pain	7 (16.7)	4 (16.7)	11 (16.7)
Nervous system disorders	13 (31.0)	13 (54.2)	26 (39.4)
Headache	4 (9.5)	5 (20.8)	9 (13.6)
Dizziness	6 (14.3)	2 (8.3)	8 (12.1)
Respiratory, thoracic and mediastinal disorders	15 (35.7)	8 (33.3)	23 (34.8)
Cough	6 (14.3)	4 (16.7)	10 (15.2)
Dyspnoea	5 (11.9)	2 (8.3)	7 (10.6)
Infections and infestations	13 (31.0)	9 (37.5)	22 (33.3)
Urinary tract infection	2 (4.8)	5 (20.8)	7 (10.6)
Metabolism and nutrition disorders	10 (23.8)	8 (33.3)	18 (27.3)
Decreased appetite	6 (14.3)	3 (12.5)	9 (13.6)
Vascular disorders	9 (21.4)	5 (20.8)	14 (21.2)
Hot flush	7 (16.7)	4 (16.7)	11 (16.7)
Blood and lymphatic system disorders	8 (19.0)	3 (12.5)	11 (16.7)
Anaemia	7 (16.7)	3 (12.5)	10 (15.2)

Adverse Event	Elacestrant 400 mg capsules (N=42)[b] n (%)	Elacestrant 400 mg tablets (N=24) n (%)	Overall (N=66)* n (%)

a Synonym terms across different SOCs are grouped together and defined in Appendix D of the Elacestrant Investigator's Brochure (Edition 9.0).
b Eight subjects initiated treatment at 200 mg for 14 days.
Coded using MedDRA v17.1.
Treatment-Emergent Adverse Events (TEAE) are those events which started on or after the first dose of study medication.
Each subject was counted once for the same system organ class and the same preferred term.
Study RAD1901-106 database lock date: November 27, 2018.
Study RAD1901-005 database lock date: December 20, 2019.
Source: SRT Table 2.16

2.3. Study Rationale

Although there are an increasing number of therapeutic options available for ER+/HER2- mBC, there are, as yet, no curative treatments for these patients. While ER+ breast cancer patients typically respond well to initial endocrine therapy, endocrine resistance (both de novo and acquired) continues to present a clinical challenge. The SERD fulvestrant and AIs used alone and in combination therapy (eg, with CDK4/6i) are important components in the treatment of ER+ mBC. Unfortunately, tumors eventually develop resistance to fulvestrant, AIs, and CDK4/6is. Thus, there is still a significant unmet medical need for a potent oral agent to treat these challenging cases, which could provide patients with a prolongation of life as well as a better quality of life.

Elacestrant is a novel selective SERD with several characteristics that portend its being best-in-class and an improvement over fulvestrant and other currently available therapies in this population. In addition to an oral route of administration, nonclinical data have demonstrated it to be efficacious in models of ER+ breast cancer with both mutant and wild-type (WT) ESR1, and further, suggest that elacestrant may provide superior antitumor activity in ESR1 mutant models compared with fulvestrant. Additionally, in RADIUS' Phase 1 studies RAD1901-005 and RAD1901-106, elacestrant demonstrated single-agent efficacy regardless of ESR1 mutational status, as well as in subjects who progressed on a CDK4/6i and fulvestrant. Five of the 6 subjects in Study RAD1901-005 who achieved a PR were found to have tumors harboring ESR1 mutations. Thus, there is the potential that elacestrant might provide a preferential benefit to patients with tumors harboring ESR1 mutations. To test for this possibility, subjects will be tested for ESR1 mutations during the screening process and stratified by mutational status (ESR1 mutation [ESR1-mut] vs no ESR1 mutation detected [ESR1-mut-nd]). Subjects with ER+/HER2- mBC who have received prior endocrine therapy and prior therapy with a CDK4/6i will be randomized to treatment with elacestrant monotherapy or treatment with standard of care (SOC) endocrine therapy (fulvestrant or an AI). The statistical analyses of the PFS primary endpoint will be performed in subjects with ESR1 mutations detected by ctDNA testing (ESR1-mut subjects) and in all subjects (ESR1-mut and ESR1-mut-nd) using the Hochberg procedure (Hochberg, 1988) to adjust for the multiplicity of the primary endpoints.

The study described herein will be conducted to determine if elacestrant provides an improvement over the SOC of fulvestrant or AIs and will determine if ESR1 mutational status impacts the response to either elacestrant or the SOC.

2.4. Rationale for Study Dose

The dose of elacestrant to be used in Study RAD1901-308, 400 mg QD, was selected based on nonclinical data and safety, efficacy, and PK data from 6 Phase 1 and Phase 2 clinical studies of elacestrant.

The initial dose of 200 mg QD used in the Phase 1 study RAD1901-005 in post-menopausal women with metastatic breast cancer was based on the nonclinical safety and efficacy profile, and the clinical safety of elacestrant in 106 healthy post-menopausal women who received doses up to 200 mg QD in study RAD1901-001 and up to 1000 mg QD in study RAD1901-004. In both studies, all doses, administered orally for 7 consecutive days, were well tolerated. At the 200 mg QD dose in both studies, there were no deaths, SAEs or discontinuations due to AEs, and all AEs were mild (RAD1901-001) or mild or moderate (RAD1901-004) in severity.

In addition, elacestrant at 200 mg QD was determined to be potentially efficacious in patients with ER-dependent breast cancers, based on extrapolation of nonclinical xenograft studies in mouse models. At doses of 30 mg/kg/d and 60 mg/kg/d in a mouse MCF-7 xenograft model elacestrant inhibited tumor growth comparable to tamoxifen and fulvestrant. The human equivalent doses are 159 mg QD and 312 mg QD, respectively, when based on a 65 kg body weight.

Based on these observations, the initial dose level of 200 mg QD for subjects enrolled in the dose escalation part of Study RAD1901-005 was selected.

Dose escalation in Study RAD1901-005 Part A proceeded to 600 mg QD. Although no dose limiting toxicities were reported per protocol, the 600 mg dose was deemed to be not tolerable due primarily to gastrointestinal events; the incidence of nausea, vomiting, and constipation were higher in patients who received 600 mg elacestrant (67% to 100%) compared with the 400 mg dose (17% to 67%) at the time of the analysis. Therefore, the 400 mg dose, which was associated with fewer of these gastrointestinal events, was selected as the RP2D for further testing. Expansion cohorts in Parts B, C and D of Study RAD1901-005 confirmed the acceptability of the safety profile, and anti-tumor activity was observed at this dose level (ORR 19.4%). This dose was also tested in Study RAD1901-106 in post-menopausal women with mBC with an acceptable safety profile. Based upon the safety and efficacy observed with elacestrant 400 mg QD in both of these studies, 400 mg once daily was selected as the dose for Study RAD1901-308.

3. TRIAL OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary and Key Secondary Objectives

- **Primary:** To demonstrate that elacestrant 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 post-menopausal women and men with ER+/HER2- 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 overall survival (OS) between treatment groups in ESR1-mut subjects
  - To compare OS between treatment groups in all subjects (ESR1-mut and ESR1-mut-nd)

3.1.2. Other Secondary Objectives

The following secondary objectives will be 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 will be assessed for ESR1-mut subjects, ESR1-mut-nd subjects, and all subjects (ESR-mut and ESR1-mut-nd)

- To compare PFS based on local Investigator assessment between treatment groups
- To compare ORRs based on blinded IRC assessment between treatment groups
- To compare 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 will be assessed for ESR1-mut and all subjects (ESR1-mut and ESR1-mut-nd):

- To compare the safety and tolerability between treatment groups
- To assess the PK of elacestrant
- To describe the changes in Patient Reported Outcomes (PROs) and Health-Related Quality of Life (HRQOL) and the changes in PROs/HRQOL between treatment groups

3.1.3. Exploratory Objectives

The following exploratory objectives will be assessed in ESR1-mut subjects, ESR1-mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd):

- To determine the difference in time to chemotherapy (TTC) between treatment groups
- To evaluate alterations in ctDNA 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

3.2. Endpoints

3.2.1. Primary and Key Secondary Endpoints

3.2.1.1. Primary Endpoints

The primary endpoints of this study are as follows:

- IRC-assessed PFS in ESR1-mut subjects
- IRC-assessed PFS in all subjects (ESR1-mut and ESR1-mut-nd)

IRC-assessed PFS is defined as the length of time from randomization until the date of objective disease progression per RECIST v1.1 (Appendix 1) as assessed by the blinded IRC or death from any cause.

3.2.1.2. Key Secondary Endpoints

The key secondary endpoints are as follows:

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

OS is defined as the length of time from randomization until the date of death from any cause.

3.2.2. Other Secondary Endpoints

The following endpoints will be analyzed for ESR1-mut-nd subjects:

- IRC-assessed PFS
- OS

The following endpoints will be analyzed for ESR1-mut, ESR1-mut-nd, and all subjects (ESR1-mut and ESR1-mut-nd):

- Local Investigator-assessed PFS, defined as the length of time from randomization until the date of objective disease progression per RECIST v1.1 as assessed by local Investigators or death from any cause

- IRC-assessed ORR, defined as the percentage of subjects with measurable disease who have achieved either a confirmed complete response (CR) or PR per RECIST v1.1 based on blinded IRC assessment
- IRC-assessed DoR, defined as the duration of time from the date when criteria are met for either a CR or PR, per RECIST v1.1, until the first date that recurrent or progressive disease (PD) is objectively documented based on blinded IRC assessment
- IRC-assessed CBR, defined as the percentage of subjects who have achieved either a confirmed CR or PR or stable disease (SD) at ≥ 24 weeks from randomization per RECIST v1.1 based on blinded IRC assessment
- Local Investigator-assessed ORR
- Local Investigator-assessed DoR
- Local Investigator-assessed CBR

The following endpoints will be assessed for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd):

- Safety and tolerability, assessed by AEs, SAEs, dose modifications, clinical laboratory parameters (ie, hematology, chemistry, and coagulation), ECGs, performance status, and vital signs
- PK, assessed by evaluation of elacestrant concentrations at pre-dose (pre-treatment) and 4 hours post-dose on Cycle 1 Day 1 (C1D1), pre-dose (trough concentration [C_{trough}]) and 4 hours post-dose on C1D15, and pre-dose (C_{trough}) on C2D1
- PRO endpoints, assessed using the HRQOL scales EuroQOL 5 Dimension 5 Level (EQ-5D-5L), European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30), and PRO Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

3.2.3. Exploratory Endpoints

The following exploratory endpoints will be assessed in ESR1-mut subjects, ESR1 mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd):

- TTC, defined as the number of days from randomization to initiation of chemotherapy
- Alterations in ctDNA relevant to ER+ breast cancer and the CDK4/6 pathway and the relationship between these findings and clinical response
- Alterations in tumor-specific genes, proteins, and RNAs related to oncogenic pathways and proliferation and cell cycle markers in tumor tissue and the relationship between these findings and clinical response

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an international, multicenter, 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 post-menopausal women and men with ER+/HER2- mBC whose disease has relapsed or progressed on at least 1 and no more than 2 prior lines of endocrine therapy for mBC, which must have included CDK4/6i therapy in combination with fulvestrant or an AI. Subjects must have received no more than 1 line of cytotoxic chemotherapy in mBC. Endocrine monotherapy with 1 of the SOC drugs (fulvestrant, anastrozole, letrozole, exemestane) must be an appropriate treatment option for subjects enrolled in this study. The primary endpoints of IRC-assessed PFS will be analyzed in ESR1-mut subjects and in all subjects (ESR1-mut and ESR1-mut-nd) using the Hochberg procedure to adjust for the multiplicity of the primary endpoints. A schematic of the study design is provided in Figure 4.

Subjects who meet all eligibility criteria will be enrolled into the active treatment phase of the study. During this phase of the study, subjects will receive study drug as defined in the protocol and will undergo the protocol-defined safety, efficacy, and exploratory assessments. Subjects will continue to receive treatment until the following: disease progression, a clinically significant AE, significant study noncompliance, the subject is unable to receive study treatment for > 14 consecutive days, treatment discontinuation in the best interest of the subject, or subject refuses treatment as defined in Section 5.3.1 requires subject withdrawal.

Subjects who discontinue the active treatment phase due to disease progression will enter a follow-up phase during which survival data and the start date and regimen name of the first new anti-cancer therapy will be collected. For subjects who discontinue treatment for reasons other than disease progression, death, consent withdrawal, toxicity, or loss to follow-up and who do not begin new anti-cancer therapy, tumor assessments will continue until disease progression or the first new anti-cancer therapy is initiated. At that time, subjects will discontinue tumor assessments and continue to be monitored for survival data and the initiation of the first new anti-cancer therapy.

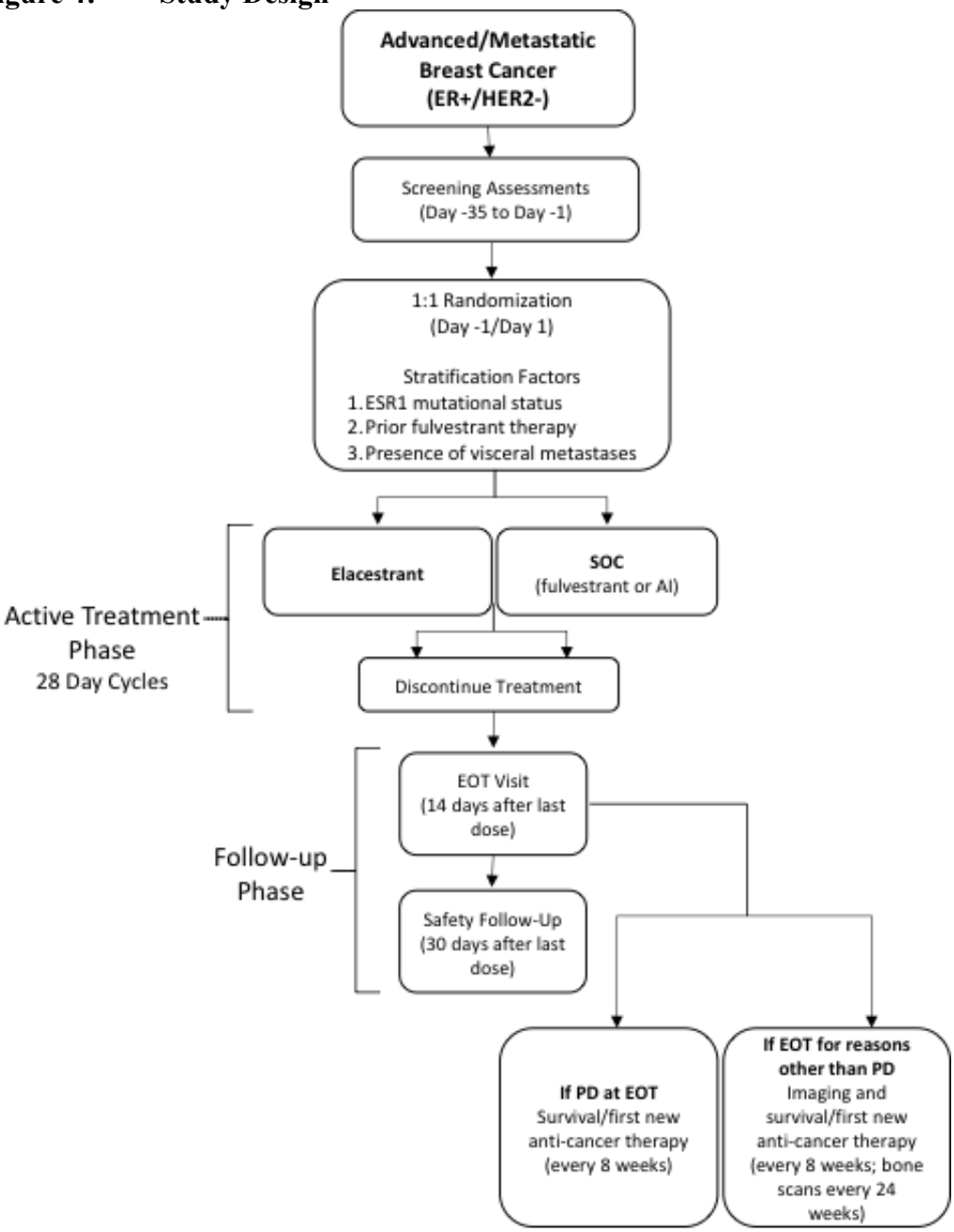
This is an open-label study and study subjects and Investigators will not be blinded to treatment assignment. However, to minimize bias in study conduct, RADIUS personnel performing statistical analyses, including biostatisticians, and programmers, will be blinded to treatment assignment until after database lock. Clinical Research Organization (CRO) study team members and select RADIUS team members will not be blinded to an individual subject's treatment assignment during the conduct of the study but will be blinded to aggregated data by treatment assignment until after database lock.

An independent IRC, blinded to subjects' treatment assignments, will review radiographic images and clinical information collected on study to determine the protocol-defined endpoints of disease response and progression.

Safety and efficacy data (PFS by IRC and local Investigator and OS) will be reviewed at prespecified intervals by an Independent Data Monitoring Committee (IDMC). An unblinded statistician at the CRO will perform all analyses in preparation for the IDMC evaluations.

A survival analysis will be performed at the same time as the final PFS analysis when approximately 160 PFS events (objective disease progression assessed by the blinded IRC or death) among the ESR1-mut subjects and 340 PFS events among all subjects (ESR1-mut and ESR1-mut-nd) have occurred and again when approximately 50% of subjects have died at which time the study will be complete.

Figure 4: Study Design



AI = aromatase inhibitor; EOT = end of treatment; ER+ = estrogen-receptor positive; ESR1 = estrogen receptor gene 1; HER2- = human epidermal growth factor receptor 2 negative; PD = progressive disease; SOC = standard of care

4.2. Number of Subjects

This study is event-driven and is planned for a total of approximately 160 PFS events (objective disease progression assessed by the blinded IRC or death) among the ESR1-mut subjects and 340 PFS events among all subjects (ESR1-mut and ESR1-mut-nd). It is estimated that approximately 466 subjects (220 ESR1-mut; 246 ESR1-mut-nd) will need to be enrolled in the study in a 1:1 randomization at approximately 230 clinical study sites experienced in conducting oncology clinical trials in Europe, North America, Middle East, Asia-Pacific and South America. Additional or fewer subjects and regions may be required to achieve the planned total number of events.

4.3. Treatment Assignment

Subjects will be randomized in a 1:1 to ratio to one of the following treatment groups:

- Elacestrant 400 mg QD orally on a continuous dosing schedule
- SOC with one of the following options:
  - Fulvestrant 500 mg administered IM into the buttocks as two 5 mL injections on C1D1, C1D15 and C2D1 and Day 1 of every subsequent 28-day cycle
  - 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

Crossover from 1 treatment group or therapy to another will not be allowed while participating in the trial.

Subjects will be stratified by the following criteria:

- ESR1 mutational status detected by ctDNA (ESR1-mut vs ESR1-mut-nd)
- Prior treatment with fulvestrant (yes vs no)
- Presence of visceral metastases (yes vs no); visceral includes lung, liver, brain, pleural, and peritoneal involvement

The following contraindications must be adhered to:

- Known hypersensitivity to any of the SOC options or their excipients would preclude treatment with that particular therapy
- Therapeutic anticoagulation therapy or bleeding disorder that would, in the Investigator's opinion, preclude treatment with fulvestrant

4.4. Disease Progression and Tumor Assessments

Tumor assessments will be performed every 8 weeks (± 7 days) from the date of randomization during the active treatment phase of the study. Subjects with bone lesions identified by radionuclide bone scan or whole body magnetic resonance imaging (MRI) at baseline (during Screening) will have repeat bone scans or whole body MRI (using the same modality as used

during Screening) performed every 24 weeks (± 7 days) from the date of randomization and at time of confirmation of a CR. All assessments will be performed as scheduled at the required intervals according to the Schedule of Events (Appendix 2), regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy.

Tumor assessments will be performed until radiographically- and/or clinically-documented (ie, for photographed or palpable lesions) disease progression as per RECIST v1.1, initiation of new anti-cancer therapy, or discontinuation from overall study participation (Section 7.4), whichever occurs first.

Subjects who discontinue study treatment for reasons other than radiographically- and/or clinically- (ie, for photographed or palpable lesions) documented disease progression, per RECIST v1.1, will continue to have tumor assessments performed every 8 weeks (± 7 days) in the follow-up period, and bone scans or whole body MRI (as applicable) as clinically indicated and/or every 24 weeks (± 7 days) until RECIST-defined disease progression, initiation of the first new anti-cancer therapy, or discontinuation from overall study participation (eg, death, withdrawal of consent, lost to follow-up), whichever occurs first.

Subjects no longer undergoing tumor evaluations will continue to be monitored every 8 weeks for survival data and the initiation of the first new anti-cancer therapy.

The follow-up period will conclude at the time of the final OS analysis when approximately 50% of subjects in the study have died.

Efficacy analyses will be performed using tumor assessments made by the blinded IRC as the primary data source. Analyses of endpoints based on local Investigator assessment will also be performed as supportive analyses.

4.5. Dose Adjustment, Interruption, or Discontinuation Criteria

4.5.1. Criteria for Elacestrant

Each subject will be assessed periodically for the development of any toxicity. Toxicity will be assessed according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) v5.0. Subjects should be monitored closely and receive supportive care and agents to treat AEs and manage cancer symptoms (pain medications, antiemetics, antidiarrheals, etc.) as per local institutional guidance.

General guidelines regarding management and dose reduction for AEs considered by the Investigator to be related to elacestrant treatment are provided in Table 7. Dose reduction decisions should be based on the judgment of the Investigator. Once a dose has been reduced, it may not be re-escalated to the original dose.

Table 7: Dose Modification Guidelines for AEs Related to Elacestrant

	Action and Dose Modification
Grade 1	Continue elacestrant treatment at current dose level
Grade 2	• Consider interruption of elacestrant treatment if clinically indicated • When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment at current dose level
Grade 3	• Interrupt elacestrant treatment if clinically indicated • When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment reduced by 1 dose level • If the Grade 3 toxicity recurs, interrupt elacestrant treatment • When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment reduced by another dose level
Grade 4	• Interrupt elacestrant treatment • When toxicity resolves to Grade 1 or baseline, restart elacestrant treatment reduced by 1 dose level • If the Grade 4 toxicity recurs either: – Permanently discontinue elacestrant treatment or – If the subject is clinically benefitting, elacestrant treatment may be reinitiated only if reduced by another dose level and with agreement of the medical monitor and RADIUS

Dose reductions of elacestrant due to AEs are allowed in this study; dose levels are provided in Table 8. A dose reduction below 200 mg elacestrant QD is not allowed and, if required in the opinion of the Investigator, the subject should be discontinued from treatment.

Dose interruptions of elacestrant of ≤14 consecutive days are permitted at any point during treatment. A dose interruption of >14 consecutive days requires discussion with RADIUS prior to continuation on study.

No dose escalations above the starting dose of 400 mg QD are permitted.

Table 8: Elacestrant Dose Reduction Guidelines

Dose Level	Elacestrant Dose
Starting dose	400 mg QD
-1 (1st dose reduction)	300 mg QD (25% dose reduction)[a]
-2 (2nd dose reduction)	200 mg QD (50% dose reduction)[b]

QD = once daily
a Three 100 mg tablets
[b] Two 100 mg tablets

4.5.2. Criteria for Standard of Care

Dose reductions for subjects receiving the SOC AI treatments are not allowed.

Dose reductions for subjects receiving the SOC fulvestrant are permitted for subjects who develop moderate hepatic impairment (Child-Pugh class B; see Appendix 7) if deemed unrelated to study drug or disease progression, for whom the dose of fulvestrant should be reduced to 250 mg.

Treatment interruptions and/or withdrawals due to AEs should be based on the Investigator's clinical judgment.

SOC dose interruptions of ≤ 14 consecutive days are permitted at any point during treatment. Dose interruptions of > 14 consecutive days requires discussion with RADIUS prior to continuation on study.

Note: During SOC treatment the Investigator will follow any warnings or precautions for use as detailed in each PI or SmPC.

4.5.3. Criteria for QTcF Prolongation

Instructions on management of prolongations in the QTcF interval, regardless of study drug assignment, are provided in Table 9.

Table 9: Mandatory Dose Interruptions and Dose Reductions for Prolonged QTcF

QTcF or QT Prolongation[a]	Action and Dose Modification
• QTcF is prolonged ≥ 500 msec or • Uncorrected QT is > 600 msec or • QTcF is > 530 msec for subjects with left bundle branch block	• Study treatment should be interrupted • Appropriate clinical assessment and treatment should be conducted (eg, assess serum electrolytes and correct with supplements if below lower limit of normal, review concomitant medication) • Cardiology consultation/management should be considered • If QTcF resolves to Grade 1 or baseline and the Investigator believes that the subject would benefit from continued treatment, study drug may be restarted with agreement of the medical monitor and RADIUS either at a reduced dose level (elacestrant only) or the current dose level (SOC) • If event does not resolve or recurs after restarting study drug, subject should permanently discontinue treatment and follow up with cardiology care as appropriate.

QTcF = QT corrected by Fridericia's formula; SOC =standard of care

[a] Based on average value of triplicate ECGs

5. SELECTION AND WITHDRAWAL OF SUBJECTS

5.1. Subject Inclusion Criteria

Subjects must meet all the following inclusion criteria:

1. Must have a 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
2. Must be appropriate candidates for endocrine monotherapy
3. Must have 1 of the following as defined by RECIST v1.1:
    a. Measurable disease
    b. Bone only disease with evaluable lesions. Subjects must have at least 1 lytic or mixed lytic/blastic bone lesion; blastic lesions only are not evaluable and allowed.

Subjects who have had prior radiation to bone must have at least 1 evaluable lesion in a nonirradiated area

4. Female or male ≥ 18 years of age
5. Female subjects must be post-menopausal women, defined by 1 of the following criteria:
    a. Documented bilateral surgical oophorectomy
    b. Age ≥ 60 years with amenorrhea ≥ 1 year since last menses
    c. Age < 60 years with amenorrhea ≥ 1 year since last menses with no alternative pathological or physiological cause (including ongoing or recent chemotherapy, treatment with tamoxifen or toremifene, or a GnRH agonist), and serum estradiol and follicle stimulating hormone (FSH) levels within the laboratory reference range for post-menopausal women
    d. Age < 60 years with tamoxifen or toremifene therapy within the last 12 months, with documentation of 12 months of amenorrhea prior to tamoxifen or toremifene therapy and serum estradiol and FSH levels within the laboratory reference range for post-menopausal women
    e. Females with hormonally-induced menopause (ie, requiring ongoing hormone suppression) are not eligible
6. Male subjects must, even if surgically sterilized (ie, status post-vasectomy):
    a. Agree to practice highly effective barrier contraception (use condoms) during the entire study treatment period and through 120 days after the last dose of study drug. For subjects (who have not undergone vasectomy) with female partners of childbearing potential, the subject and his partner must, in addition to condoms, use highly effective contraceptive measures when engaging in sexual intercourse throughout the treatment period and for at least 120 days after the last dose of study drug (ie, oral contraceptive and condoms; intrauterine device and condoms; diaphragm with spermicide and condoms; other forms of contraception must be approved by the medical monitor)

        OR

        Agree to practice true abstinence during the entire study treatment period and through 120 days after the last dose of study drug

        Note: Abstinence should only be used as a contraceptive method if it is in line with the subject's usual and preferred lifestyle. Periodic abstinence (calendar symptothermal, post-ovulation methods) is not an acceptable method of contraception.

    b. Agree not to donate sperm during the course of treatment period of this study or within 120 days after receiving the last dose of the study drug
7. Must have ER+ and HER2- tumor status confirmed per local laboratory testing. Status may be confirmed on original diagnosis tissue samples or post-treatment samples (most recent biopsy preferred, if testing available). ER and HER2 testing must be performed in the following manner:

a. Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry (IHC) as defined in the 2010 American Society for Clinical Oncology (ASCO) recommendations for ER testing (Hammond et al, 2010), with or without PGR positivity

AND

b. Documentation of HER2- tumor with an IHC result of 0 or 1+ for cellular membrane protein expression or an in situ hybridization negative result as defined in the 2013 or 2018 ASCO recommendations for HER2 testing (Wolff, 2013; Wolff, 2018)

8. 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 (eg, phosphoinositide 3-kinase [PI3K] inhibitor), for mBC
    a. Must have progressed during or within 28 days of completion of each line of endocrine therapy; ie, if a subject was discontinued due to toxicity without progression, this would not count as a line of prior therapy
    b. For subjects who progress during or within 12 months of adjuvant endocrine therapy, this will count as 1 line of endocrine therapy for mBC. In the absence of such progression, adjuvant therapy does not count as 1 of the required lines of endocrine therapy
9. 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
    a. Prior treatment with a CDK4/6 inhibitor not in combination with fulvestrant or an AI will not fulfill this criterion
    b. Discontinuation of prior CDK4/6 inhibitor due to toxicity, in the absence of progression, will not fulfill this criterion
10. Must have received no more than 1 line of cytotoxic chemotherapy in the advanced/metastatic setting
    a. Cytotoxic chemotherapy does not include: CDK4/6 inhibitors, mTOR inhibitors, PI3K inhibitors, or immunotherapy. There are no restrictions on prior use of these agents
    b. There is no requirement for documentation of progressive disease to prior chemotherapy
    c. Chemotherapy given in combination with endocrine therapy counts as both a line of endocrine therapy and a line of chemotherapy
    d. Chemotherapy administered for less than 1 cycle will not be counted as a prior line of chemotherapy
    e. For subjects who progress within 12 months of neoadjuvant or adjuvant chemotherapy, this will count as 1 prior line of therapy for advanced/metastatic disease
11. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

12. Resolution of all toxic effects of prior therapies or surgical procedures to Grade ≤ 1 (except alopecia and peripheral neuropathy)
13. Adequate organ function as defined below:
    a. Hematologic function (in the absence of transfusion of red blood cells or platelets or the use of growth factors within the preceding 4 weeks)
       - Absolute neutrophil count ≥ 1.0 x 10^9/L
       - Platelet count ≥ 75 x 10^9/L
       - Hemoglobin ≥ 9.0 g/dL
    b. Renal function
       - Estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 or creatinine clearance calculated by Cockcroft-Gault equation ≥ 30 mL/min (Appendix 4)
    c. Hepatic function
       - Alanine aminotransferase (ALT) ≤ 3x upper limit of normal (ULN)
       - Aspartate aminotransferase (AST) ≤ 3x ULN
       - Total bilirubin ≤ ULN or total bilirubin ≤ 1.5x ULN with direct bilirubin ≤ ULN of the laboratory in subjects with documented Gilbert's Syndrome
    d. Chemistry
       - Potassium, sodium, calcium (corrected for albumin), magnesium, and phosphorus NCI CTCAE v5.0 Grade ≤ 1. If Screening assessments are abnormal, chemistry assessments may be repeated up to 2 times; subjects may receive appropriate supplementation or treatment (eg, for hypercalcemia) prior to re-assessment
    e. Coagulation
       - International normalized ratio (INR) ≤ 1.5

       Note: Subjects who are receiving anticoagulation treatment which is monitored by INR (eg, warfarin) may be allowed to participate if they have a stable INR (ie, within therapeutic range) for at least 28 days prior to the first dose of study drug, in the absence of any exclusionary medical conditions, and provided that an AI would be appropriate therapy for the subject
14. Ability to understand the protocol and provide informed consent

5.2. Subject Exclusion Criteria

Subjects must meet none of the following exclusion criteria:

1. Prior treatment with elacestrant or investigational SERD or ER antagonist (eg, D-0502, GDC-0810, GDC-0927, GDC-9545, G1T-48, LSZ102, AZD9496, SAR439859, ZN-c5, H3B-6545, bazedoxifene, lasofoxifene)

2. Prior anti-cancer or investigational drug treatment within the following windows:
    a. Fulvestrant treatment (last injection) < 42 days before first dose of study drug
    b. Any other endocrine therapy < 14 days before first dose of study drug
    c. Chemotherapy or other anti-cancer therapy < 21 days before first dose of study drug
    d. Any investigational anti-cancer drug therapy < 28 days or 5 half-lives (whichever is shorter) before the first dose of study drug. Enrollment of subjects whose most recent therapy was an investigational agent should be discussed with RADIUS
    e. Bisphosphonates or RANKL inhibitors initiated or dose changed < 3 months prior to first dose of study drug
3. Radiation therapy within 14 days (28 days for brain lesions per Exclusion Criterion 4) before the first dose of study drug
4. Presence of symptomatic metastatic visceral disease, including but not limited to, extensive hepatic involvement, untreated or progressive central nervous system (CNS) metastases, or symptomatic pulmonary lymphangitic spread. Subjects with discrete pulmonary parenchymal metastases are eligible provided their respiratory function is not significantly compromised as a result of disease in the opinion of the Investigator. Subjects with previously treated CNS metastases are eligible provided that all known lesions were previously treated, they have completed radiotherapy at least 28 days prior to first dose of study drug and are clinically stable. If anticonvulsant medication is required, subjects must be stable on a non-enzyme inducing anticonvulsant regimen (Appendix 8)
5. Intact uterus with a history of endometrial intraepithelial neoplasia (atypical endometrial hyperplasia or higher-grade lesion)
6. Diagnosis of any other malignancy within 5 years before enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or second primary breast cancer
7. Any of the following within 6 months before enrollment: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE v5.0 Grade ≥2, prolonged QTcF ≥ Grade 2 (ie, > 480 msec), uncontrolled atrial fibrillation of any grade, coronary/peripheral artery bypass graft, heart failure ≥ Class II as defined by the New York Heart Association guidelines (Appendix 6), or cerebrovascular accident including transient ischemic attack
8. Child-Pugh Score greater than Class A (ie, score > 6; Appendix 7)
9. Coagulopathy or any history of coagulopathy within the past 6 months, including history of deep vein thrombosis or pulmonary embolism. However, subjects with the following conditions will be allowed to participate:
    a. Adequately treated catheter-related venous thrombosis occurring > 28 days prior to the first dose of study drug
    b. Treatment with an anticoagulant, eg, warfarin or heparin, for a thrombotic event occurring > 6 months before enrollment, or for an otherwise stable and allowed medical condition (eg, well controlled atrial fibrillation), provided dose and coagulation parameters (as defined by local standard of care) are stable for at least 28

days prior to the first dose of study drug and provided that an AI would be an appropriate therapy for the subject

10. Known bleeding disorder which, in the opinion of the Investigator, would prohibit administration of fulvestrant if that would be SOC choice for the subject
11. Known difficulty in tolerating oral medications or conditions which would impair absorption of oral medications such as: uncontrolled nausea or vomiting (ie, CTCAE ≥ Grade 3 despite antiemetic therapy), ongoing gastrointestinal obstruction/motility disorder, malabsorption syndrome, or prior gastric bypass
12. Unable or unwilling to avoid prescription medications, over-the-counter medications, dietary/herbal supplements (eg, St. John's wort), and/or foods (eg, grapefruit, pomelos, star fruit, Seville oranges and their juices) that are moderate/strong inhibitors or inducers of CYP3A4 activity (Appendix 8). Participation will be allowed if the medication, supplements, and/or foods are discontinued for at least 5 half-lives or 14 days (whichever is longer) prior to study entry and for the duration of the study
13. Major surgery < 28 days before the first dose of study drug
14. Any concurrent severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with compliance with study procedures or the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study
15. Known hypersensitivity reaction to drugs chemically related to elacestrant or their excipients
16. Known hypersensitivity to fulvestrant, anastrozole, letrozole, or exemestane (or to any of their excipients), unless treatment with 1 of the other 3 of these 4 treatment options would be appropriate therapy
17. Subjects who meet any contraindication, according to the respective PI or SmPC, for any SOC drug that the Investigator would choose for that subject should the subject be randomized to the SOC group

5.3. Subject Withdrawal Criteria

5.3.1. Subject Withdrawal from Active Treatment Phase

Discontinuation of treatment or subject withdrawal is not the same as interruption of treatment. An interruption in treatment occurs when a subject stops taking the study drug for a period of time, with the intention of subsequently resuming study medication. All treatment interruptions should be noted and the dates and reasons for treatment interruptions should be documented. Note: a maximum interruption of 14 consecutive days is permitted. Dose interruptions of > 14 consecutive days require discussion with RADIUS prior to continuation on study.

Treatment discontinuation refers to the permanent discontinuation of study treatment. When treatment is discontinued, the subject is no longer in the active treatment phase of the study; however, the subject continues on study with appropriate follow-up as outlined in the Schedule of Events (Appendix 2).

Reasons for treatment discontinuation include:

- Disease progression (per RECIST v1.1 or symptomatic deterioration that in the opinion of the Investigator represents disease progression)
- A clinically significant AE, laboratory abnormality, or other medical condition or situation that in the opinion of the Investigator precludes further study treatment
- Significant study noncompliance (with discussion with the medical monitor and RADIUS)
- Subject unable to receive study treatment for > 14 consecutive days (at the discretion of RADIUS)
- Investigator believes that treatment discontinuation is in the best interest of the subject
- Subject refusal of further investigational treatment

Based on median duration of treatment of 3.8 months in Study RAD1901-005 for all subjects treated with 400 mg elacestrant, subjects randomized to treatment with elacestrant are expected to remain on treatment for approximately 4 months. Subjects exhibiting a response would be expected to have longer treatment duration.

5.3.2. Subject Withdrawal from the Study

Subjects are free to withdraw from participation in the study for any reason at any time. The reason for terminating study participation will be recorded in each subject's medical records (source documents) and entered into the End of Study electronic Case Report Form (eCRF).

If a subject withdraws from the study, every effort should be made to complete the end of treatment (EOT) assessments; however, if a subject withdraws consent, no further assessments should be performed and no additional data should be collected. RADIUS may retain and continue to use any data collected before consent was withdrawn.

Reasons for a subject to be withdrawn from the study include:

- Subject or proxy withdraws consent
- In the opinion of the Investigator it is not in the best interests of the subject to continue on study
- Inability of the subject to comply with the protocol
- Lost to follow-up
- RADIUS decision to terminate study
- Death

6. STUDY TERMINATION

The study may be terminated by the sponsor for any of the following reasons:

- Serious safety concern
- Reduced efficacy for elacestrant compared to SOC drugs
- Recommendation of the IDMC
- Administrative decision (eg, termination of product development)

7. STUDY PROCEDURES

The Schedule of Events is provided in Appendix 2.

7.1. Demographic, Medical History, Prior and Concomitant Medication

Each subject's demographic and medical history and all prior anti-cancer treatments, including all surgical procedures related to the cancer diagnosis will be collected.

All prior and concomitant medications (including over-the-counter medicines, herbal treatments, supplements, vitamins, and substance use) and treatments taken from 35 days prior to signing consent until 30 days after the last dose of study drug will be recorded.

7.2. Physical Examination and Vital Signs

A full physical examination, including a total body examination of all major body systems (eg, general appearance, skin, neck [including thyroid], ears, eyes, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities and a clinical neurological examination), height, weight, respiratory rate, sitting blood pressure, and sitting pulse rate must be performed by a physician, registered nurse, or other qualified health care provider at Screening. Post-Screening physical examinations should be performed per the Schedule of Events and may be targeted based on findings present at Screening or subject complaints (see Appendix 2). Vital sign measurements should also be performed according to the Schedule of Events.

Clinically-significant findings at Screening should be recorded either as medical history or as an AE as appropriate. Clinically-significant new findings at post-Screening visits should be recorded as AEs.

7.3. Electrocardiograms and Prolonged QTcF Guidelines

ECG machines to be utilized in this study will be supplied by a third-party vendor. All ECG tracings will be sent electronically to a central ECG laboratory; this laboratory will provide all ECG results to the study site.

Twelve-lead ECGs will be performed according to the schedule in the Pharmacokinetic and ECG Schedule of Events (Table 19 of Appendix 2). Each ECG, both at Screening and during the study, is to be performed in triplicate approximately 2 minutes apart after the subject has been supine for at least 5 minutes. Mean QTcF interval will be calculated by the central ECG laboratory using the average of the triplicate ECG measurements. The pre-treatment on Day 1

average value will serve as each subject's baseline QTcF value to which all subsequent ECGs will be compared. Information and instructions for performing the ECGs are provided in the Investigator Site Manual.

Instructions on management of prolongations in the QTcF interval are outlined in Section 4.5.3.

7.4. Tumor Assessments

7.4.1. Overview

- Tumor assessments will be performed following the RECIST v1.1 criteria (Appendix 1)
- Tumor assessments will be performed at Screening and every 8 weeks, (± 7 days) from the date of randomization during the active treatment phase of the study (and in the follow-up period for subjects who have discontinued study drug for reasons other than PD [clinical PD or PD confirmed by RECIST] and have not yet started new anti-cancer therapy)
  - For Screening assessments, radiographic assessments obtained per the subject's SOC prior to signing consent for the study do not need to be repeated and are acceptable to use as Screening evaluations, if (1) they were obtained within 28 days before randomization (with the exception of radionuclide bone scans/ whole body MRI scans which must be within 12 weeks of randomization and brain computed tomography (CT) or MRI scans which must be within 6 weeks of randomization); (2) they were performed using the method requirements outlined in RECIST v1.1 and they meet all imaging requirements as outlined herein and the Bioclinica Site Manual; (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given subject; and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as SOC is available in the subject's source notes
  - All assessments performed during the active treatment phase of the study will be performed as scheduled at the required intervals according to the Schedule of Events, regardless of any dosing delay, to prevent the introduction of bias into the assessment of efficacy (Table 18 in Appendix 2)
- All tumor assessments, including those performed during Screening to assess eligibility and baseline tumor measurements, will be collected and sent to a core imaging vendor for blinded IRC analysis. Instructions on collection and transmission/shipping will be provided in the Bioclinica Site Manual

7.4.2. CT or MRI Tumor Assessment

- CT of the chest and CT or MRI of the abdomen and pelvis, and other sites as clinically indicated will be performed at Screening and every 8 weeks (± 7 days) from the date of randomization during the active treatment phase of the study
- Diagnostic CT for tumor assessment may be used even if acquired during PET/CT hybrid imaging providing the CT images are of sufficient quality

- A contrast agent should be used, except when contraindicated for medical reasons. (See RECIST v1.1 and the Bioclinica Site Manual for recommended/required imaging modalities for each required scan)
- For subjects who achieve a CR or PR, a confirmation scan must be repeated at least 4 weeks after the first documented response
- All lesions followed for tumor response should continue to be assessed using the same modality (CT scan, PET CT, bone window settings on CT scan, or MRI)
- Enrolled subjects with history of stable brain metastases should have brain CT or MRI imaging in parallel with systemic imaging for evaluation of non-target lesions in the brain; brain CT or MRI scans are not otherwise required as part of standard imaging unless new metastases are suspected

7.4.3. Radionuclide Bone Scan or Whole Body MRI Tumor Assessment of Bone Lesions and Follow-up Assessments of Bone Lesions

- A radionuclide bone scan or whole body MRI should be performed at Screening in all subjects. Positive areas on bone scans must be assessed by CT scan with bone windows (PET hybrid with bone window settings on CT scan is acceptable providing the CT images are of sufficient quality) or MRI prior to the first dose of study medication and continue to be assessed throughout the study using the same modality. Screening CT of chest and CT or MRI of abdomen and pelvis acquired for tumor assessment are sufficient for evaluation of bone lesions involving the axial skeleton. Additional imaging of appendicular skeletal lesions (eg, skull, cervical spine, extremities) by bone window settings on CT scan or MRI is required if these sites are the only bone lesions to be followed.
- If subjects present with both irradiated and nonirradiated bone lesions, all lesions should be followed for tumor assessments, but only non-irradiated lesions should be followed as target lesions per RECIST v1.1 (f they meet criteria for a bone target lesion); previously irradiated lesions should be followed as non-target lesions. Subjects with bone only disease must have at least 1 non-irradiated lesion to be eligible.
- If bone lesions were identified by radionuclide bone scan or whole body MRI at baseline, bone scans or whole body MRI (using the same modality as used during Screening) will be repeated during the active treatment phase as clinically indicated and every 24 weeks (±7 days) from the date of randomization and at the time of confirmation of a CR. If no bone lesions were identified at baseline, bone scans or whole body MRI will only be repeated during the active treatment phase when clinically indicated (ie, subject describes new or worsening bone pain, has an increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), but are required at the time of confirmation of a CR. Bone lesions confirmed by CT or MRI (or PET CT when CT images are of sufficient quality) at baseline, and documented as target (when a measurable soft tissue component is present) and/or non-target lesions will be assessed every 8 weeks (± 7 days) using the required CT of chest and CT or MRI of abdomen and pelvis (or

PET CT when PET CT was used at baseline) and additional imaging by bone window settings on CT scan or MRI of any appendicular bone lesions that are being followed as a target and/or non-target lesions. New abnormalities found on subsequent bone scans or whole body MRI must also be confirmed by bone window settings on CT scan or MRI (Table 20 in Appendix 2)

7.4.4. Clinical Lesions

- Any skin lesions that are to be followed as either target or nontarget lesions must have color photographs taken at Screening and every 8 weeks (± 7 days) from the date of randomization during the active treatment phase of the study. Photographs should include measurement markers, such as a ruler
- Palpable lesions that are to be followed as either target or nontarget lesions must be assessed and measured at Screening and every 8 weeks (± 7 days) from the date of randomization during the active treatment phase of the study

7.5. Laboratory Assessments

During the treatment period, laboratory tests in addition to those mandated per protocol (shown in the Schedule of Events in Appendix 2) may be obtained at the Investigator's discretion if clinically indicated.

7.5.1. Estradiol and Follicle Stimulating Hormone

Estradiol and FSH levels will be tested at Screening in female subjects only. These tests do not need to be performed in subjects who have undergone bilateral surgical oophorectomy.

7.5.2. Urinalysis

Urinalysis will be performed at Screening. Urinalysis includes protein, glucose, blood, ketones, nitrites, and leukocyte esterase. Microscopic examination is required only when urinalysis is positive for nitrites, leukocyte esterase, protein, or blood. Urinalysis after Screening may be performed if indicated, based on the clinical judgment of the Investigator.

7.5.3. Chemistry

Chemistry assessments will be performed as shown in the Schedule of Events (Appendix 2). Chemistry includes blood urea nitrogen (BUN) or urea, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, magnesium, albumin, total protein, total bilirubin (direct and indirect if total is > ULN), alkaline phosphatase, ALT, AST, and a glucose and lipid panel (total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides). If possible, the glucose and lipid profile should be performed with the subject in a fasting state.

7.5.4. Special Chemistry

Hemoglobin A1c is to be measured at Screening and EOT.

7.5.5. Coagulation

Coagulation profile, including prothrombin time (PT), or INR (per the site's standards for follow-up assessments; INR is required at Screening), activated partial thromboplastin time (aPTT; PTT is allowed if aPTT is not available), and fibrinogen will be performed as outlined in the Schedule of Events (Appendix 2).

7.5.6. Hematology

Hematology assessments will be performed as shown in the Schedule of Events (Appendix 2). Hematology includes hemoglobin, hematocrit, white blood cell with differential (including absolute neutrophil count and lymphocyte, monocyte, eosinophil, and basophil counts), and platelet count.

7.6. Tumor Biomarkers

7.6.1. Tumor Biopsy

Analysis of pharmacodynamic biomarkers predictive of elacestrant response is an important exploratory objective of this study.

All subjects with accessible lesions are requested to provide tumor biopsies; however, these biopsies are optional and are not required for eligibility. For subjects agreeing to provide biopsies, biopsies will be taken at 3 time points during the study: pre-treatment, on-treatment, and post-treatment. On-treatment and post-treatment biopsies are only required if the pre-treatment biopsy was successful (ie, tissue obtained; confirmed to contain adequate tumor cells by central laboratory).

Pre-treatment biopsies should be obtained after progression on the most recent systemic anticancer therapy and should be performed on a metastatic lesion or site of recurrent disease, if accessible. Biopsies obtained for other reasons within 3 months of first dose of study treatment that meet these criteria may be submitted in lieu of a fresh biopsy. On-treatment biopsy should be performed between C1D28 and C3D28, as close as feasible to C2D28. Post-treatment biopsy should be performed at the time of study drug discontinuation and prior to initiation of new anti-cancer therapy. Biopsies should be taken from the same lesion at each time point, when feasible.

All biopsies will be used for retrospective pharmacodynamic analysis of ER and other oncogenic pathway markers (eg, PGR, PIK3CA) and proliferation markers (eg, Ki67, pRb). Results from biopsy samples will be analyzed and correlated with clinical response to support the identification of biomarkers that may be predictive of a subject's response to treatment.

Details of sample collection, processing, shipping, and storage are described in the Medpace Laboratory Manual.

7.6.2. Circulating Tumor DNA

Blood samples for ctDNA analysis will be collected and submitted to Guardant Health at Screening (see Guardant Laboratory Manual). These samples will be analyzed using the Guardant360 (Guardant Health, Redwood City, CA) assay to determine ESR1 mutational status.

The Guardant360 assay uses digital sequencing technology to detect all missense nucleotide variants within the ligand binding domain (LBD) of the ESR1 gene. Detection of any ESR1 mutation(s), as defined by Guardant Health for the assay, will be reported as ESR1 mutation present (ie, ESR1-mut). No mutation may be detected if there is no mutation present in the ESR1 gene (ie, wild-type) or if there is no detectable ctDNA present in the blood sample; these will be reported and analyzed together as ESR1 mutation not detected (ESR1-mut-nd).

ESR1 test results will be used for stratification at randomization; however, the site will not be provided with a subject's mutational status during the subject's active treatment phase, unless otherwise required by regulation. Results will be provided back to sites semi-blinded to ESR1 mutational status (ie, coded as Group A or Group B) for randomization. ESR1 mutational status may be requested by the study site to help guide treatment decisions at the time of discontinuation of study treatment; study sites may also request results for subjects who fail screening.

Additional ctDNA samples will be collected and submitted to the central laboratory as indicated in the Schedule of Assessments (Appendix 2) (see Medpace Laboratory Manual).

Other tumor alterations relevant to ER+ breast cancer, such as PIK3CA, CDK4/6, and RB1, may also be assessed using this same assay run on the same blood sample.

Details on sample collection, processing, and shipping are provided in the Medpace Laboratory Manual.

7.6.3. Residual Samples for Exploratory Biomarker Analysis

Any residual biological samples collected during the conduct of the study will be stored in a central location for potential exploratory biomarker research to be conducted either during or after the study. Samples may be stored at a central laboratory facility for up to 15 years after completion of the final study report or for a length of time dictated by local laws and regulatory requirements, whichever is shorter.

Note: The exploratory biomarker research component of the study may include analysis of pre-treatment and post-treatment samples for additional exploratory biomarkers to assess potential correlations between known signal transduction pathway markers, or other associated biological activities and antitumor response. The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

Further, the results of this exploratory biomarker research may be pooled with biomarker data from other studies with elacestrant to generate hypotheses to be tested in future studies.

7.6.4. Disposal of Samples

Biological samples will be destroyed no later than after the maximum storage duration of 15 years or according to local legal and regulatory requirements, whichever is shorter.

Subjects who withdraw consent following collection of biological study samples may request the destruction of their biological study samples and any materials derived from the collected samples which have not yet been processed.

7.7. Patient Performance Status and Patient Reported Outcomes

7.7.1. ECOG Performance Status

ECOG performance status (Appendix 3) will be assessed per the Schedule of Events (Appendix 2).

7.7.2. Patient Reported Outcomes

Three PROs, EQ-5D-5L, EORTC QLQ-C30 and PRO-CTCAE, with relevance to the mBC population, will be used during this study to assess the subject's self-report of his/her well-being and quality of life.

- The EQ-5D-5L is a simple descriptive profile developed by the EuroQol Group (an international network of multidisciplinary researchers) with broad applicability for use in clinical trials. The EQ-5D-5L measures a subject's self-assessment of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
- The EORTC QLQ-C30 was developed by the European Organization for Research and Treatment of Cancer (EORTC). This is a questionnaire developed to measure the self-reported quality of life of cancer subjects. The instrument was designed to measure several dimensions of HRQOL, including disease and treatment-related symptoms, physical, psychological and social functioning
- The PRO-CTCAE was developed by the National Cancer Institute/National Institute of Health to measure subject reporting of symptomatic toxicity while participating in cancer clinical trials. It characterizes the frequency, severity and interference of symptomatic treatment toxicities, such as pain, fatigue, nausea, and cutaneous side effects, reported from the subject's perspective. It was designed as a correlate to the NCI CTCAE standard for reporting of AEs

The PRO questionnaires EQ-5D-5L, EORTC QLQ-C30 and PRO-CTCAE are to be completed by the subject using the provided electronic tablets containing the PRO questionnaires at the study site as per the Schedule of Events (Appendix 2). These assessments are to be performed at the start of the visit, prior to other assessments, and prior to any significant interactions between the subject and study staff.

Note: If a certified translation for any PRO questionnaire is not available for a subject, that specific PRO assessment can be omitted, but the reason must be documented.

7.8. Pharmacokinetic Samples

Pharmacokinetic samples are to be collected as per the Schedule of Events (Table 18 in Appendix 2). Additionally, Investigators may obtain blood samples for elacestrant plasma concentrations at the time(s) significant AEs and SAEs occur that are considered potentially related to the study drug. Refer to the Medpace Laboratory Manual for detailed instructions on the collection, handling, and shipment of PK samples.

PK sampling and measurement will not be performed for the SOC treatment group.

7.9. Adverse and Serious Adverse Events

7.9.1. Definition of Adverse Events

7.9.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with study drug treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the informed consent form (ICF) is signed.

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs should be performed and those deemed a clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment should be provided rather than the abnormal test result alone (eg, urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself should be listed as the AE (eg, lung nodule on CT scan).

Investigators will be requested to evaluate abnormal study assessments for clinical significance. A clinically-significant finding could include:

- Worsening from baseline (eg, by at least 1 grade)
- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention is required
- A change in the dose of study drug, if study drug is withheld, or discontinuation from study drug

Determination of clinical significance must be made by the Investigator.

Events that do not meet the definition of an AE or SAE (see Section 7.9.1.2) include:

- Planned hospital admissions or surgical procedures for a condition that existed before the subject signed the informed consent are not to be considered AEs unless the condition deteriorates in an unexpected manner during the study (eg, surgery had to be performed earlier than planned)
- Anticipated day-to-day fluctuations of pre-existing disease(s), condition(s), and signs or symptoms present or detected prior to the start of the study that are not more severe than expected for the subject's condition
- Disease progression, hospitalization, or death due to disease progression

7.9.1.2. Serious Adverse Event

An AE is considered serious if, in the view of either the Investigator or RADIUS, it meets any of the following criteria:

- Death
  - Death due to disease progression is not considered an SAE and should not be reported as such.

- Life-threatening
  - An AE is considered life-threatening if, in the view of either the Investigator or RADIUS, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization

  Note: Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect
- Important medical events that may not result in death, are not life-threatening, and do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.9.2. Relationship to Study Drug

Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to study drug, indicating on the eCRF that an AE is either related or unrelated. The following guidance should be taken into consideration when determining the relationship of an AE to study drug (either elacestrant or SOC):

- Temporal relationship of event onset to initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the subject or environment, or use of concomitant medications known to be associated with the event
- Presence of treatment-unrelated factors that are known to be associated with the occurrence of the event
- Whether there is a reasonable alternative explanation for the event

7.9.3. Study Drug Action Taken

The Investigator will determine the study drug action (either elacestrant or SOC) taken with regard to the AE. The action taken should be classified according to the categories shown in Table 10.

Table 10: Classification for Study Drug Action Taken with Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose or frequency not changed in response to an AE
Dose Reduced[1]	Study drug dose reduced in response to an AE
Drug Interrupted	Study drug administration interrupted in response to an AE
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the investigational treatment had ended before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

AE = adverse event
[1]Dose reduction is not allowed for aromatase inhibitors.

7.10. Adverse Event Outcome

An AE should be followed until the Investigator has determined and provided the final outcome. The outcome should be classified according to the categories shown in Table 11.

Table 11: Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms
Recovering/Resolving (Ongoing)	Improvement of an AE but not yet resolved
Not Recovered/Not Resolved (Ongoing)	No improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the AE
Unknown	Outcome of an AE is not known (eg, a subject lost to follow-up)

AE = adverse event

7.10.1. Treatment Given

The Investigator will ensure adequate medical care is provided to subjects for AEs. In addition, the Investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications, hospitalization, radiation therapy, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

7.10.2. Follow-up of Adverse Events

All subjects will be followed for AEs until 30 days post-treatment or until resolution or stabilization of all treatment-related AEs to either ≤ Grade 2 or baseline, whichever is longer, or until the subject is lost to follow-up.

At any time after 30 days from the last dose of study treatment, the Investigator may report any SAE that he/she believes is related to study treatment.

7.10.3. Overdose and Medication Error

Occurrences of events of overdose and medication error must be reported to RADIUS.

Any AEs/SAEs associated with either an overdose or medication error should be reported as AEs or SAEs as appropriate (Section 7.12).

An overdose is defined as administration of a quantity of a medicinal product greater than the dose or more frequently than defined in the protocol for the investigational product.

A medication error is defined as an error made in prescribing, dispensing, administration, and/or use of study drug. The administration and/or use of expired study drug should be considered as a reportable medication error to RADIUS. Cases of subjects missing doses of the study drug are not considered reportable as medication errors to RADIUS.

7.10.3.1. Elacestrant

In the event of an elacestrant overdose, the Investigator should contact the Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. No specific treatment is recommended; the Investigator will use clinical judgment to treat any overdose. Decisions regarding dose modifications or interruptions should be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject. A plasma sample for PK analysis may be requested by the Medical Monitor on a case-by-case basis. This plasma sample should be collected as soon as possible. Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

7.10.3.2. Standard of Care

In the event of a fulvestrant or AI overdose, the Investigator should contact the Medical Monitor immediately and closely monitor the subject for AEs/SAEs and laboratory abnormalities. The PI or SmPC should be consulted; during SOC treatment the Investigator will follow any warnings or precautions for use as detailed in the PI or SmPC. Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the eCRF.

7.11. Recording Adverse Events

All AEs will be collected from the time the ICF is signed until the following time points:

- For subjects who are not enrolled: until time of screen failure
- For enrolled subjects: through 30 days after the last dose of study treatment

- For subjects who remain on study after the EOT safety follow-up visit, no AE reporting is required post safety follow-up; however, the Investigator may report any SAE that he/she believes is related to study treatment
- At any time after 30 days from the last dose of study treatment, the Investigator may report any SAE that he/she believes is related to study treatment (AEs other than treatment-related SAEs should not be reported during this time)

All AEs will be entered into the eCRF whether or not the event is believed to be associated with use of the study drug. Signs or symptoms reported as AEs will be graded and recorded by the Investigator according to the NCI CTCAE v5.0.

When specific AEs are not listed in the NCI CTCAE v5.0, they will be graded by the Investigator according to grades and definitions listed in Table 12.

Table 12: Grading of Adverse Events

Grade	Description
Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (eg, packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

AE = adverse event

All subjects will be queried using nonleading questions about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms should be identified as one overall event or diagnosis. All AEs for enrolled subjects will be recorded in the eCRF and the subject's source documents. AEs for subjects who are screened, but not subsequently enrolled in the study will be recorded only in the subject's source documents unless an AE is related to a study-mandated procedure (eg, hemorrhage post tumor biopsy; anaphylaxis to CT contrast dye), in which case the AE should be reported as a pre-treatment AE. The following data should be documented for each AE:

- Description of the event term as diagnosis, if possible
- Classification of "serious" or "not serious"
- Start date and date of resolution (if applicable)
- Severity (using NCI CTCAE v5.0 criteria when applicable)
- Causal relationship to study drug (see Section 7.9.2)
- Action taken with study drug (Table 10)
- Outcome (Table 11)
- Concomitant medication or other treatment given

7.12. Reporting Adverse Events

SAEs (initial reports and follow-up information) must be reported by the Investigator using the SAE reporting form; the form must be completed and emailed to PV@radiuspharm.com within 24 hours after learning of the event. Prompt notification of SAEs by the Investigator is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

RADIUS will comply with country-specific regulatory requirements related to safety reporting to regulatory authorities, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Investigators.

Safety reports will be prepared for Suspected Unexpected Serious Adverse Reactions according to local regulatory requirements and RADIUS policy and will be forwarded to Investigators as necessary.

An Investigator who receives a safety report describing an SAE or other specific safety information from RADIUS will file it in the Trial Master File and will notify the IRB/IEC, if appropriate, according to local requirements.

7.13. Partner Pregnancy

Any pregnancy for the female partner of a male study participant must be reported within 24 hours to the RADIUS Pharmacovigilance Department using the Pregnancy Report Form. Every effort should be made to gather information regarding the pregnancy course and outcome. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

8. SCHEDULE OF PROCEDURES AND OBSERVATIONS

Study-specific assessments are outlined in the Schedule of Events (Appendix 2). All on-study visits procedures are allowed a window of ± 2 days unless otherwise noted.

8.1. Screening and Randomization

Written informed consent for participation in the study must be obtained before performing any study-specific Screening tests or evaluations. ICFs for enrolled subjects and for subjects who are not subsequently enrolled will be maintained at the study site.

Screening tests and evaluations will be performed within 35 days prior to C1D1. All imaging must be completed within 28 days prior to C1D1. All Screening evaluations must be completed and reviewed by the Medical Monitor to confirm that patients meet all eligibility criteria before randomization. If hematology, chemistry, coagulation assessments are performed > 7 days prior to C1D1, they must be repeated and eligibility criteria must still be met. Randomization may occur on Day -1 or on Day 1. Note: there is no Day 0 in this study. The planned first dose of C1D1 is to start within 1 day after randomization.

See Appendix 2 for the schedule of Screening assessments.

8.2. Assessments during Treatment

All assessments must be performed on the day of the specified visit (± 2 days). Assessments scheduled on the day of study drug administration should be performed prior to administration of study drug, unless otherwise noted in the schedule of assessments (see Appendix 2). PRO assessments should be performed prior to the completion of other study assessments.

8.3. Assessments at End of Treatment

Subjects who complete the study or discontinue from the study early will return to the site 14 days after the last dose of study drug. If the EOT visit falls on Day 1 of a cycle and the subject is withdrawing, the EOT assessments are to be completed instead of Day 1 assessments.

Unless otherwise specified, assessments that have been completed within the previous 14 days of the EOT visit do not need to be repeated at the EOT visit.

See Appendix 2 for the schedule of EOT assessments.

8.4. Post-Treatment Safety Follow-Up

The Safety Follow-Up assessments are to be completed at 30 days (± 3 days) after the last dose of study drug (see Appendix 2). An onsite visit is preferred; however, if this is not feasible, telephone contact is acceptable. PRO assessments should be performed prior to the completion of other safety follow-up assessments. If follow-up assessments are conducted by telephone, the PRO assessments are to be omitted.

8.5. Post-Treatment Follow-Up

Post-treatment Follow-Up is to occur every 8 weeks (± 7 days) (see Appendix 2).

For subjects who discontinue study treatment because of objective disease progression or clinical progression in the absence of progression by RECIST, survival data will be collected every 8 weeks (± 7 days), calculated from the last dose of study treatment, for the duration of the study. The start date and regimen name of the first new anti-cancer therapy will also be collected. Telephone contact is acceptable.

Note: Subjects who discontinue treatment for reasons other than disease progression and who do not begin a new anti-cancer therapy will continue to have tumor assessments every 8 weeks (± 7 days) from the date of randomization, and bone scans or whole body MRI every 24 weeks (± 7 days) as indicated, until disease progression is documented, or new anti-cancer therapy is initiated, at which time they will continue to be monitored every 8 weeks (± 7 days) for first new anti-cancer therapy and survival for the duration of the study.

At any time after 30 days from the last dose of study treatment, the Investigator may report any SAE that he/she believes is related to study treatment.

8.6. Study Completion

The study will be complete when approximately 50% of subjects have died. However, subjects will be provided with study treatment, if still on active treatment, until all subjects discontinue

study participation or elacestrant is approved for marketing in a subject's country, at which time the study may be closed for subject participation.

9. TREATMENT OF SUBJECTS

9.1.1. Description of Study Drugs

9.1.1.1. Elacestrant (Investigational Product)

Information about the investigational product in this study, elacestrant, is provided in Table 13.

Table 13: Investigational Product

	Investigational Product
Product Name	Elacestrant
Dosage Form	Tablet
Unit Dose	100 mg or 400 mg of elacestrant·2HCl per tablet
Route of Administration	Oral
Physical Description	White, immediate release Opadry II film-coated tablet, containing 100 mg or 400 mg of elacestrant·2HCl drug substance per tablet and microcrystalline cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate (nonbovine), mannitol, and partially pre-gelatinized maize starch
How Supplied	Tablets (30 counts) are filled into 30 cc (100 mg tablet) or 100 cc (400 mg tablet) high density polyethylene (HDPE) bottles equipped with a child resistant cap and a desiccant. The cap contains an inner foil liner which is induction sealed during the packaging process
Manufacturer	Patheon Inc., Ontario Canada

9.1.1.2. Standard of Care Options

SOC option includes 1 of the following single agents:

- Fulvestrant (Faslodex®): 500 mg administered IM into the buttocks as two 5 mL injections on C1D1, C1D15 and C2D1 and Day 1 of every subsequent 28-day cycle
- Anastrozole (Arimidex®): 1 mg QD orally on a continuous dosing schedule
- Letrozole (Femara®): 2.5 mg QD orally on a continuous dosing schedule
- Exemestane (Aromasin®): 25 mg QD orally on a continuous dosing schedule

For subjects randomized to SOC, the Investigator should select 1 of the above options according to what is appropriate based on an individual subject's prior treatment history and the Investigator's judgment. The following is provided as general guidance:

- Subjects who have not previously received fulvestrant should be treated with fulvestrant (unless there is a known contraindication, see contraindications below)
- Subjects who have progressed on prior fulvestrant should be treated with an AI

- The selection of an AI should be based on prior AI therapy and any known contraindications
    - If the subject has previously progressed on a non-steroidal AI (anastrozole or letrozole) but not received exemestane, the preferred option would be exemestane
    - If the subject has previously progressed on exemestane but not received a non-steroidal AI, the preferred option would be a non-steroidal AI

They may not be given in combination with any other anti-cancer agent.

9.1.2. Prior and Concomitant Medications

All prior and concomitant medications (including oral, topical, intravaginal, rectal and inhaled over-the-counter medicines, herbal treatments, supplements, vitamins, and substance use) taken from 35 days prior to signing consent until 30 days after the last dose of study drug will be recorded. Subjects may receive supportive care agents to treat AEs and manage cancer symptoms (such as pain medications, heartburn medications, anti-emetics, anti-diarrheals) as per local institutional guidance.

Prothrombin time (or INR) should be monitored in subjects receiving elacestrant concurrently with warfarin or other coumadin derivatives.

9.1.3. Prohibited Medications

All subjects are prohibited from taking any of the following medications:

- Hormonal medications or medications known to affect serum luteinizing hormone (LH), FSH (except spironolactone which is allowed if medically indicated), or estrogen estradiol levels within 14 days (42 days for fulvestrant) of the first dose of study drug or anytime during the study. This includes, but is not limited to medications, herbal remedies, and/or supplements for the treatment of vasomotor hot flush symptoms administered via any route, including topical or intravaginal administration.
- Any systemic anti-cancer therapy or any other chemotherapeutic agents.
- Bisphosphonates and RANKL inhibitors to manage bone metastases are permitted only if the subject was receiving these agents and was on a stable dose for at least 3 months prior to first dose of study treatment; such agents should not be initiated during study treatment.
- In general, surgical tumor resection, tumor embolization, and radiation therapy are not permitted. Localized palliative radiation therapy may be permitted if no other option is available for pain management, only with approval of the Medical Monitor.

For Elacestrant Treatment Group:

- Medications, herbal preparations, supplements, and herbs or foods known to be moderate/strong inhibitors or inducers of CYP3A should not be used or consumed for the duration of the study because elacestrant undergoes biotransformation primarily by CYP3A. A more detailed listing of these products is provided in Appendix 8

For SOC Treatment Group:

- Refer to the PI or SmPC for complete information about potential drug interactions
- For subjects taking exemestane: CYP3A4 inducers may significantly decrease exposure. Therefore, medications and supplements that are known to be strong inducers of CYP3A4 should not be used/consumed for the duration of the study for subjects taking exemestane (Appendix 8)

9.1.4. Compliance

For subjects taking elacestrant or an AI, the elacestrant bottles or AI bottle(s)/blisters including any unused tablets will be returned to the clinic for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.

For subjects taking fulvestrant, the dose, date and time of fulvestrant administration must be documented in both the medical record (source) and the eCRF.

9.1.5. Randomization and Blinding

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria and eligibility has been confirmed by the Medical Monitor prior to randomization. Randomization is to occur after eligibility is determined. The planned first dose of study drug for C1D1 is to start within 1 day after randomization; randomization may occur on Day -1 or on Day 1. Note: there is no Day 0 in this study.

The Investigators will randomize eligible subjects by Interactive Randomization Technology (IRT) as described in the IRT User Guide. Eligible subjects will be randomized in a 1:1 ratio to either elacestrant or SOC with randomization stratified by the following:

- ESR1 mutational status as detected by ctDNA at central laboratory (ESR1-mut or ESR1-mut-nd)
- Prior treatment with fulvestrant (yes vs no)
- Presence of visceral metastases (yes vs no); visceral includes lung, liver, brain, pleural, and peritoneal involvement

At the time of randomization, information about subject demographics and stratification factors will be entered into the IRT system. The IRT will provide the randomization number and treatment assignment.

This is an open-label study; thus, study subjects and Investigators will not be blinded to treatment assignment. However, to minimize bias in study conduct, RADIUS personnel performing statistical analyses, including biostatisticians and programmers, will be blinded to treatment assignments and aggregated data by treatment assignment until after database lock. CRO study team members and select RADIUS team members will not be blinded to an individual subject's treatment assignment during the conduct of the study but will be blinded to aggregated data by treatment assignment until after database lock.

An independent central IRC, blinded to subjects' treatment assignments, will review radiographic images and clinical information collected on-study to determine the endpoints of disease response and progression.

Safety data and efficacy data based on local Investigator and IRC assessment and OS will be reviewed at pre-specified intervals by the IDMC. An unblinded statistician at the CRO will perform all analyses in preparation for the IDMC evaluations.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Elacestrant

Elacestrant is a white, IR film-coated tablet, containing 100 mg or 400 mg of elacestrant·2HCl per tablet.

10.1.2. Standard of Care

Investigators should refer to the PI or SmPC for a description of each agent (fulvestrant, anastrozole, letrozole, exemestane).

10.1.2.1. Fulvestrant

Commercially-available fulvestrant, 50 mg/mL solution.

10.1.2.2. Anastrozole

Commercially-available anastrozole, 1 mg tablets.

10.1.2.3. Letrozole

Commercially-available letrozole, 2.5 mg tablets.

10.1.2.4. Exemestane

Commercially-available exemestane, 25 mg tablets.

10.1.3. Elacestrant Packaging and Labeling

Tablets (30 counts) are filled into 30 cc (100 mg tablet) or 100 cc (400 mg tablet) HDPE bottles equipped with a child resistant cap and a desiccant. The cap contains an inner foil liner which is induction sealed during the packaging process.

10.1.4. Storage, Handling, and Accountability

A drug inventory/dispensing record must be kept up to date and maintained by the site at all times to document the receipt, distribution, return and/or destruction of all study drug received.

All study drug will be dispensed by the pharmacist, the Investigator, or by a qualified individual under the Investigator's supervision. Training on study drug dispensing and return will be

provided to the site by the Clinical Research Associate (CRA) at the Site Initiation Visit, then as needed during the study.

Storage conditions and instructions on dispensation and management of temperature excursions and Product Quality Complaints are provided in the Pharmacy Manual.

Investigators and site staff are reminded to monitor temperatures on an ongoing basis (see Pharmacy Manual) and ensure that thermometers are working correctly as required for proper storage of study drugs. These include thermometers for both room storage and refrigerator storage. Any temperature excursion and Product Quality Complaint must be reported to RADIUS. The study drugs must be stored as outlined in the Pharmacy Manual. Deviations from the storage requirements and product quality, including any actions taken, must be documented and reported to RADIUS. Once a deviation is identified, the study drug must be quarantined and not used, unless and until RADIUS provides documentation of permission to use it.

10.1.4.1. Elacestrant Storage

Elacestrant should be stored in a limited access secure location according to the storage conditions provided on the label and instructions provided in the Pharmacy Manual.

Instructions regarding the storage and handling of elacestrant for off-site treatment will be provided in the Pharmacy Manual.

10.1.4.2. Standard of Care Storage

SOC study drugs should be stored in a limited access secure location according to the storage conditions and instructions provided in the Pharmacy Manual.

Instructions for storage and handling of SOC therapies for off-site treatment (if applicable) are provided in the Pharmacy Manual.

10.1.5. Administration

On days of study visits, subjects should be told to not take their medication prior to coming to the study site. If possible, they should come to the clinic in a fasting state. If the subject is fasting, a light meal (eg, juice, toast and jam, yogurt) will be eaten after laboratory samples have been drawn and approximately 30 minutes prior to study drug administration.

10.1.5.1. Elacestrant

Elacestrant will be administered at the study visit as follows:

- If fasting, subjects will be given a light meal (eg, juice, toast and jam or yogurt) approximately 30 minutes prior to taking their study medication
- Subjects should take their study medication with a glass of water (at least 250 mL or 8 oz.) and should remain in an upright position for at least 2 hours after taking their study medication. With the exception of water, subjects should fast for 1 hour after taking their study medication
- Subjects should be instructed to swallow the tablet(s) whole (unchewed), 1 tablet at a time

Elacestrant will be administered on an outpatient basis as follows:

- Subjects should be instructed to take their study medication at approximately the same time each day, preferably in the morning
- Subjects are recommended to have a light meal (eg, juice, toast and jam or yogurt) at approximately 30 minutes prior to taking their study medication
- Subjects should take their study medication with a glass of water (at least 250 mL or 8 oz.) and should remain in an upright position for at least 2 hours after taking their dose(s). With the exception of water, subjects should fast for 1 hour after taking their dose(s)
- Subjects should be instructed to swallow the tablet(s) whole (unchewed), and 1 tablet at a time
- Subjects will receive a daily dosing diary and will be instructed to record at a minimum:
    - The date and time they took their dose
    - If a dose was missed or delayed, the subject must record the event and the duration of delay

Note: In the event that dose reductions are warranted, the appropriate number of 100 mg tablets should be provided to the subject. No subject will take more than one 400 mg dose per day and no subject will take less than one 200 mg dose per day.

If vomiting occurs within 1 to 2 hours following a dose, the subject does not need to take a replacement dose but should attempt to take their next scheduled dose.

If the subject forgets to take a dose at the scheduled time, the subject should take the scheduled dose if less than 6 hours have passed. If more than 6 hours have passed after the scheduled time, then that missed dose should be omitted, and the subject should continue treatment with the next scheduled dose.

Dose interruptions of elacestrant of ≤ 14 consecutive days are permitted at any point during treatment. Dose interruptions of > 14 consecutive days requires discussion with RADIUS prior to continuation on study.

10.1.5.2. Standard of Care

10.1.5.2.1. Fulvestrant

Fulvestrant will be administered by qualified study personnel at the site. Fulvestrant administration will be documented on the corresponding study drug administration e-CRF. Fulvestrant will be administered at the study visits as follows:

- Fulvestrant drug preparation and administration will be performed at the site by a physician, registered nurse, or other qualified health care provider
- The 500 mg dose should be administered IM into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock on C1D1, C1D15, and

Day 1 of every cycle thereafter. Refer to the PI or SmPC for instructions and steps necessary for drug preparation and administration of fulvestrant

A single fulvestrant injection can be skipped in case of a fulvestrant-related toxicity or dosing can be delayed. Treatment delay for fulvestrant-related toxicities will be performed as per the Investigator's best medical judgment, but by no more than 28 days (± 2 days). If delay of longer than 28 days (± 2 days) is required, then the dose should be skipped. Fulvestrant should not be administered if the platelet count is < 50 x 10^9/L.

10.1.5.2.2. Aromatase Inhibitors

AIs will be administered at the study visits as follows:

- Subjects will be given a light meal prior to taking their study medication
- Subjects should take their study medication with a glass of water (at least 250 mL or 8 oz.)
- Subjects should be instructed to swallow the tablet(s) whole (unchewed)

AIs will be administered on an outpatient basis as follows:

- Anastrozole will be administered on an outpatient basis as one 1 mg tablet taken orally once daily
- Letrozole will be administered on an outpatient basis as one 2.5 mg tablet taken orally once daily
- Exemestane will be administered on an outpatient basis as one 25 mg tablet taken orally QD after a meal

Subjects taking an AI will receive a daily dosing diary and be instructed to record at a minimum the date and time they took their dose

Subjects should be instructed that if they miss a dose, they should take it as soon as they remember, however, if it is almost time for their next dose they should skip the missed dose and go back to their regular dosing schedule. They should not "double up" to make up for a missed dose.

If a dose was missed or delayed, the subject must record the event and the duration of delay.

Dose interruptions of any study drug of up to ≤ 14 consecutive days are permitted at any point during treatment. Dose interruption of > 14 consecutive days requires discussion with RADIUS prior to continuation on study.

10.1.5.3. Unused Study Drug

Patients will be required to return all bottles/blister packs of study drug as well as the completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle (drug accountability will also be performed on C1D15; drug may be dispensed at this visit if needed). The number of remaining tablets will be documented and recorded.

11. DATA ANALYSIS AND STATISTICAL METHODS

A Statistical Analysis Plan (SAP) will be developed and finalized before database lock. This plan will specify all statistical methods to be used in analysis of the data.

11.1. Statistical Hypotheses and Type I Error Control

11.1.1. Statistical Hypotheses

The null hypothesis for the primary endpoint in ESR1-mut subjects is that elacestrant does not differ from the SOC treatment group in IRC-assessed PFS for ESR1-mut subjects; the alternative hypothesis is that elacestrant differs from the SOC treatment group in IRC-assessed PFS for ESR1-mut subjects.

The null hypothesis for the primary endpoint in all subjects (ESR1-mut and ESR1-mut-nd) is that elacestrant does not differ from the SOC treatment group in IRC-assessed PFS for all subjects (ESR1-mut and ESR1-mut-nd); the alternative hypothesis is that elacestrant differs from the SOC treatment group in IRC-assessed PFS for all subjects (ESR1-mut and ESR1-mut-nd).

11.1.2. Type I Error Control

The 2 primary endpoints will be evaluated using the Hochberg procedure to maintain the overall alpha level at 2-sided 5.0%:

- 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

Unless otherwise specified, analyses of all other efficacy endpoints will be performed at the 2-sided alpha level of 5% without adjustment for p-values.

11.2. Analysis Populations

The following populations will be defined and used for analysis:

- The Intention-to-Treat (ITT) population consists of all randomized subjects. This is the primary population for PFS and OS analyses. Subjects will be analyzed according to randomized treatment assignments.
- The Safety population consists of all subjects who received at least 1 dose of study medication. All safety analyses will be performed using the Safety population. Subjects will be analyzed according to the treatments they actually received in Cycle 1.

- The Response Evaluable (RE) population includes all ITT subjects who had measurable disease (ie, at least 1 target lesion) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion. The RE population is used for the analyses of best overall response and ORR.
- The Clinical Benefit Evaluable (CBE) population includes all ITT subjects who had measurable and/or evaluable disease (ie, target and/or non-target lesions) at baseline and at least 1 post-baseline RECIST assessment on any (target or non-target) lesions and/or had a new lesion. The CBE population is used for the analyses of CBR.
- The PK population consists of all subjects who received at least 1 dose of elacestrant and have PK concentration data for at least 1 scheduled time point. PK analyses will be performed using the PK population.
- The Biomarker population consists of all subjects in the Safety population for whom adequate quality and volume of biomarker samples are available for analysis. The exploratory biomarker analysis will be performed using the Biomarker population.

11.3. Description of Statistical Methods

11.3.1. General Approach

For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum. For categorical variables, descriptive statistics will include the frequency counts and percentages.

Unless otherwise stated, baseline is defined as the last value obtained before the start of study drug.

11.3.2. Procedures for Handling Missing, Unused, and Spurious Data

All available data will be included in the analysis. For time-to-event analysis such as that of PFS, subjects who did not experience the event will be censored in the analysis. For other analyses where appropriate, imputations of values for missing data will be performed as specified in the SAP.

All data recorded on the CRF will be included in the data listings that accompany the clinical study report.

11.3.3. Demographics and Baseline Subject Characteristics

Subject characteristics will be summarized by treatment group using the ITT population for 2 sets of study subjects: ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd). Standard descriptive statistics for continuous and categorical variables will be provided for subject demographics, baseline disease characteristics, prior anti-cancer therapies, and other baseline characteristics. No hypothesis testing will be conducted.

11.3.4. Treatment Exposure

Treatment exposure will be summarized by treatment group as duration on treatment and extent of exposure to study drug. Duration on treatment will be calculated as the days from first dose until last dose and summarized quantitatively.

Measures of extent of exposure include the total number of doses per subject and compliance. Compliance will be calculated as the percentage of total number of doses relative to the expected number of doses and summarized quantitatively. The reasons for dose(s) withheld or delayed will also be summarized.

11.3.5. Analysis of the Primary Endpoints

The primary endpoints are

- PFS based on blinded IRC assessment in the ESR1-mut subjects
- PFS based on the blinded IRC assessment in all subjects (ESR1-mut and ESR1-mut-nd)

Final analyses of the primary endpoints will be performed when approximately 160 events for IRC-assessed PFS have occurred among the ESR1-mut subjects and approximately 340 events for IRC-assessed PFS have occurred among all subjects (ESR1-mut and ESR1-mut-nd). Based on an enrollment period of 15 months, this is estimated to occur at approximately 27 months after randomization of the first subject.

For subjects without objective disease progression or death, PFS will be 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. Detailed censoring rules are described in Table 14.

Table 14: Rules for Deriving Date of Progression or Censor for IRC-Assessed PFS

Situation	Date of Progression or Censor	Outcome
No baseline tumor assessments	Date of Randomization	Censored
No post-baseline assessments and no death	Date of Randomization	Censored
No documented progression and no death (with a post-baseline tumor assessment)	Date of last adequate tumor assessment	Censored
Subject lost to follow-up (or withdrew consent) before documented progression or death	Date of last adequate tumor assessment	Censored
Documented progression	Date of documented progression	Progressed
Death without documented progression	Date of death	Progressed
Documented progression or death after missing one post-baseline tumor assessment	Date of documented progression or death	Progressed
Documented progression or death after missing ≥2 consecutive post-baseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored

Note: If more than one situation applies, date of PFS and associated outcome will be determined by the earliest date and associated outcome above.

The analyses will be 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 will be 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 log-rank test will be performed as a sensitivity analysis. The Cox regression model, including treatment and the stratification factors as above, will be used to estimate the hazard ratio and 95% CI.

11.3.6. Analyses of Secondary Endpoints

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) will be 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 will be analyzed at the following 2 time points:

- At the time of the final PFS analysis (when approximately 160 and 340 PFS events are observed among the ESR1-mut and all subjects [ESR1-mut and ESR1-mut-nd], respectively)
- At the time of the final OS analysis (when 50% of the subjects have died)

At each time point, OS for the treatment groups will be 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) will be used to estimate the hazard ratio and 95% CI. In addition, the difference between treatment groups will be analyzed using the stratified log-rank test. A 2-sided alpha level of 0.01% will be 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.

Other Secondary Endpoints

The following secondary efficacy endpoints will be analyzed for ESR1-mut-nd subjects:

- IRC-assessed PFS
- OS

The following endpoints will be analyzed for ESR1-mut, ESR1-mut-nd, and all subjects (ESR1-mut and ESR1-mut-nd):

- Local Investigator-assessed PFS
- IRC-assessed ORR and DoR
- IRC-assessed CBR
- Local Investigator-assessed ORR and DoR
- Local Investigator-assessed CBR

Analyses of IRC-assessed PFS in ESR1-mut-nd subjects will be performed using the ITT population for the ESR1-mut-nd subjects in the same manner as the analyses of the primary endpoints.

Analyses of OS in ESR1-mut-nd subjects will be performed using the ITT population for the ESR1-mut-nd subjects in the same manner as the analyses of OS in ESR1-mut subjects and in all subjects (ESR1-mut and ESR1-mut-nd).

Local Investigator-assessed PFS will be analyzed in the same manner as IRC-assessed PFS.

ORR will be summarized for the RE population.

ORR and CBR will be summarized as a binomial response rate and compared between treatment groups using stratified Fisher's exact test.

DoR will be summarized for subjects in the RE population who achieved either a confirmed CR or PR post-baseline using the KM method. Estimated median values of DoR along with 95% CI will be provided.

Results of the efficacy analyses for the 3 sets of study subjects, ESR1-mut subjects, ESR1-mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd), will be presented using Forest plots.

Subgroup analysis of PFS, OS, ORR, and CBR based on prior treatment with fulvestrant and presence of visceral metastases will be performed in the same manner as the analyses in the overall populations.

11.3.7. Patient Reported Outcomes

Analyses of the PROs will be performed using the ITT population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd).

For each set of study subjects, the PRO endpoint values and changes from baseline by visit will be summarized by treatment group. A 95% CI for changes from baseline by visit will also be provided.

11.3.8. Pharmacokinetic Analysis

Elacestrant plasma concentrations will be summarized descriptively (with n, mean, standard deviation, coefficient of variation [CV], median, minimum, maximum, geometric mean and its associated CV) by visit and nominal time point (pre-dose or 4 hours post-dose; see Table 18 and Table 19 in Appendix 2) for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd). Plot of geometric mean of elacestrant plasma concentrations by nominal time point will also be presented.

11.3.9. Safety Analyses

Safety analyses will be performed using the Safety population for ESR1-mut subjects and all subjects (ESR1-mut and ESR1-mut-nd).

For each set of study subjects, safety analysis will be performed by treatment group and include summaries of the following:

- AEs, including NCI CTCAE v5.0 severity grade and relationship to study drug
- Deaths, SAEs, and AEs leading to study drug withdrawal
- Dose interruptions and reductions due to AEs
- Laboratory values over time and shifts in laboratory measurements by NCI CTCAE v5.0 grade
- ECG values over time and change from baseline
- ECOG performance status over time and shifts in ECOG performance status
- Vital sign values over time and incidence of potentially clinically significant values

11.3.10. Exploratory Analyses

The following exploratory analyses will be assessed in ESR1-mut subjects, ESR1-mut-nd subjects, and all subjects (ESR1-mut and ESR1-mut-nd):

- TTC, defined as the number of days from randomization to initiation of chemotherapy will be summarized by treatment group descriptively for the subjects who require initiation of chemotherapy due to disease progression
- Alterations in ctDNA relevant to ER+ breast cancer and the CDK4/6 pathway and the relationship between these findings and clinical response
- Alterations in tumor-specific genes, proteins, and RNAs related to oncogenic pathways and proliferation and cell cycle markers in tumor tissue and the relationship between these findings and clinical response

11.4. Interim Analysis

At about 70% enrollment, an interim futility analysis will be provided to the IDMC. At this interim data look, the IDMC will evaluate the primary endpoint in conjunction with other efficacy endpoints, including OS, ORR, DoR and CBR. These additional efficacy data will assist the IDMC in checking consistency of the totality of the data. The IDMC will make 1 of the following recommendations according to the conditional power of the primary efficacy endpoint for all subjects (ESR1-mut and ESR1-mut-nd), which will be derived based on the observed data at the interim futility analysis:

- Continue trial unmodified if the conditional power is $\geq 20\%$ at the alpha level of 2.5%
- Terminate enrollment of ESR1-mut-nd subjects due to futility if the conditional power is $< 20\%$ at the alpha level of 2.5%

If the conditional power is $< 20\%$ for all subjects at the alpha level of 2.5%, further enrollment of ESR1-mut subjects will be evaluated by the IDMC. Study drug administration for ongoing subjects will remain unchanged unless otherwise determined by the Investigator.

Further details of the statistical methods will be specified in the interim SAP as part of the IDMC Charter.

11.5. Sample Size Assumptions

Among the ESR1-mut subjects, the study requires approximately 160 PFS events to have a power of 80% power to detect a hazard ratio of 0.610 at the 2-sided alpha level of 2.5%. Assuming a median PFS of 5.3 months for the SOC treatment group, this treatment effect represents a median PFS of 8.7 months for the elacestrant treatment group, an increase of approximately 3.4 months among the ESR1-mut subjects.

Among all subjects (ESR1-mut and ESR1-mut-nd), a total of approximately 340 PFS events will have 92% power to detect a hazard ratio of 0.667 at the 2-sided alpha level of 2.5%.

The 2-sided alpha level of 2.5% for sample size calculation was selected to ensure that at least 1 of the 2 primary efficacy endpoints will pass the Hochberg procedure to control the overall alpha level at 5.0% (see Section 11.1.2).

The study will need to randomize approximately 220 ESR1-mut subjects (110/treatment group) and a total of approximately 466 subjects of both types (ESR1-mut and ESR1-mut-nd; 233/treatment group) in a 1:1 ratio to the 2 treatment groups. To prevent exceeding the target recruitment by more than 10% (ie, 512 subjects total), if a total of 292 ESR1-mut-nd subjects is reached before 220 ESR1-mut subjects are enrolled, further enrollment will be restricted to ESR1-mut subjects only until the target of 220 is achieved.

Final analysis of the primary endpoints will be performed at approximately 160 PFS events among the ESR1-mut subjects and 340 PFS events among all subjects (ESR1-mut and ESR1-mut-nd), estimated to occur at 30-33 months after the first subject is randomized.

11.6. Study Committees

11.6.1. Independent Data Monitoring Committee

An IDMC external to both RADIUS and the CRO will be responsible for ongoing monitoring of the safety and efficacy according to the IDMC Charter. The IDMC will meet on a regular basis and will make recommendations as to whether the trial should continue, be amended, or be discontinued based on ongoing reviews of safety and efficacy data. Details of the IDMC responsibilities are described in the IDMC Charter.

11.6.2. Study Steering Committee

A Study Steering Committee (SSC) composed of international physicians with expertise in management of ER+ mBC has been convened by RADIUS. The remit of the SSC is to provide guidance to RADIUS on protocol development and implementation, Investigator selection, and recruitment strategies. The SSC will also inform RADIUS on advances in the field that could impact the trial. The SSC will not be provided with any efficacy or safety data during the trial.

11.6.3. Imaging Review Committee

A blinded, independent IRC will perform a review of radiographic images and clinical information collected on study to determine the protocol-defined endpoints of disease response and progression. Further information on the independent review process will be provided in the Bioclinica Imaging Charter.

12. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

12.1. Study Monitoring

RADIUS is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded in the clinical database. RADIUS or its designee will assign CRAs to the study. The CRA is responsible for reviewing the study at regular intervals, verifying adherence to the protocol, completeness, consistency and accuracy of the data, study source documents, and drug accountability records. Data will be verified against the original medical records and laboratory results as part of source document verification to ensure its validity. The Investigator is responsible for ensuring that any issues detected in the course of a monitoring visit are resolved.

12.2. Audits and Inspections

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, quality assurance audits may be conducted. Regulatory agencies may also conduct regulatory inspections of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditors/inspectors direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditors/inspectors to respond to requests and questions, and discuss findings and any relevant issues. In the case of an audit or inspection, the Investigator or a delegate will alert RADIUS as soon as he/she becomes aware of an audit or inspection.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by RADIUS, its designees, and/or regulatory agencies. In signing this protocol, the Investigator understands and agrees to give access to study-related documentation and files to the Study Monitor, RADIUS, other authorized representatives of RADIUS, representatives of the IRB/IEC, and regulatory agencies.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, RADIUS may conduct a quality assurance audit. Please see Section 12.2 for more details regarding the audit process.

14. ETHICS

14.1. Ethics Review

It is the responsibility of the Investigator to submit this protocol, the final approved ICF that has been previously approved by RADIUS or its designee, relevant supporting information, and all types of subject recruitment or advertisement information (approved by RADIUS or its designee) to the IRB/IEC for review and all material must be approved before the study is initiated. Prior to

implementing changes in the study, RADIUS will provide a protocol amendment and the IRB/IEC must also approve any protocol amendments.

On the IRB/IEC approval letter, the study (title, protocol number and version), the documents reviewed (protocol, informed consent material, amendments), and the date of review should be clearly stated. Drug supplies will not be released, and subject recruitment will not begin until this written approval has been received by RADIUS or its designee.

The Investigator is responsible for keeping the IRB/IEC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, at least once a year. The Investigator must also keep the IRB/IEC informed of any serious and significant AEs.

All materials approved by the IRB/IEC for this study, including the subject consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference of Harmonization/GCP, applicable regulatory requirements and RADIUS' policy on Bioethics.

14.3. Written Informed Consent

The Investigator will submit the site-specific ICF to RADIUS for approval prior to submitting to the IRB/IEC. The Investigator is responsible for obtaining written, informed consent from each subject interested in participating in this study prior to conducting any study-related procedures.

Written informed consent should be obtained after an adequate, thorough, and clear explanation of the study objectives, procedures, and the potential hazards of the study. The Investigator must use the most current IRB/IEC approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the subject and the person obtaining consent. The site must retain the original signed ICF and provide a copy to the subject.

14.4. Subject Confidentiality and Privacy

Subjects will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the Health Insurance Portability and Accountability Act form or local equivalent and informed consent documents. The original signed document will become part of the subject's medical records and each subject will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and RADIUS. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of RADIUS.

All research activities will be conducted in as private a setting as possible.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/IEC, Institutional policies, or RADIUS.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at RADIUS. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by RADIUS research staff will be secure and password protected. At the end of the study, all study databases will be de-identified and archived at RADIUS.

15. DATA HANDLING AND RECORD KEEPING

15.1. Inspection of Records

RADIUS, and authorized representatives of RADIUS, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, study source documents, and other records related to study conduct.

15.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or, if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for RADIUS or a regulatory authority to review any documentation related to the study, the Investigator must permit access to such records. Records will be retained by the Sponsor per the local regulations.

16. PUBLICATION POLICY

The Investigator must submit to RADIUS any proposed publication or presentation along with information about the scientific journal or presentation forum at least 30 days prior to submission of the publication or presentation (2 weeks for abstracts). The Investigator will comply with requests from RADIUS to delete references to its confidential information in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days to obtain patent protection if deemed necessary.

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18. APPENDICES

APPENDIX 1. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) V1.1

Response and progression will be evaluated in this trial using the new international criteria proposed by the RECIST committee (Eisenhauer, 2009). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria for determination of tumor response. Additionally, per the RECIST working group, CT scan (with contrast) is currently the best available and reproducible method to measure lesions selected for response assessment.

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness ≤ 5 mm)

10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable).

20 mm by chest x-ray.

- Malignant lymph node: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. Lymph nodes < 10 mm are non-pathological. Lymph nodes measuring ≥10 mm to < 15 mm are considered non-target.

Non-measurable disease: Non-measurable disease is defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm in short axis) as well as truly nonmeasurable lesions. Lesions considered to be truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of the skin or lung, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations

Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT scan or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurable disease. Blastic bone lesions are considered nonmeasurable disease. Note: Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these can be used to confirm the presence or disappearance of bone lesions.

Cystic lesions: Lesions that meet the criteria to be radiographically defined as simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) because they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurable disease. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Measurement of Lesions: All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Target lesions: When more than one measurable lesion is present at baseline, all measurable lesions, up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ), representative of all involved organs should be identified as target lesions and be recorded and measured at baseline. This means that, in instances where subjects have only one or 2 organ sites involved, a maximum of 2 or 4 lesions, respectively, will be recorded. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to reproducible repeated measurements. In situations in which the largest lesion does not lend itself to reproducible measurement, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes as target lesions: Pathological nodes, which are defined as measurable and may be identified as target lesions, must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize the objective tumor response in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required but these lesions should be noted at baseline and should be followed as "present", "absent", or in rare cases, "unequivocal progression". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Best response

All subjects will have their **best response** on trial classified as outlined below and summarized in Table 15, Table 16, and Table 17.

Evaluation of response in target lesions

Complete response (CR): disappearance of all target lesions (both target and non-target). Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions taking as the reference the baseline sum of diameters.

Stable disease (SD): steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference, the smallest sum of diameters while in the trial.

Progressive disease (PD): at least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study (this includes the baseline sum if that is the smallest on trial). In addition to a relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of new lesions will also constitute PD.

Special notes on assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero, even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 1 0mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions

Target lesions that become too small to measure

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

Evaluation of response in non-target lesions

Complete response: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR / Non-PR: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)

Disease progression in subjects with only non-measurable disease

For subjects with only non-measurable disease, disease progression is defined as development of new lesions or "unequivocal progression" of existing lesions. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden, based on the change in non-measurable disease, is comparable in magnitude to the increase that would be required to declare PD for measurable disease, i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point.

New lesions

The appearance of new malignant lesions denotes disease progression; however, the finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (eg, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal (eg, because of small size), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Table 15: Target and Non-Target Lesion Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	4-6 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	4-6 weeks Confirmation
CR	Not evaluated	No	PR	4-6 weeks Confirmation
PR	Non-PD or not all evaluated	No	PR	4-6 weeks Confirmation
SD	Non-PD or not all evaluated	No	SD	Documented at least once >6 weeks from baseline
PD	Any	Yes or No	PD	—
Any	PD	Yes or No	PD	—
Any	Any	Yes	PD	—
Not all evaluated	Non-PD	No	Unevaluable	—

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease
Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 16: Time Point Response: Subjects with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response	Best Response Also Requires
CR	No	CR	4-6 weeks Confirmation
Non-CR/Non-PD	No	Non-CR/Non-PD[a]	—
Unequivocal PD	Yes and No	PD	—
Any	Yes	PD	—

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease
a: 'Non-CR/non-PD' is preferred over 'SD' for non-target disease because SD is increasingly used as an endpoint for assessment of efficacy in some trials, therefore, to assign this category when no lesions can be measured is not advised.

Table 17: Best Overall Response when Confirmation of CR or PR is Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response; NE = non-evaluable; PD = progressive disease; PR = partial response; SD =stable disease.
a: If a CR is truly met at the first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (because the disease must have re-appeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely present and, in fact, the subject had PR, or CR at the first time point. Under this circumstances, the original CR should be changed to PR and the best response is PR.

Response duration

Response duration will be measured from the time that measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent disease or PD is objectively documented.

Stable disease duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as a reference the smallest measurements recorded since the start of treatment.

Methods of measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions - Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken because it is more objective and may also be reviewed at the end of the study.

Chest x-ray - Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT/MRI - CT scan is the best currently available and reproducible method to measure target lesions selected for response assessment. MRI is acceptable in certain situations (eg, for body scans). CT scans should be performed with cuts of 5 mm or less in slice thickness, contiguously. This applies to the chest, abdomen and pelvis. Head and neck and extremities usually require specific protocols.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy/laparoscopy - The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers - Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated.

Cytology/histology - These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Bone lesions - Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these can be used to confirm the presence or disappearance of bone lesions.

APPENDIX 2. SCHEDULE OF EVENTS

Table 18: Schedule of Events

Procedures/Assessments	**Screening[a]**	**Active Treatment Period**			**End of Treatment (EOT)[b]**	**Post-Treatment (PTx)**	
		Cycle 1[c]		**Subsequent Cycles[c]**			
Study Day (visit window in days)	**Day -35 to -1**	**Day 1[d]**	**Day 15[d] (± 2 d)**	**Day 1[d] (±2 d)**	**(+14 d; within 14 d of last dose of study drug)**	**PTx Safety Follow-up 30 days after last dose of study drug[e] (± 3 d)**	**PTx Follow-up every 8 week[f] (± 7 d)**
Demography/Informed consent[g]	X						
Inclusion/Exclusion criteria	X						
Medical/Surgical history/Current medical conditions	X						
Breast cancer diagnosis, ER, HER2 status[h]	X						
Prior anti-cancer therapy[i]	X						
Randomization[j]		X					
Patient Reported Outcomes[k] EQ-5D-5L EORTC QLQ-C30 PRO-CTCAE		X	X	X	X	X[e]	
Height	X						

Procedures/Assessments	**Screening[a]**	**Active Treatment Period**			**End of Treatment (EOT)[b]**	**Post-Treatment (PTx)**	
		Cycle 1[c]		**Subsequent Cycles[c]**			
Study Day (visit window in days)	**Day -35 to -1**	**Day 1[d]**	**Day 15[d] (± 2 d)**	**Day 1[d] (±2 d)**	**(+14 d; within 14 d of last dose of study drug)**	**PTx Safety Follow-up 30 days after last dose of study drug[e] (± 3 d)**	**PTx Follow-up every 8 week[f] (± 7 d)**
Weight	X	X		X	X		
Physical examination[l]	X	X		X	X		
Vital signs[m]	X	X	X	X	X		
ECOG performance status	X	X		X	X		
12-lead ECG[n]	X	X[n]	X[n]	X[n]	X[n]		
Estradiol and FSH testing (women only)[o]	X						
Urinalysis[p]	X						
Hematology[q]	X[r]	X	X	X	X		
Chemistry[s]	X[r]	X	X	X	X		
Special Chemistry[t]	X				X		
Coagulation[u]	X[r]	X	X	X	X		
CT of chest, CT/MRI of abdomen, pelvis, and clinically indicated sites of disease; color photographs with measurement markers of superficial disease[v]	X[w]	◄----------► Performed every 8 weeks (± 7 days) from the date of randomization)			X		X[f]

Procedures/Assessments	**Screening[a]**	**Active Treatment Period**			**End of Treatment (EOT)[b]**	**Post-Treatment (PTx)**	
		Cycle 1[c]		**Subsequent Cycles[c]**			
Study Day (visit window in days)	**Day -35 to -1**	**Day 1[d]**	**Day 15[d] (± 2 d)**	**Day 1[d] (±2 d)**	**(+14 d; within 14 d of last dose of study drug)**	**PTx Safety Follow-up 30 days after last dose of study drug[e] (± 3 d)**	**PTx Follow-up every 8 week[f] (± 7 d)**
Radionuclide bone scan or whole body MRI[x]	X[w]	◄----------► Performed every 24 weeks (± 7 days) from the date of randomization			X[v]		X[f]
Evaluation of abnormal bone scan or whole body MRI[y]	X[w]	X			X[v]		X[f]
Blood sample for PK[z]		X	X	Cycle 2 only			
Blood sample for ctDNA (Biomarker testing)[aa]	X			Cycle 2 and Cycle 3 only	X		
Tumor biopsy[bb]	X			X[cc]	X[cc]		
Elacestrant group[dd]		◄---------► Once Daily					
SOC treatment group -aromatase inhibitor[ee]		◄---------► Once Daily					
SOC treatment group – fulvestrant[ff]		C1D1, C1D15, and Day 1 of every subsequent cycle					
Drug compliance[gg]		◄----------►					
Adverse events[hh]	◄----------►						

Procedures/Assessments	**Screening[a]**	**Active Treatment Period**			**End of Treatment (EOT)[b]**	**Post-Treatment (PTx)**	
		Cycle 1[c]		**Subsequent Cycles[c]**			
Study Day (visit window in days)	**Day -35 to -1**	**Day 1[d]**	**Day 15[d] (± 2 d)**	**Day 1[d] (±2 d)**	**(+14 d; within 14 d of last dose of study drug)**	**PTx Safety Follow-up 30 days after last dose of study drug[e] (± 3 d)**	**PTx Follow-up every 8 week[f] (± 7 d)**
Prior/Concomitant medications/treatments[ii]	◄----------					----------►	
Survival follow-up for subjects who discontinue treatment[f]						X	

a. All Screening assessments must be completed within 35 days prior to randomization (all imaging must be completed within 28 days prior to randomization unless otherwise specified). All surgical procedures related to breast cancer diagnosis must be recorded.

b. If EOT falls on Day 1 of a cycle and the subject is withdrawing, the EOT assessments are to be completed instead of the Cycle Day 1 assessments. Assessments completed within the previous 14 days do not have to be repeated at the EOT visit.

c. A Cycle is 28 days.

d. All assessments are to be performed pre-dose on scheduled visit days unless otherwise indicated. Procedures may be performed ±2 days relative to the visit.

e. Onsite visit preferred; if this is not feasible, telephone contact is acceptable. If follow-up assessments are conducted by telephone, the PROs are to be omitted.

f. For subjects who discontinue study treatment due to objective disease progression, survival data and start date and regimen name of the first new anti-cancer therapy should be collected every 8 weeks (± 7 days) calculated from the last dose of study drug for the duration of the study. For subjects who discontinue treatment for reasons other than disease progression, and who do not begin new anti-cancer therapy, tumor assessments will continue every 8 weeks (± 7 days, from the date of randomization), and for subjects with bone lesions at baseline radionuclide bone scan or whole body MRI will be performed every 24 weeks (± 7 days), as indicated, until disease progression is documented, or new anti-cancer therapy is initiated; at that time, they will continue to be monitored every 8 weeks for survival and first new anti-cancer therapy information for the duration of the study.

g. Informed consent must be obtained prior to any protocol-required assessments (except for certain imaging assessments if they meet the criteria defined in Table 20).

h. ER and HER2 status must be confirmed per local laboratory testing.

i. Prior anti-cancer therapy, including drug names, treatment start/end date, dose, setting (neoadjuvant, adjuvant, or recurrent/metastatic line of therapy), best response, date of disease progression, and reason for treatment discontinuation, are to be recorded.

j. Randomization is to occur after eligibility is determined by the study site and and confirmed by the Medical Monitor. The planned first dose of C1D1 is to start within 1 day after randomization; randomization may occur on D-1 or on D1. Note: there is no Day 0 in this study. C1D1 is the date of first dose of study drug.

k. PRO questionnaires are to be completed by the subject using the electronic tablet provided while in clinic (cannot be taken home) at the beginning of the study visit and prior to any other assessments or significant interactions with site staff. PRO questionnaires will be performed on C1D1, C1D15, C2D1, and D1 of each subsequent cycle through C4, then D1 of every other cycle thereafter starting with C6 (ie, C2, C3, C4, C6, C8, C10, etc), at EOT, and at the Safety Follow-Up visit (unless this visit is performed via phone contact). Note: If a certified translation for any PRO questionnaire is not available for a subject, that specific PRO assessment can be omitted, but the reason must be documented.

l. Physical examination at Screening to include total body examination of general appearance, skin, neck (including thyroid), ears, eyes, nose, throat, lungs, heart, abdomen, back, lymph nodes and extremities and a clinical neurological examination. Post-Screening physical examinations may be targeted based on findings present at Screening or subject complaints. Significant findings at Screening should be recorded as medical history or AEs as appropriate and clinically significant findings at subsequent visits should be recorded as AEs.

m. Vital signs (temperature, respiratory rate, sitting blood pressure, and sitting pulse rate) are to be performed prior to phlebotomy at Screening and at every visit. On C1D1 and C1D15, all vital signs are to be assessed pre-dose and blood pressure is to be performed 4 hours (± 30 minutes) post-dose (all subjects) and prior to phlebotomy for PK assessment (subjects taking elacestrant). On Day 1 of every subsequent cycle, all vital signs are to be assessed pre-dose.

n. 12-lead ECG is to be performed in triplicate, 2 minutes apart, at all time points after the subject has been supine for at least 5 minutes using the Sponsor-provided ECG equipment. ECGs will be performed pre-dose and 4 hours (± 30 minutes) post-dose on C1D1 and pre-dose and 4 hours (± 30 minutes) post-dose on C1D15. ECG will be performed pre-dose on C2D1, and each subsequent cycle through cycle 4, then D1 of every other cycle thereafter starting with C6 (ie, C6, C8, C10, etc) and at EOT. See Table 19.

o. Not required in women who have undergone bilateral surgical oophorectomy.

p. Urinalysis includes protein, glucose, blood, ketones, nitrites, and leukocyte esterase. Microscopic examination is required only when urinalysis is positive for nitrites, leukocyte esterase, protein, or blood.

q. Hematology includes hemoglobin, hematocrit, white blood cell count with differential (including absolute neutrophil count, lymphocyte, monocyte, eosinophil, and basophil counts), and platelet count.

r. If performed > 7 days prior to C1D1, must be repeated and eligibility criteria must still be met.

s. Chemistry includes BUN or urea, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, magnesium, albumin, total protein, total bilirubin (direct and indirect if total is > ULN), alkaline phosphatase, ALT, AST, glucose and lipid panel (total cholesterol, LDL, HDL, and triglycerides). If possible, the glucose and lipid panel should be performed with the subject in a fasting state. If performed > 7 days prior to C1D1, must be repeated and eligibility criteria must still be met.

t. Hemoglobin A1c is to be measured at Screening and EOT.

u. Coagulation tests include PT or INR (per the sites's standards), aPTT (PTT is allowed if aPTT is not available), and fibrinogen. INR is required at Screening. If performed > 7 days prior to C1D1, must be repeated and eligibility criteria must still be met.

v. Diagnostic CT for tumor assessment may be used even if acquired during PET/CT hybrid imaging providing the CT images are of sufficient quality. Screening tumor assessments must be performed during the Screening period (Day -28 through Day -1) as noted in Table 20. For subjects who achieve a CR or PR, a confirmation scan must be repeated at least 4 weeks after the first documented response. Subjects with history of stable brain metastases should have brain CT or MRI imaging in parallel with systemic imaging for evaluation of non-target lesions in the brain; brain CT or MRI scans are not otherwise required as part of standard imaging. Color photographs must be taken of any skin lesions that will be followed as either target or non-target lesions. Tumor evaluation will be performed at EOT unless an evaluation has been performed within the preceding 28 days or disease progression has already been documented per RECIST v1.1. See Table 20. For subjects who discontinue treatment for reasons other than disease progression (clinical PD or PD by

RECIST criteria), and who do not begin new anti-cancer therapy, tumor assessments will continue every 8 weeks from the date of randomization until documentation of progression or start of new anti-cancer treatment; for these subjects, additional assessments do not need to be performed at the EOT visit.

w. To be completed within 28 days prior to randomization.

x. If bone lesions are identified at baseline (ie, during Screening), bone scans or whole body MRI are to be repeated during the active treatment phase (using the same modality used during Screening), every 24 weeks (±7 days), and as clinically indicated, from the date of randomization, and at time of confirmation of CR. If no bone lesions are identified at baseline, bone scans or whole body MRI are to be repeated during active treatment phase only when clinically indicated and are required at time of confirmation of CR. At EOT, bone scans or whole body MRI are required for subjects with bone lesions identified at Screening, unless disease progression has been confirmed elsewhere or a scan has been performed within the last 12 weeks. See Table 20.

y. Suspicious abnormalities (ie, hotspots) identified on bone scan or whole body MRI at baseline and on subsequent bone scans or whole body MRI MUST be confirmed. Diagnostic CT of chest and CT (with bone window settings) or MRI of abdomen and pelvis (or PET CT if CT images are of sufficient quality) are sufficient for evaluation of bone lesions involving the axial skeleton. Additional imaging of appendicular skeletal lesions (eg, skull, cervical spine, extremities) by bone window settings on CT scan or MRI are required if these sites are the only bone lesions to be followed. If a lesion is not confirmed to be metastatic by CT with bone windows or MRI, it should not be followed as a target or non-target lesion and it does not require re-assessment. The same modality must be used throughout the study for confirmation for a given lesion/subject. Areas that have received palliative radiotherapy should be followed as non-target lesions.

z. Blood samples for PK are to be collected at the following time points for subjects randomized to the elacestrant group only: C1D1 and C1D15: 0 h (pre-dose) and 4 h (± 30 min) post-dose; C2D1: 0 h (pre-dose). Investigators may obtain additional blood samples for PK analysis at the time(s) that significant AE or SAEs occur that are considered potentially related to the study drug. See Table 19.

aa. Blood sample for ctDNA to be collected at Screening, pre-dose on C2D1, pre-dose on C3D1, and at EOT. Four tubes of blood will be drawn at Screening, and 2 tubes will be drawn for all other time points (see Guardant's Whole Blood Sample Collection, Handling, Shipping and Result Instructions for the RAD1901-308 (EMERALD) study for Screening ctDNA samples; see Medpace Laboratory Manual for management of on-treatment ctDNA samples)

bb. All subjects with accessible lesions are requested to provide tumor biopsies; however, these biopsies are optional and are not required for eligibility. For subjects agreeing to provide biopsies, biopsies will be taken at 3 time points during the study: pre-treatment, on-treatment, and post-treatment. Pre-treatment biopsies should be obtained after progression on the most recent systemic anticancer therapy and should be performed on a metastatic lesion or site of recurrent disease, if accessible. Biopsies obtained for other reasons within 3 months of first dose of study treatment that meet these criteria may be submitted in lieu of a fresh biopsy.

cc. On-treatment and post-treatment biopsies are only required if the pre-treatment biopsy was successful (ie, tissue obtained; confirmed to contain adequate tumor cells by central laboratory). On-treatment biopsy should be performed between C1D28 and C3D28, as close as feasible to C2D28. Post-treatment biopsy should be performed at the time of study drug discontinuation and prior to initiation of new anti-cancer therapy. Biopsies should be taken from the same lesion at each time point, when feasible.

dd. For subjects randomized to elacestrant, elacestrant should be taken at approximately the same time(s) each day on a continuous dosing schedule. However, on days of planned clinic visits, subjects should be informed to take their study drug at the study site. Subject is to be instructed to complete a daily dosing diary.

ee. For subjects randomized to SOC, with Investigator selection of AI, AI should be taken at approximately the same time(s) each day on a continuous dosing schedule. However, on days of planned clinic visits, subjects should be informed to take their study drug at the study site. Subject is to be instructed to complete a daily dosing diary.

ff. For subjects randomized to SOC, with Investigator selection of fulvestrant, fulvestrant dose (500 mg) is to be administered IM slowly (1-2 minutes per injection) divided as two 5-mL injections into gluteal area (one in each buttock) on C1D1, C1D15 and Day 1 of each subsequent cycle.

gg. Elacestrant or AI bottle(s) or blisters, including any unused capsules/tablets, are to be returned to clinic for drug accountability. Drug accountability is to be performed on Day 1 of every cycle. Dose, date and time of fulvestrant administration must be documented in both medical record and electronic Case Report Form.

hh. All AEs are to be recorded from time of signed informed consent until 30 days after last dose of study drug. At any time after 30 days from the last dose of study treatment, the Investigator may report any SAE that he/she believes is related to study treatment.

ii. All prior medications and concomitant medications (including oral, topical, intravaginal, rectal, and inhaled over-the-counter medications, herbal treatments, supplements, vitamins, or any substance use) and medical treatments taken from 35 days prior to signing informed consent until 30 days after the last dose of study drug are to be recorded.

AI = aromatase inhibitor; C1D1 = Cycle 1 Day 1; CR = complete response; CT = computed tomography; ctDNA = circulating tumor DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = End of Treatment; EQ-5D-5L = EuroQol 5 dimension 5 level; ER = estrogen receptor; FSH = follicle stimulating hormone; HER2 = human epidermal growth factor receptor 2; MRI = magnetic resonance image; PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcome; PRO-CTCAE = Patient Reported Outcome-Common Terminology Criteria for Adverse Events; PTx = Post-treatment; RECIST = Response Evaluation Criteria in Solid Tumors; ULN = upper limit of normal.

Table 19: Pharmacokinetics, Vital Signs, and ECG Schedule of Events Relative to Elacestrant and SOC Dosing

	Screening	Active Treatment Phase							Post-Treatment
		Cycle 1				Cycle 2	Cycle 3	Cycle 4 and every other cycle thereafter (ie, 4, 6, 8 etc.)	EOT
Protocol Activity	**Day -35 to Day -1**	**Day 1**		**Day 15**		**Day 1**	**Day 1**	**Day 1**	
		Pre-dose 0 Hrs	**Post-dose 4 Hrs (± 30 min)**	**Pre-dose 0 Hrs**	**Post-dose 4 Hrs (± 30 min)**	**Pre-dose 0 Hrs**	**Pre-dose 0 Hrs**	**Pre-dose 0 Hrs**	
Pulse Rate, Respiratory Rate, Temperature	X	X		X		X	X	X	X
Blood Pressure	X	X	X	X	X	X	X	X	X
ECG 12-lead	X	X	X	X	X	X	X	X	X
Pharmacokinetics		X	X	X	X	X			

Notes:
The following sequence should be followed: (1) vital sign assessment, (2) ECG recording, and (3) PK blood sampling.
Vital signs are to be collected at every cycle.
PK assessments only to be performed for subjects randomized to elacestrant; ECG and vital sign assessments to be performed for all subjects.
All ECGs will be performed using the Sponsor-provided ECG equipment and sent electronically to a central ECG laboratory. A 12-lead ECG will be performed in triplicate, 2 minutes apart, at all protocol defined time points after the subject has been supine for at least 5 minutes as per the ECG Manual. Additional ECGs may be performed as clinically indicated. ECGs for eligibility will be performed during the Screening period for all subjects, to determine the mean QTc interval for eligibility purposes. ECGs should be performed immediately before PK blood draws.
Study treatment should be administered immediately after the Day 1 and Day 15 pre-dose sample for PK has been collected (preferably within 30 minutes).
Additional PK blood samples may be collected in subjects experiencing unexpected or SAEs, or AEs that lead to discontinuation.

Table 20: Tumor Assessment Requirements Flowchart

Procedure	Screening[a] (Day -28 to Day -1)	Treatment Period[b]	End of Treatment (EOT)[c]	Post-Treatment Follow-up[c] (for subjects who have discontinued study drug for reasons other than PD and who have not yet started new anti-cancer therapy)
CT of chest and CT or MRI of abdomen and pelvis[d]	Required[e]	Required	Required	Required
CT[d] or MRI of any other site of disease, as clinically indicated	Required[e,f]	Required for sites in which disease identified at Screening and if new metastases clinically suspected	Required for sites in which disease identified at Screening and if new metastases clinically suspected	Required for sites in which disease identified at Screening and if new metastases clinically suspected
Radionuclide bone scan or whole body MRI	Required[g]	Required for subjects in which disease identified at Screening, if clinically indicated, and in all subjects with CR[h]	Required for subjects in which disease identified at Screening or if clinically indicated[h]	Required for subjects in which disease identified at Screening or if clinically indicated[h]
Evaluation of abnormal bone scan or whole body MRI[i]	Required	Required for sites in which disease identified by bone scan or whole body MRI[j]	Required for sites in which disease identified by bone scan or whole body MRI[j]	Required for sites in which disease identified by bone scan or whole body MRI[j]
Color photographs of all superficial lesions as applicable[k]	Required	Required for sites in which disease identified at Screening	Required for sites in which disease identified at Screening	Required for sites in which disease identified at Screening

Note: Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the Investigator. If progressive disease is confirmed per RECIST v1.1, subjects are expected to discontinue study therapy and begin the follow-up phase of the trial. For subjects who achieve a CR or PR, confirmatory scans, including bone scan or whole body MRI, as applicable, must be repeated at least 4 weeks after first documentation of CR or PR.

[a] Screening scans must occur within 28 days prior to randomization unless otherwise specified.
[b] Tumor assessment by CT and/or MRI (or PET CT if CT images are of sufficient quality), including bone lesions followed as non-target lesions, and assessment of superficial lesions by photography, must be done during the treatment period every 8 weeks (± 7 days), and in subjects with baseline bone lesions, bone scans or whole body MRI (as applicable) every 24 weeks (± 7 days), from randomization until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v1.1, initiation of new anti-cancer therapy, or discontinuation of subject from overall study participation (eg, death, subject's request, lost to follow up), whichever occurs first. The tumor assessment schedule should be fixed from the date of randomization, according to the Schedule of Events, regardless of treatment delays/interruptions. Imaging assessment delay to conform to treatment delay is not permitted. Imaging assessments are to be scheduled using the randomization date as the reference date for all time points and are NOT to be scheduled based on the date of the previous imaging time point. The same tumor assessment technique MUST be used throughout the study for a given lesion/subject.
[c] Subjects who have already demonstrated objective disease progression as per RECIST v1.1 do not need to have scans repeated at the end of treatment visit or during the post-treatment follow-up. For subjects who do not have documented objective disease progression at time of study treatment discontinuation, tumor assessment will continue to be performed every 8 weeks (± 7 days), and bone scans or whole body MRI (as applicable) every 24 weeks (± 7 days) until radiographically and/or clinically confirmed objective disease progression, initiation of first new anti-cancer therapy, or discontinuation of subject from overall study participation (eg, death, subject's request, lost to follow-up).
[d] CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the Investigator in conjunction with the local radiologist per RECIST v1.1. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such cases, CT will be performed without contrast. MRI of the chest should only be performed in extenuating circumstances. If MRI is used to follow bone lesion(s), it must be performed a few days before any treatment that may affect bone marrow cellularity (eg, G-CSF). Diagnostic CT for tumor assessment may be used even if acquired during PET/CT hybrid imaging providing the CT images are of sufficient quality.
[e] Radiographic assessments obtained per the subject's standard of care prior to randomization into the study do not need to be repeated and are acceptable to use as baseline evaluations if: (1) obtained within 28 days before randomization, (2) they were performed using the method requirements outlined in RECIST v1.1 (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given subject, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the subject's source notes.
[f] Baseline brain CT or MRI scans are only required if signs and symptoms suggest presence of metastatic brain disease and for subjects with a history of stable brain metastases. Brain CT or MRI scans performed before the signing of informed consent as routine procedures (but within 6 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given subject (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the subject's source notes. Post-baseline brain CT or MRI scans in subjects without documented lesions at baseline will only be required if metastases are suspected.
[g] Bone scans or whole body MRI will be carried out at baseline (ie, during Screening) for all subjects within 12 weeks prior to randomization in order to detect bone metastases. Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given subject (3) appropriate documentation confirming that these radiographic tumor assessments were performed as standard of care is available in the subject's source notes.
[h] If bone lesions were identified on baseline bone scan or whole body MRI (regardless of whether these lesions were confirmed by CT scan with bone windows or MRI to be metastatic), these scans will be repeated during the active treatment phase (using the same modality as used during Screening) as clinically indicated and every 24 weeks (± 7 days) from the date of randomization and at the time of confirmation of CR. If no bone lesions were identified at baseline, bone scan or whole body MRI will only be repeated during the active treatment phase when clinically indicated (ie, subject describes new or worsening bone

pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases), but is required at the time of confirmation of a CR.

[i] Suspicious abnormalities (ie, hotspots) identified on bone scan or whole body MRI at baseline and on subsequent bone scans or whole body MRI MUST be confirmed. Diagnostic CT of chest and CT (with bone window settings) or MRI of abdomen and pelvis (or PET CT if CT images are of sufficient quality) are sufficient for evaluation of bone lesions involving the axial skeleton. Additional imaging of appendicular skeletal lesions (eg, skull, cervical spine, extremities) by bone window settings on CT scan or MRI are required if these sites are the only bone lesions to be followed. If a lesion is not confirmed to be metastatic by CT with bone windows or MRI, it should not be followed as a target or non-target lesion and it does not require re-assessment. The same modality must be used throughout the study for confirmation for a given lesion/subject. Areas that have received palliative radiotherapy should be followed as non-target lesions.

[j] Bone lesions confirmed by CT or MRI (or PET CT when CT images are of sufficient quality) at baseline, and documented as target (when a measurable soft tissue component is present) and/or non-target lesions will be assessed every 8 weeks (± 7 days) using the required CT of chest and CT or MRI of abdomen and pelvis (or PET CT when PET CT was used at baseline) and additional imaging by bone window settings on CT scan or MRI of any appendicular bone lesions that are being followed as a target and/or non-target lesions. New abnormalities found on subsequent bone scan or whole body MRI must be confirmed by bone window settings on CT scan or MRI. At EOT, bone scan or whole body MRI is required if abnormalities were identified at Screening, unless disease progression has been confirmed elsewhere or a scan has been performed within the last 12 weeks

[k] Clinical assessment of superficial disease must be carried out within the same +/- 7-day window applied to imaging studies and any other modalities which are part of the tumor evaluation by RECIST v1.1. and will include photographs with measurement markers of all superficial metastatic lesions.

CR = complete response; CT = computed tomography; EOT = end of treatment; MRI = magnetic resonance image; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

APPENDIX 3. ECOG PERFORMANCE STATUS

Grade	Descriptions
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed <50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours
3	In bed >50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair
5	Dead

NOTE: From https://training.seer.cancer.gov/followup/procedures/dataset/ecog.html

APPENDIX 4. COCKCROFT-GAULT FORMULA

To determine eligibility for the study, Investigators may calculate a subject's creatinine clearance (CrCL) by the Cockcroft-Gault formula as follows [Cockcroft and Gault, 1976]:

Creatinine when reported in mg/dL:

$$\text{CrCL for females (mL/min)} = \frac{0.85 \times (140 - \text{age [years]}) \times (\text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

$$\text{CrCL for males (mL/min)} = \frac{(140 - \text{age [years]}) \times (\text{weight [kg]})}{72 \times (\text{serum creatinine [mg/dL]})}$$

Creatinine when reported in International System of Units (SI):

$$\text{CrCL for females (mL/min)} = \frac{(140 - \text{age [years]}) \times (\text{weight [kg]}) \times 1.04}{(\text{serum creatinine [umol/L]})}$$

$$\text{CrCL for males (mL/min)} = \frac{(140 - \text{age [years]}) \times (\text{weight [kg]}) \times 1.23}{(\text{serum creatinine [umol/L]})}$$

APPENDIX 5. NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS NCI-CTCAE V 5.0

NCI-CTC Version 5.0 reference, accessible through the NCI website at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average. When 2 criteria are available for similar toxicities, the one resulting in the more severe grade should be used. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms. An accurate baseline prior to therapy is essential.

APPENDIX 6. NEW YORK HEART ASSOCIATION GUIDELINES

The New York Heart Association Functional Classification provides a simple way of classifying the extent of heart failure [The Criteria Committee of the New York Heart Association, 1994]. It places subjects in one of 4 categories based on the level of limitation experienced during physical activity:

Functional Capacity	Objective Assessment
Class I: Subjects with cardiac disease, but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A:** No objective evidence of cardiovascular disease.
Class II: Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B:** Objective evidence of minimal cardiovascular disease.
Class III: Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C:** Objective evidence of moderately severe cardiovascular disease.
Class IV: Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D:** Objective evidence of severe cardiovascular disease.

APPENDIX 7. CHILD-PUGH ASSESSMENT OF HEPATIC FUNCTION

	Points Scored for Observed Findings		
Parameter	**1**	**2**	**3**
Hepatic encephalopathy grade[a]	0	1 or 2[b]	3 or 4[b]
Ascites[c]	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2	≥2 to ≤3	>3
Serum albumin (g/dL)	>3.5	≥2.8 to ≤3.5	<2.8
International normalized ratio	<1.7	≥1.7 to ≤2.3	>2.3

[a] Grade 0: normal consciousness, personality, neurological examination, or electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second (cps) waves.
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cps delta activity.

[b] A subject with hepatic encephalopathy of Grade 2 or above would not be admitted into the study.

[c] Absent: No ascites is detectable by manual examination or by ultrasound investigation, if ultrasound investigation is performed.
Slight: Ascites palpation doubtful, but ascites measurable by ultrasound investigation, if performed.
Moderate: Ascites detectable by palpation and by ultrasound investigation, if performed.
Severe: Necessity of paracentesis; does not respond to medication treatment. Subject would not be admitted into the study.

	Class A	**Class B**	**Class C**
Total points	5-6	7-9	10-15

Source: https://www.mdcalc.com/child-pugh-score-cirrhosis-mortality

APPENDIX 8. MEDICATIONS AND FOODS THAT ARE MODERATE OR STRONG INDUCERS OR INHIBITORS OF CYP3A4/5

CYP3A4/5 Moderate or Strong Inducers	CYP3A4/5 Moderate or Strong inhibitors
Apalutamide	Aprepitant
Bosentan	Boceprevir
Carbamazepine	Ciprofloxacin
Enzalutamide	Cobicistat
Etravirine	Conivaptan
Mitotane	Crizotinib
Phenobarbital	Cyclosporine
Phenytoin	Diltiazim
Primidone	Dronedarone
Rifampin	Eruthromycin
St. John's Wort	Fluconazole
	Fluvoxamine
	Grapefruit[a]
	Imatinib
	Itraconazole
	Ketoconazole
	Pomelo[a]
	Posaconazole
	Ritonavir (alone or with danoprevir, dasabuvir, elvitegravir, indinavir, lopinavir, paritaprevir, ombitsavir, saquinavir, tipranavir)
	Seville Orange[a]
	Star Fruit[a]
	Telaprevir
	Telithromycin
	Tofisopam
	Troleandomycin
	Verapimil
	Voriconazole

[a]Note: Subjects should avoid consumption of the following fruits, and juices and products derived from them: grapefruit, pomelo, Seville orange and Star Fruit
Source: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

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